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DISEASES OF THE
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SYMPOSIUM ON DISEASES OF THE ESOPHAGUS

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SYMPOSIUM ON DISEASES OF THE ESOPHAGUS

INTRODUCTION

During the past two decades, there has accumulated a tremendous store of information and new knowledge concerning the various physiological and pathological abnormalities affecting the esophagus and cardiac end of the stomach. Many of us remember that, not many years ago, the esophagus, especially the thoracic portion, was regarded as one of the surgical imponderables and that any surgeon who dared to venture into the dark recesses of the posterior mediastinum was surely imbued with a peculiar form of surgical bravado which was bound to end in disaster. In spite of many disappointments which followed the early attempts to learn more about the diseases which affect this organ and to develop new methods of therapy, dogged persistence on the part of a few investigators has opened new vistas.

It cannot be too strongly emphasized that the rapid progress in the diagnostic and therapeutic aspects of esophageal disease noted in the past few years has been made possible by newer developments in the general field of medicine. These include the remarkable improvements in the field of roentgenographic diagnosis, perfection of the technical aspects of endoscopy, a clearer appreciation of the physiological changes that accompany open thoracic operations, the unusual development of the field of anaesthesiology, the perfection of the various techniques necessary to carry out many complicated operative procedures and, finally, the advent of the antibiotics. We have learned a great deal, during this time, about the life history of some esophageal diseases which, in earlier years, were seen only at the postmortem table. For instance, as a result of large operative experience with cancer of the esophagus, the third most common of the gastrointestinal tract, information concerning the pathological sequence of events in the growth of these tumors has been obtained which was not known before. This information has helped the surgeon appraise a particular pathological setup at the time of exploration which determines therapy, prognosis and cure rate. The same sort of experience has been accumulated from therapy of other conditions involving the esophagus.

In more recent years, the investigative approach has served to clarify many of the physiological disturbances that affect the esophagus and cardia of the stomach. There are many problems which are as yet unsolved; although there is at the present time a better understanding of many of the underlying causative mechanisms than was the case a decade back. The provocative article of Dr. Wolf in this symposium on the disturbed function of the hiatal area is an excellent example of the physiological approach to one of the unsolved problems facing us today. The same is true of peptic esophagitis, achalasia and the interpretation of the endoscopic findings in the inflammatory diseases of the lower esophagus.

It is a pleasure to state that many members of the staff of the Mount Sinai Hospital have been in the forefront of this intriguing search for new facts and methods of therapy for the various pathological states that affect the esophagus and cardia. It is the purpose of the following symposium to acquaint the busy practitioner of medicine with the newer developments in this rather specialized field. The general excellence of the articles published in this issue should aid the physician immeasurably in his search for the latest information concerning this important organ of the body.

John H. Garlock, M.D.
Guest Editor

THE NORMAL ANATOMY AND PHYSIOLOGY OF THE ESOPHAGUS

VICTOR WILLNER, M.D., JOSEPH BANDES, M.D., AND FRANKLIN HOLLANDER, PH.D.

New York, N. Y.

The esophagus is a muscular tube, usually 23 to 26 cm. long in the adult, extending from the pharynx at the 6th cervical vertebra to its union with the stomach at the 11th thoracic. In the neck it is situated in the mid-line; toward the base of the neck, its direction is slightly toward the left; in the mid-thoracic region, at the level of the 5th thoracic vertebra, it again reaches the mid-line and then passes to the left as it goes through the diaphragm. The tube also shows anterior and posterior flexures, following the curves of the cervical and thoracic portions of the spinal column (1). For clinical purposes, it is useful to know that the distance from the incisor teeth to the cardia is approximately 40 centimeters (16 inches). This measurement varies with the individual (2), and although it possesses no absolute validity it does have great practical value.

Viewed roentgenoscopically, the esophagus presents three regions of narrowing, all slight and physiologically normal, one near the cricoid cartilage, another near the arch of the aorta, and the third, two to six centimeters above the level of the diaphragmatic hiatus. The abdominal portion of the esophagus is slightly conical, with its base directed toward the cardia of the stomach, and lying in a depression on the posterior surface of the left lobe of the liver. Sometimes this conical portion may be narrower than that above, because of pressure from the neighboring liver and spleen. The esophagus is attached to the diaphragm by the phreno-esophageal membrane which gives it poor anchorage.

In view of the recent studies of the function of the esophagus, particularly its distal eighth, it is important to note the interesting description of this latter region by Lerche (3). On the basis of extensive anatomical studies, this investigator divides (fig. 1) the distal eighth of the esophagus into: (a) the ampulla, not to be confused with the ampulla described radiologically; (b) the inferior esophageal sphincter just below the ampulla and 2–3.5 centimeters above the junction of esophagus and stomach; (c) the gastro-esophageal vestibule, approximately two centimeters long, encircled in part by the right crus of the diaphragm, and followed immediately by; (d) the constrictor cardiae. Although this description lacks conclusive confirmation, it has been found useful in explaining some of the findings encountered in recent pressure studies, as will be seen below.

The wall of the esophagus is composed of four layers. The external layer is formed by fibrous tissue. Deep to this is the muscular layer, composed of external longitudinal and internal circular fibers. At the beginning of the esophagus

From the Gastroenterology Research Laboratory, The Mount Sinai Hospital, New York City.

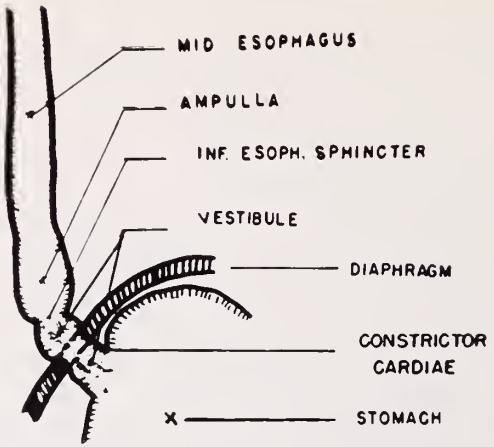

FIG. 1. Diagrammatic drawing, lower two-thirds of the esophagus [Lerche, 1950]

the longitudinal fibers are arranged in three bands which run separately for a short distance and later join to form a uniform layer. The circular fibers have a transverse direction in the proximal and distal parts of the esophagus and an oblique direction in the mid-portion. In the upper fifth of the esophagus the longitudinal muscle fibers are striated, in the second fifth there is a mixture of striated and smooth muscle fibers, and in the remainder usually only smooth muscle. The circular muscle fibers are striated only in the first two to three centimeters, after which they become entirely smooth. The third layer of the esophagus is the submucosa and the fourth is the mucosa. This innermost layer is about 500 microns thick (4), has longitudinal folds (usually four) which are sometimes bunched near the diaphragmatic hiatus, giving it the appearance of a "rosette", but which disappear on distension. The mucosa itself is composed of three different layers: a thick stratified squamous epithelium on the surface, an intermediate layer called the lamina propria, and beneath this the muscularis mucosae, immediately adjacent to the submucosa. The muscularis mucosae is more prominent in the lower portion of the esophagus than in the upper portion. The change from stratified squamous epithelium at the cardia to the cuboidal type of gastric epithelium is distinct, although the line of demarcation may be irregular because of small projections of the esophageal mucosa toward the stomach.

The mucous glands of the esophagus are of two types: (a) superficial cardial glands, limited to the lamina propria of the mucosa and lined by columnar or cuboidal cells, and (b) true esophageal mucus glands, located in the submucosa.

Aberrant gastric mucosa in the esophagus was first mentioned by Schmidt in 1805 (5), but since then, it has been described many times by other observers. Reports of its incidence in man vary from Taylor's 0.6 per cent (6) to Schridde's 70 per cent (7). There is general agreement that ectopic gastric mucosa occurs with more frequency in the upper and middle thirds, than in the lower third of the esophagus. The occurrence of parietal cells in islands of aberrant gastric

mucosa is rather infrequent according to Rector and Connerly (8), but this generalization may not be valid, because only the mouths and necks of the glands were included in the histological specimens as a result of superficial sampling. In the early reports on peptic ulcer of the esophagus, allusions were almost always made to the existence of gastric rests, and some observers believed that such ulceration developed exclusively in these islands of aberrant gastric mucosa. More recent observers, however, attach major importance to acid reflux from the stomach as a causative factor and believe that aberrant gastric mucosa, present in the distal esophagus, is more susceptible to peptic digestion than is the surrounding esophageal mucosa. Such ulceration occurs only in the presence of free hydrochloric acid in the stomach, and 25 per cent of these esophageal ulcers were associated with peptic ulcer elsewhere in the digestive tract. It must be borne in mind that there is another type of ulceration of the distal esophagus which occurs as the result of acid reflux producing a severe esophagitis with secondary superficial erosions and ulceration. This is not to be confused with true solitary peptic ulcer referred to above. Because peptic ulcer usually occurs in the distal esophagus and most gastric rests are found in the upper two thirds, it was suggested by Rector and Connerly (8) that acid from ectopic gastric mucosal rests flows down the esophagus to the cardia, where it is prevented from entering the stomach by the cardiac sphincter mechanism and so accumulates sufficiently to produce true peptic ulceration. However, Palmer (4) believes that the acid produced by the ectopic gastric rests is insignificant as compared to the amount which may be regurgitated from the stomach, especially in patients with the gastric hyper secretion associated with duodenal ulcer.

The arterial supply of the cervical portion of the esophagus is derived from the inferior thyroid artery, and that of the thoracic portion from the bronchial and thoracic arteries which are branches of the aorta. The blood supply to the abdominal portion comes from the left gastric and the left phrenic arteries. The veins which drain the esophagus form a plexus on its wall. The upper portion of the esophagus drains to the azygous and thoracic veins, and from there to the superior vena cava. The lower portion drains to the left gastric vein and thence to the portal vein. The lymphatics of the upper portion of the esophagus drain to the deep cervical lymph nodes, whereas those of the lower portion drain to the superior mediastinal nodes.

There is both an extrinsic and an intrinsic nerve supply to the esophagus. The former derives from the vagi and sympathetics; the intrinsic supply includes the myenteric and submucous plexuses. The vagus supply to the cervical portion of the esophagus comes from the recurrent laryngeal nerve; that to the thoracic portion comes from the right and left vagi; and that to the cardia, from the left division of the right vagus and a plexus near the cardia. The sympathetic innervation of the upper part of the esophagus arises from the inferior cervical and stellate ganglia, branches of which join the recurrent laryngeal nerve to form the esophageal and thoracic plexuses. The sympathetics in the lower esophagus come from the celiac ganglia, fibers running along the left gastric and left phrenic arteries and from the greater and lesser splanchnic nerves.

The motor (efferent) component of the nerve supply to the esophagus is derived from both vagus and sympathetics. The vagus effects synaptic connection with the neurons in the myenteric plexus, whereas the sympathetic is solely postganglionic, its fibers being terminal. The afferent portion consists of the visceral afferent component of the spinal nerves. Their fibers traverse the myenteric plexus and form no synaptic connections with it.

The chief nerve pathway of esophageal pain sensations is provided by the sympathetics, from the third cervical to the seventh and eighth dorsal spinal nerves. It is believed that the vagi may contain sensory fibers, but this has not been definitely established. The distribution, character and severity of pain varies considerably. When the stimulus acts over a prolonged period, the pain is usually burning in character; when intermittent and strong, it tends to produce a griping type of pain (9). Experimentally, fullness, pressure, and a sense of constriction have been noted when the upper and middle parts of the esophagus are distended. The sensation of heartburn is caused not only by regurgitation of acid from the stomach, but it can be elicited by rapid distension of the distal part of the esophagus as well. Esophageal pain is usually referred to the substernal or posterior mid-thoracic regions, or occasionally to the neck, face or ears. It is not unusual for pain initiated by a hiatus hernia to radiate from the mid-thoracic region into the left shoulder or arm, thus simulating anginal pain.

The myenteric or Auerbach plexus is situated between the longitudinal and circular muscle layers of the esophagus and constitutes part of the intrinsic nerve plexus. It begins three to four centimeters below the lower border of the pharynx. Intercommunicating with this is a second component of the intrinsic nerve supply, Meisner's plexus, which is situated in the submucosa, and also receives fibers from the extrinsic nerves. Ganglion cells are less abundant in the myenteric plexus of the esophagus and small intestine than in the rest of the gastrointestinal tract, and there may be some loss of ganglion cells with advancing age.

In order to gain a broad understanding of the detailed aspects of the motor physiology of the esophagus which follows, a comprehension of the act of swallowing is essential. Following voluntary projection of the masticated bolus of food to the back of the mouth, accomplished by elevation of the tongue and contraction of the mylohyoid muscles, a complicated series of involuntary events is initiated. The deglutition center in the medulla receives afferent impulses from the soft palate, the posterior wall of the pharynx and the epiglottis, and in turn sets off the following motor phenomena. The soft palate is elevated and the posterior pharyngeal wall bulges forward, thus effectively closing the posterior nares. Approximation of the posterior faucial pillars closes the mouth cavity. The larynx is pulled up toward the root of the tongue, the vocal cords are approximated, and the superior constrictor muscle is relaxed to receive the bolus. Meanwhile, respiration is inhibited. After the bolus passes through the pharyngoesophageal junction, with relaxation of the cricopharyngeus, it is carried down the esophagus by peristalsis. During the swallowing of fluids, the mechanism is somewhat different (10). The liquid is forcibly squirted into the pharynx and

down the esophagus by the mylohyoid contraction. Although gravity plays some part in the transport of ingesta, especially fluids, its role is not essential. For instance, it has been shown that a patient standing on his head can swallow a barium suspension which progresses to the stomach (11).

In order to effect these movements of the esophagus and control of the cardiac sphincter, various neuromuscular mechanisms are brought into operation. For the investigation of these physiological activities, two different techniques have been employed; roentgenoscopy (12), and pressure measurements (13). By these means, alone or in combination, studies of the influence of divers drugs and surgical procedures on motor behavior of the esophagus in human beings as well as animals have contributed much to our knowledge in this area. The occurrence of a true peristaltic wave, designated the *primary peristaltic wave* and initiated by the act of deglutition, is now well established. This wave is preceded by a wave of relaxation which travels down the entire length of the esophagus. Its function is to sweep the swallowed food or liquid into the stomach. A *secondary peristaltic wave* is also described (12, 14). This is essentially the same as the primary wave, except that it is not initiated by swallowing, but by distension of the esophageal wall and usually begins at the level of the aortic arch, below the origin of the esophagus. This is the type seen in balloon studies when the balloon is inflated. *Tertiary waves* have also been described, mostly in children and elderly people. These are segmental in nature, are not propulsive, and are inconstant in appearance; they seem to be purposeless and their significance is as yet unknown.

The dynamic pattern of the normal peristaltic wave varies at different levels, with respect to both amplitude and rate of travel. The greatest amplitude is usually seen in the mid-portion of the esophagus, but occasionally waves of considerable amplitude are encountered in the upper segment as well. As these peristaltic waves reach the distal portion of the esophagus, they slow considerably. This is particularly striking in the "vestibule", where the waves are also much reduced in amplitude. These differences in wave characteristics agree with differences in the rate at which a bolus of solid food is transported through different segments of the esophagus. In the cervical portion, the bolus travels about six centimeters per second; in the upper and lower and mid-thoracic regions, the rate is about five centimeters per second, and in the terminal esophagus it slows to three centimeters per second. In general, it takes swallowed food approximately seven seconds to reach the stomach. These differences in rate of transport and wave characteristics are accounted for, at least in part, by the variations in the type of muscle with which the esophagus is invested. The more powerful striated muscle of its upper portion accounts for the greater rapidity in this segment. In the mid-thoracic region, the speed is diminished because the muscle is partly striated and partly non-striated. The lower esophageal segment consists entirely of smooth muscle; hence the speed of propulsion is least in this portion.

At the terminus of the esophagus, a definite anatomical sphincter has never been satisfactorily demonstrated but there is abundant evidence for the existence

of a sphincter-like mechanism. For many years the factors responsible for the function of this cardiac sphincter mechanism have engaged the attention of both clinicians and laboratory workers, and an extensive literature on this subject has accumulated. Unfortunately, many of the published reports are conflicting and lead to confusion. This has arisen, probably, because (a) the vagus contains inhibitory as well as motor fibers, (b) motor effects observed experimentally vary with depth of anesthesia and intensity of electrical stimulation, and (c) different kinds of animals with differences in type of musculature, have been used by different investigators. However, there are some areas of general agreement. It is believed that the cardiac sphincter mechanism is normally in a state of tonic contraction but is relaxed by the arrival of the wave of relaxation which moves down the esophagus in advance of the peristaltic wave. The tonic contraction prevents regurgitation of the gastric contents into the esophagus; relaxation allows of the passage of the swallowed bolus into the stomach. The sphincteric function of the cardia is probably influenced by both sympathetic and parasympathetic nerve supplies. It is believed that stimulation of the vagus induces relaxation of the cardia. Conversely, interruption of the vagal nerves ought to result in a failure to relax. This theory, incidentally, is currently used to explain the occurrence of cardiospasm or achalasia, in which vagal interruption is believed to occur as a result of degeneration of the myenteric plexus.

It may be of interest at this point to note that complete removal of the sympathetic nerve supply to the esophagus (performed as a part of the sympathectomy in patients with hypertension) has failed to influence the function of the esophagus in any of the patients subsequently investigated (15). Similarly, bilateral vagotomy for peptic ulcer (16) has been found to be without lasting effect on esophageal function. Furthermore, fairly recent balloon-kymograph studies on human subjects (17) showed various drugs to be without effect on the motility of the normal esophagus. The substances so studied were the parasympathomimetic drugs, methacholine, acetylcholine, and physostigmine; the sympathomimetic drugs, epinephrine, and norepinephrine; and the adrenergic blocking agents, dibenzyline and regitine. Thus it can be seen that the role of the autonomic nervous system in the regulation of the function of the esophagus, including the cardiac sphincter mechanism, is still poorly understood.

Much of our present knowledge about esophageal motility, derived from visual records of pressure changes within the esophagus, has depended on the use of the classic balloon-kymograph technique. Unless the drawbacks peculiar to this technique are well understood, proper evaluation of the data which it affords is not possible. An inflated balloon tends to act as a foreign body and stimulates contractions of the esophageal wall. With a balloon large enough to record changes in two adjacent segments, the record may evince a summation of effect if the two segments contract in sequence (as in a peristaltic wave), or it may indicate no contraction whatever if the two segments are in opposite phase (one contracting and the other relaxing). Air present in any part of the tubular pressure conducting system exerts a cushioning effect on the waves of pressure transmitted to the recording device. Also, the whole system is re-

sponsive only to comparatively slow changes in pressure and is not adaptable to a succession of rapid changes. Because of these inherent difficulties, newer techniques of direct pressure measurement are receiving considerable attention. Pressures are imparted directly to a transducer which converts them to a variable electrical impulse. This, in turn, is amplified and recorded as waves on sensitized paper. The pressure may be picked up directly by a tiny transducer at the end of the stomach tube, or it may be transmitted through a column of water in an open-tipped intra-esophageal catheter to an outside transducer. Simultaneous recordings of pressure changes occurring at two or three different levels—as little as five centimeters apart—can be obtained by the use of a like number of catheters terminating at the desired positions in the esophagus. Because respiratory movements affect the intraluminal pressures, respiratory changes must be recorded simultaneously. The relative merits of such direct pressure methods may seem evident, but they also entail serious disadvantages which are gradually being brought to light. The apparatus for studies of this type is exceedingly complex, especially if it be desired to make two or more records simultaneously from different levels of the esophagus. Some notion of this complexity may be gained from figures 2 and 3, which depict the four channel setup in current use in this laboratory for studies of the pathophysiology of the digestive tract—particularly in patients with cardiospasm.

Let us now consider some of the information acquired by means of such nonroentgenoscopic methods. Butin et al (18), using a transducer at the distal end of a stomach tube, to record pressure changes following the swallowing of water, obtained evidence of a combination of changes which they designated the "swallowing complex". This complex consists of four components, one or more of which were absent in about two-thirds of the records and all of which were absent in 9 per cent. These components are shown in figure 4; [1.] an initial negative wave, indicative of a small drop in pressure almost immediately after the onset of swallowing; [2.] a first positive wave, corresponding to a sudden small increase in pressure closely (often within one second) after the negative wave; [3.] a second "gradual and at times indistinct" positive wave, persisting for several seconds and terminating in [4.] a third and final positive wave, usually of high amplitude, abrupt in onset, and declining sharply to the mean basal pressure level. The investigators also noted that 3.6 per cent of their records of people without esophageal abnormalities showed rhythmic phasic activities other than those of the swallowing complex, and not related to deglutition.

The interpretation given to the four components of the swallowing complex by Butin et al (18) is that the initial negative wave is not the result of a negative pressure transmitted from the pharynx at the beginning of swallowing, nor of the intrathoracic negative pressure. Evidence for this is suggested by the fact that the initial negative pressure wave occurs much less often in the midportion of the esophagus than in either the upper or lower thirds. Instead, these investigators believe that this negative wave results from stretching of the esophagus associated with elevation of the pharynx at the beginning of deglutition. This increase in length induces an increase in volume and hence a

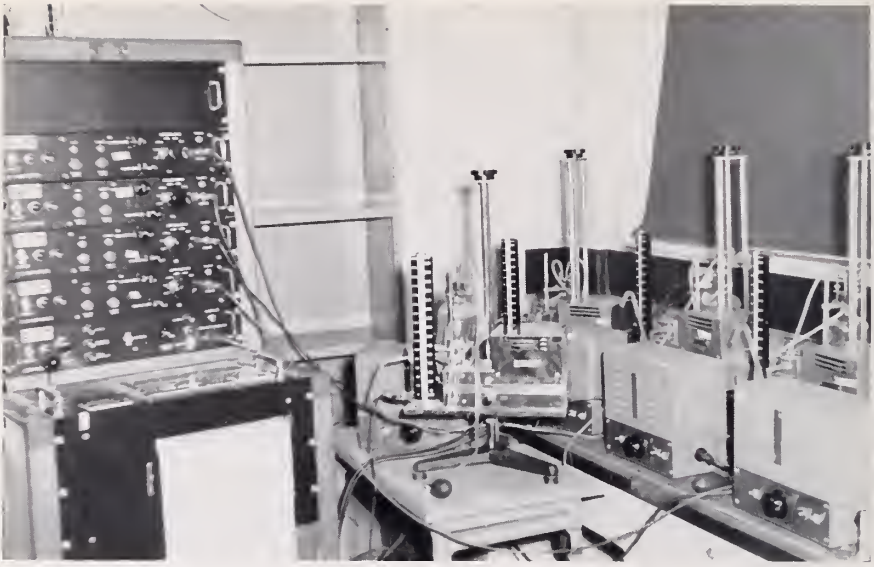

FIG. 2

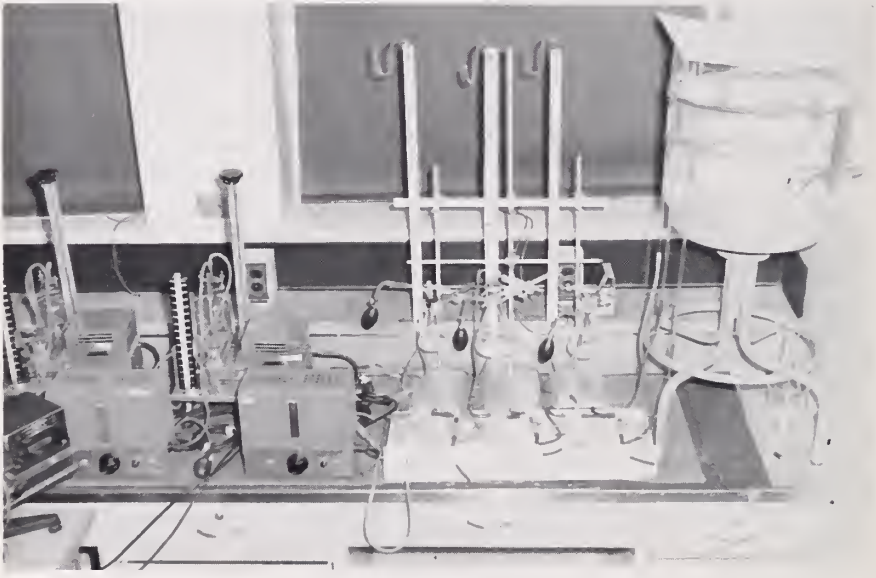

FIG. 3

FIGS. 2 AND 3. Apparatus for recording pressures directly or by way of balloons from three different levels of the esophagus simultaneously. A fourth channel permits the recording of simultaneous respiratory movements*.

decrease in intraluminal pressure because the two ends of the esophagus have firm circumferential attachments which maintain its length invariant. Also because of these terminal fixations, as well as the fact that it lacks support from

* The acquisition of this apparatus was made possible by a grant from the Siegfried and Irma Ullmann Foundation.

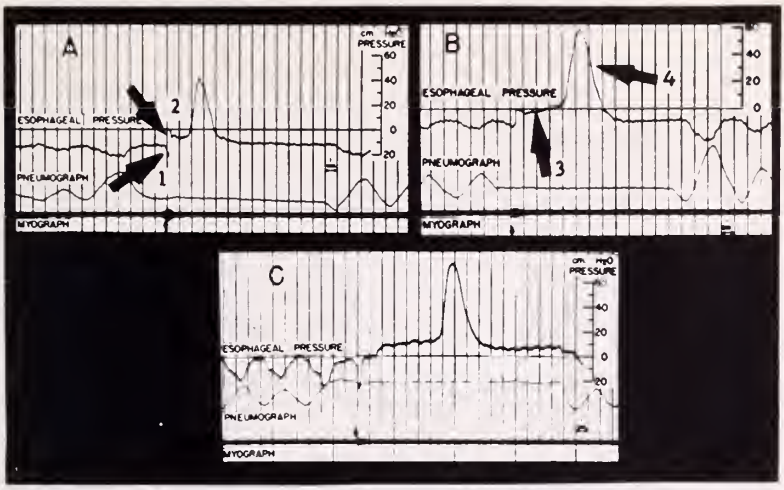

FIG. 4. Four waves constituting the "swallowing complex".
Illustrative examples from upper (A), middle (B), and lower (C) portions of the esophagus, [Butin et al, 1953].
[1] Initial negative—immediately after swallowing
[2] First positive—small, closely after [1]
[3] Second positive—"gradual, at times indistinct"
[4] Third positive—high amplitude

its surrounding structures in its mid-portion and therefore collapses and closes its lumen almost completely, the negative wave is observed less frequently in the middle than at either end of the esophagus. The first positive wave of pressure appears to be caused directly by the passage of the swallowed material into the esophagus, but actually, it is an extension of the bucco-pharyngeal pressure associated with it. In favor of this explanation, Butin and his associates (18) point to the fact that this wave appears almost instantaneously after the swallowing, with the same frequency and amplitude regardless of whether the subject was supine or sitting. In contrast with this first pressure wave, the second and third waves are probably reflections of the passage of a peristaltic wave, because their appearance at different levels of the esophagus is not simultaneous but follows a definite time sequence. The final wave of positive pressure is seen only infrequently in the lower esophagus, and when it does occur there, its amplitude is smaller than in the upper or middle segments. The authors explain this by postulating that the cardia may open just before the peristaltic wave reaches it, and this permits of a gradual dissipation of the descending front of elevated pressure.

Sanchez, Kramer and Ingelfinger (11) made similar studies on the motor behavior of the esophagus, particularly its distal portion, using two open-tipped intravenous catheters placed eight centimeters apart within its lumen. The catheters were filled with water and were connected to electromanometers containing the transducers. They were thus able to obtain simultaneous recordings at two levels of the esophagus. The recordings of the swallowing complexes obtained from the upper seven-eighths of the esophagus were similar to those obtained by Butin and his co-workers (18) in regard only to two of its components.

With but two exceptions, all their subjects failed to manifest the initial negative wave. Also, the second slow-rising positive wave was frequently absent, with occasional replacement by a gradually decreasing wave of pressure. When present, it was seen just before the final peristaltic wave. The swallowing complex in the upper esophagus of normal individuals, following the ingestion of liquids, is described as an almost instantaneously appearing positive pressure wave, caused by the sudden arrival of the fluid into the esophagus (11). Since this wave appears almost simultaneously at different levels of the esophagus—all but the lowermost one-eighth—it is probably an extension of the pressure with which the material is injected from the mouth into the esophagus, and therefore does not reflect a downward travelling peristaltic wave. This interpretation is confirmed by the fact that the first positive pressure wave is absent after a dry swallow, which usually contains too little saliva to increase the intraluminal pressure materially. The first positive pressure wave is followed by a plateau, usually with a slight downward slope, which is probably part of the first positive pressure wave. Following this plateau, there is a sudden appearance of the final high positive pressure wave which reflects passage of the true peristaltic wave. Between successive swallowing complexes, the esophagus is quiescent and no spontaneous waves are seen; the only pressure changes recorded are those caused by respiration or heart beat. It was also found by these investigators that repeated acts of deglutition, following each other rapidly, inhibited the appearance of the final peristaltic wave until after the last swallow when it occurred in normal fashion.

In contradistinction to the upper seven-eighths of the esophagus, the configuration of the swallowing complex in the lowermost portion two to five centimeters is different. In the ampulla, which is situated above the "gastroesophageal vestibule of expulsion" of Lerche, the swallowing complex differs from that in the upper esophagus only by reason of the fact that the final peristaltic wave declines gradually instead of dropping suddenly—similar to the observation of Butin et al (18). In the vestibule, however, the swallowing complex is decidedly different. The first positive wave and its plateau are absent. The second peristaltic pressure wave is present, but its amplitude is considerably smaller than in the upper esophagus and it both rises and falls more gradually. The latter characteristic of these vestibular waves is probably the result of slow accumulation of the swallowed fluid combined with its discharge out of the segment through the cardia. Apparently the peristaltic wave is not propagated into the vestibule, pointing therefore to the likelihood that the vestibule does not function as a unit integrated with the rest of the esophagus. The lower amplitude of the final pressure wave in the vestibule may be due to the weak muscular fibers of this region and also to the greater ease with which fluid leaves this region.

In a study recently reported by Sleisenger and associates (19), the initial negative wave and the sharp rise in pressure following it is ascribed to the inspiration and expiration associated with the act of sipping. This interpretation has been advanced by previous investigators, but its acceptance still awaits

general acceptance. Also, these authors agree with Ingelfinger and his group that it is probable that the vestibule has a "motor function separate from the remainder of the organ . . .".

The patterns of esophageal motility encountered in cardiospasm and some of the other causes of dysphagia differ from the foregoing in varying degree. Consideration of the motor behavior of the esophagus in these clinical conditions, however, belongs in the realm of pathophysiology, and consequently must be reserved for discussion elsewhere.

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BENIGN TUMORS OF THE ESOPHAGUS

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INTRODUCTION

In the rapidly expanding field of surgery of the esophagus, benign tumors have come to occupy a small but important segment. Formerly they were regarded as pathological curiosities and were rarely disclosed endoscopically. During the past two decades, however, newer knowledge of esophageal disease has clarified the roentgenologic, esophagoscopic, pathologic and therapeutic aspects of these tumors. Much of this information has probably resulted from the development of esophageal surgery. Before 1932, only 61 cases of benign tumors of the esophagus were reported in the literature (1), but by 1952 this figure had increased to 350 (2). Since 1947 the emphasis has been on the clinical and surgical features which are particulalry stressed in the reports from the Massachusetts General Hospital (3) and the Mayo Clinic (4).

CLASSIFICATION

The exhaustive classification of benign esophageal tumors as indicated in Table I gains in usefulness if the lesions are grouped in anatomico-clinical categories.

A. *Mucosal (intraluminal, polypoid) tumors*

Benign tumors arising from the mucosa of the esophagus are asymptomatic unless they are of fairly large size and fill the lumen as pedunculated or polypoid masses, or if they are vascular and bleed, as a result of surface ulceration.

The pedunculated type causes dysphagia and mild substernal distress. Cough, secondary to overflow of secretions into the tracheo-bronchial tree is occasionally seen. The stalk of a pedunculated intra-luminal mass may become progressively stretched and elongated by the propulsive effects of deglutition. Such a lesion may be regurgitated into the mouth, and on rare instances has been known to be aspirated into the larynx producing suffocation. These tumors are usually best dealt with endoscopically in much the same way as rectal polyps. Occasionally open operation may have to be performed. One must be certain of the histological nature of the tumor because the pedunculated shape may be assumed by a malignant growth (leiomyosarcoma). Under such circumstances, radical esophagectomy is necessary because of the likelihood of invasion of the stalk by tumor cells (5).

Occasionally the surface of a polypoid lesion may become abraded and ulcerated by the trauma of swallowed food. In such instances bleeding may be a symptom. Occasionally this may be severe if the tissue is angiomatous. In general, bleeding is a rare symptom of benign esophageal tumors.

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TABLE I (from Palmer)

Classification of benign esophageal tumors

I. Epithelial
  A. Stratified Squamous Epithelium
    1. Papilloma
    2. Acanthosis nigricans
    3. Hemangio-epithelioma
    4. Mucosal polyp
  B. Glandular Epithelium (Adenomas)
    1. Esophageal glands (submucosal)
    2. Heteropic mucosa (i.e. gastric)
    3. Aberrant thyroid tumor
    4. Aberrant pancreatic rests
II. Non-epithelial (wall of esophagus)
  A. Leiomyoma
  B. Fibroma
  C. Angioma
  D. Lipoma
  E. Schwannoma
  F. Chondroma
  G. Osteoma
  H. Myxoma
  I. Compound lesions
  J. Benign giant cell tumor
  K. Eosinophilic granuloma
  L. Rhabdomyoma
III. Cysts
  A. Retention Cysts
  B. Heterotopic Mucosa
    1. Gastrogenous
    2. Tracheo-bronchial
    3. Reduplications

B. *Mural (muscle-wall) tumors*

Neoplasms arising from the muscular coat of the esophagus constitute the largest and most important group of benign growths. This muscular layer varies from striated muscle in the upper third of the organ, to mixed striated and smooth muscle in the middle third, and smooth muscle alone in the lower third. Practically all benign muscle wall tumors are leiomyomas, occurring most commonly in the middle and lower thirds. Rhabdomyomas are exceedingly rare.

The leiomyomas are firm, rubbery, elastic, well-circumscribed tumors which are usually encapsulated. They may become firmly adherent to surrounding tissues without being invasive. Cystic degeneration and calcification may occur. The overlying esophageal mucosa is usually intact, a characteristic esophagoscopic finding. Ulceration of the overlying mucosa is extremely rare which is in sharp contrast to its frequency of occurrence in leiomyomas of the stomach and small bowel. Therefore bleeding is a most unusual symptom. Leiomyomas exhibit great variations in form and size. They can be single, multiple, simple, nodular, bosselated, or lobulated. At times they may be intra- or extra-mural;

they may be U-shaped, or may encircle the esophagus. Such variations in shape may affect the technique of surgical excision to the extreme of partial esophagectomy for their complete removal.

SYMPTOMS

The main symptoms of the leiomyomas are pain, dysphagia, and vague digestive complaints.

Pain is substernal or epigastric, usually radiating to the back, scapula, shoulder, neck, or down either arm. This pain usually occurs at the time of eating. Dysphagia varies from occasional sticking of food to constant inability to swallow solids. Rarely the dysphagia may be severe enough to cause significant weight loss. On the other hand very large tumors may be completely asymptomatic due to the fact that the lumen is not compromised. Vague digestive complaints are frequently associated with these lesions but it has always been difficult to explain the mechanism of their production. Gaseous eructations, heartburn, nausea, vomiting, or post-prandial distress have been noted. In only one patient in Sweet's series (3) was relief of these vague digestive complaints obtained by operation.

DIAGNOSIS

In the course of roentgenologic investigation of the symptoms of dysphagia, chest pain, epigastric or substernal distress, and indigestion, the discovery of a benign esophageal tumor constitutes a happy circumstance. The polypoid and endo-luminal lesions present as smooth, round or oval filling defects. The pedicle may be seen occasionally, or its existence and size may be surmised by noting the degree of mobility of the mass. Intra-mural tumors appear as smooth indentations into the lumen of the esophagus with intact overlying mucosa. Widening and flattening of the longitudinal folds are noted as a result of inward bulging of the mass. The unusual giant leiomyoma of the lower third presents as a large lobulated mass with smooth surface and with a variable degree of proximal dilatation of the esophagus. Disturbances in motility of the esophageal wall are rare in the presence of benign tumors.

The smooth deformity of the lower end of the esophagus that is sometimes produced by upward submucosal spread of adenocarcinoma of the cardia may rarely simulate the deformity produced by a leiomyoma. More often extrinsic pressure by enlarged mediastinal lymph nodes may produce a deformity in the esophagram which may be mistaken for leiomyoma. Under such circumstances search must be made for the primary source and most often a neoplasm of the lung will be disclosed.

Such positive roentgenographic findings should be followed by esophagoscopy whenever possible. In the pedunculated mucosal lesions the diagnosis is confirmed and endoscopic removal may be carried out at the same time. Muscle wall tumors characteristically present intact overlying mucosa. The diagnosis is therefore made by exclusion. Biopsy through intact mucosa is not advisable because of the likelihood of complicating the subsequent operation. The only

exception would be in the case of cardia carcinomas with upward submucosal spread. If such a lesion is suspected because of clinical and radiologic findings, a deep biopsy will usually establish the diagnosis.

SURGICAL TREATMENT

The muscle wall tumors are by far the most common benign growths requiring surgery. The characteristic circumscription and encapsulation of the leiomyomas permits easy enucleation. A transthoracic approach is carried out from either side depending upon the direction of maximum projection of the lesion. After incision of the mediastinal pleura, the location of the tumor in the esophageal wall is determined by inspection and palpation. In the group of smaller tumors which constitute the great majority, a longitudinal incision of the muscle coat over the mass permits easy enucleation without entering the lumen of the esophagus. If, however, an opening is made, it should be recognized and closed in a longitudinal direction with interrupted silk sutures followed by similar suture of the muscular coat. The mediastinal pleura is then closed, the lung is inflated, and the chest is closed. Underwater drainage is optional. Larger more complicated tumors may require resection of the esophagus with intra-thoracic esophago-gastric anastomosis utilizing the techniques described for the removal of cancer of the organ.

SUMMARY

Benign tumors of the esophagus, although relatively uncommon, are being recognized and treated with increasing frequency.

The clinically significant tumors fall into two main categories: (a) the intraluminal polypoid type and (b) those arising from the muscle wall, the leiomyomas.

Most benign esophageal tumors are asymptomatic or give very few symptoms which at times may be out of all proportion or actually unrelated to the lesion itself. These symptoms are reviewed and the criteria for diagnosis are outlined.

Esophagoscopic diagnosis and removal is the method of choice in the treatment of the first group. Transthoracic excision is the recommended therapy in the second group.

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PEPTIC ESOPHAGITIS AND PEPTIC ULCER OF THE ESOPHAGUS

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INTRODUCTION

The esophagitides are of many varieties (acute, subacute and chronic) and result from a wide variety of etiologic agents. Early in the 1930's I became interested in *one special* group of these cases, those with "*peptic* esophagitis". In 1934 I presented before the American Medical Association a paper entitled "Peptic Esophagitis as a New Clinical Entity" (1). Since that group was constantly associated with ulcer of the duodenum, it was concluded that these cases were "peptic" in origin.

Other types of esophagitis in which the activity of hydrochloric acid and pepsin probably plays a prominent role are (a) reflux esophagitis with marginal ulceration at the cardia secondary to sliding hiatus hernia, (b) esophagitis due to severe vomiting, (c) esophagitis resulting from prolonged esophageal intubation or gastric lavages, (d) esophagitis secondary to esophagogastrostomies, and (e) the "*solitary peptic ulcer*" of the lower esophagus.

Only three of these categories will be discussed, namely (a) peptic esophagitis with duodenal ulcer (rarely with gastric ulcer), (b) marginal ulceration with hiatus hernia, and (c) the solitary peptic ulcer of the esophagus.

PEPTIC ESOPHAGITIS

Apparently this disease is quite uncommon. However, it is probable that patients with gastric or duodenal ulcer who have severe heartburn and acid regurgitation would, upon esophogoscopy and biopsy, reveal evidence of a mild esophagitis.

Our material includes twenty cases (2), of which eleven patients were over sixty years of age. This seems to be a disease of older individuals. There were nineteen males and only one female, an overwhelming preponderance in males.

In addition to the usual ulcer symptoms, presenting symptoms of esophagitis included dysphagia, heartburn, regurgitation, vomiting, substernal pain and loss of weight. Dysphagia was the first and most prominent symptom in seventeen of the twenty cases. Regurgitation or vomiting of sour fluid with or without food was also a common symptom. Lower substernal pain on swallowing without radiation to the back was noted occasionally.

Hyperchlorhydria occurred in seventeen of twenty patients or eighty-five per cent of the cases. This finding may have etiologic significance.

The chief complications were stenosis, hemorrhage and, in one case perforation. Stenosis occurred in nine cases. Inflammatory swelling, spasm, and fibrous stricture are all involved. Fibrous stenosing esophagitis occurs regularly in the late stages of the severe cases. Massive hemorrhage occurred in four cases. In all of

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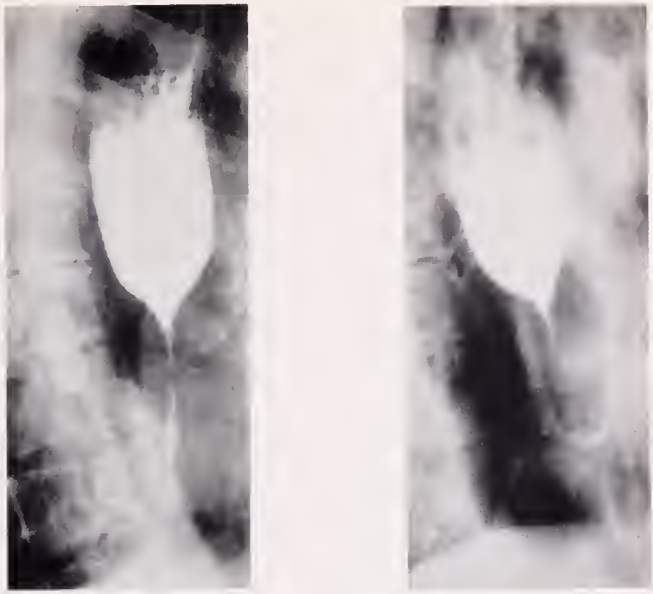

FIG. 1. Marked stenosis of the lower half of the esophagus with moderate dilatation above.

these it took the form of hematemesis and, therefore, it probably came from the esophagitis and not from the duodenal ulcer.

Fifteen patients had a co-existent duodenal ulcer and two had a gastric ulcer. A gastric ulcer in one case and a duodenal ulcer in another developed at a later date. One case had had a previously solitary peptic ulcer of the esophagus.

The radiologic findings are essentially of two varieties, (a) changes in distensibility with irregular narrowing of the lower third or half or more of the esophagus, and (b) changes in the mucosal pattern. In the severe cases, the lack of distensibility may be so marked as to produce a long segment of considerable narrowing involving the lower third or one-half of the esophagus (Fig. 1). The junction between the moderately dilated esophagus above and the narrowed portion below is gradual and symmetrical. The mucosal pattern throughout the narrowed segment is distorted and may have a hazy irregular appearance. The margins of this narrowed segment may show a fine serration. In contrast to the severe cases of peptic esophagitis described above, individuals with minimal inflammatory changes show considerably less striking findings on x-ray examination. The lower esophagus then appears as a narrow cylindrical structure. Within this segment the contours may show a fine irregularity (Fig. 2). A few cases developed secondarily a small, tent-like traction hernia of the stomach.

In a small number the differential diagnosis from carcinoma cannot be decided radiographically and esophagoscopy with biopsy is usually necessary. In peptic esophagitis esophagoscopy reveals marked edema and congestion of the affected part. Multiple small superficial ulcerations may be seen on the surface of irregular folds. Occasionally, a larger narrow area of flat ulceration runs longitudinally immediately above the cardia on the posterior wall. Small nodular excrescences

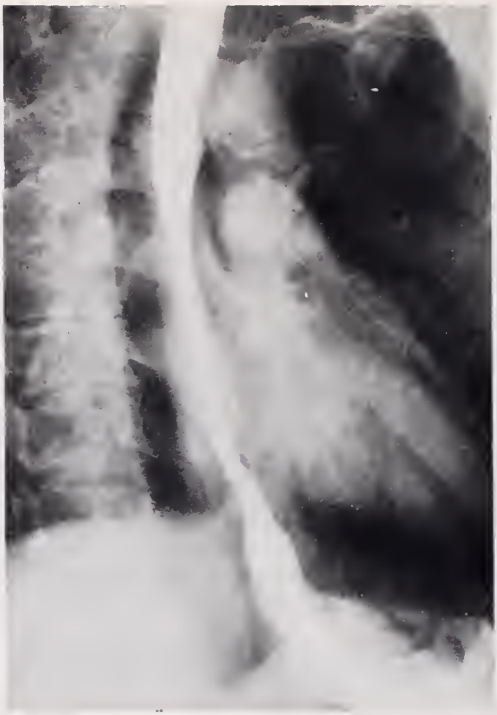

FIG. 2. Earlier stage. Moderate narrowing of lower half of the esophagus with irregular edges and hazy mucosa with a small traction hiatus hernia.

or a diffuse granular appearance may be present. In addition, there may be white exudates in small patches or larger plaques. There is marked narrowing of the lumen in the lower esophagus due to spasm or edema. However, in the advanced cases, impassable organic stenosis due to fibrous stricture is often encountered.

The microscopic features seen in the biopsy section include: (a) epithelial necrosis, (b) erosions, (c) hyaline mucosal zones, (d) polynuclear infiltration, and (e) hypertrophy of the muscularis mucosa (3). These changes are generally accepted by pathologists as evidence of "peptic" inflammation and form perhaps the best diagnostic criteria of "peptic" esophagitis. Later in the disease one sees more erosions and epithelial proliferations. Finally, fibrotic stenosis sets in.

The erosions, as a rule, do not penetrate through the muscularis mucosa. This diffuse superficial ulceration seen in "peptic" esophagitis does not, in our experience, eventuate in a deep, circumscribed, solitary "peptic" ulcer seen rarely in the lower esophagus lined with gastric mucosa.

All twenty patients were given the conventional Sippy type of therapy with anticholinergic drugs and alkalies. Six patients were treated with the continuous intraesophageal milk-soda drip therapy. Mechanical dilatation was employed in all the cases with stenosis. The results of this type of therapy are frequently strikingly good and usually eventuate either in a cure or a remission. We have seen a markedly constricted esophagus widen to an almost normal diameter after

mechanical dilatations. Sixteen cases have remained well; three were refractory to medical therapy, and one died of a perforated ulcer within a small traction hernia of the stomach.

With reference to the surgical therapy, the surgeons have run through the gamut of transthoracic bilateral vagotomy alone, gastro-enterostomy *with* vagotomy, and exclusion subtotal gastrectomy. In general, the results of these operations have been disappointing. Whether the poor results are due to the persistence of free acid or to a continuation of the disease process into greater stenosis is conjectural. The fact remains that subsequent dilatations were necessary to relieve these patients of progressive stenosis. The surgical procedure of resection of the involved lower esophagus and upper half of the stomach with bilateral vagotomy and *esophagogastrostomy* or *esophagojejunostomy* seems more logical and should be carried out in selected cases. Surgery seems only rarely necessary in my experience.

It should be emphasized that this disease is important not only as a disease entity per se, but also in the differential diagnosis from carcinoma of the lower end of the esophagus.

MARGINAL ULCERATION WITH SLIDING ESOPHAGEAL HIATUS HERNIAS

Marginal esophageal ulceration, that is, reflux esophagitis associated with the sliding hiatus hernia presents three noteworthy features:

(a) A short esophagus (from 25 to 37 centimeters instead of 38 to 40 centimeters).

(b) Reflux of acid gastric contents occurs constantly.

(c) Ulceration at the junction of the esophagus and stomach.

Endoscopically, one sees a one to three centimeter oval white exudate over a granular bleeding surface or an open flat ulcer. There is usually some degree of stenosis at the cardia. Radiographically, there is a short stenosing lesion, one to two centimeters long. The area below this may resemble the esophagus unless studied with the patient in a supine or Trendelenburg position. Biopsy of the mucosa of this narrowed area reveals gastric mucosa. Reflux of barium is seen in the proper positions in most cases. The non-stenosing type also does not distend normally and the mucosal pattern in the lower esophagus is distorted. Prompt reflux of acid gastric contents occurs. An ulcer niche is usually seen. It is generally small, rounded or flat, and appears as a rule on the right side at the esophago-gastric junction (Fig. 3).

This disease represents the effect of regurgitated acid and pepsin on a susceptible esophageal and gastric mucosa. There is first a sliding hiatus hernia due to relaxation of the diaphragmatic crura. With the hernia there exists an incompetency of the cardia. The esophagus then accommodates to this herniation by shortening itself. Rarely this condition may be congenital; usually it is acquired.

Marginal ulceration differs from the previously described peptic esophagitis associated with duodenal ulcer. In the latter condition, a long segment (one-half, one-third or more) of the esophagus is involved. If there is a large hiatus

FIG. 3. Hiatus hernia with ulcer niche at the esophago-gastric junction (right side)

hernia and an associated duodenal ulcer the area of esophagitis may be a long one; not the one to two centimeters usually seen in the marginal ulceration of a hiatus hernia without a concomitant duodenal ulcer.

About forty cases of marginal ulceration in older patients (ages fifty to seventy years) have been seen at The Mount Sinai Hospital in the last few years (4). Dysphagia, heartburn and hemorrhage occurs but perforation has not been seen. With the usual ulcer regimen and bouginage these patients often remain well for several months. When the ulceration is healed it seems advisable to repair the hernia.

In severe cases with marked stenosis it is possible that resection of the lower esophagus and upper half of the stomach may be necessary for a permanent cure. This requires further study.

It is important to emphasize that both in peptic esophagitis with duodenal ulcer and in marginal ulceration with hiatus hernias, the ulceration is superficial; it does not penetrate or perforate; and, therefore, it seems definitely to differ from the solitary peptic ulcer. We have been impressed by the fact that the inflammation in squamous epithelium is in the form of a diffuse esophagitis with only superficial ulceration.

SOLITARY PEPTIC ULCER OF THE ESOPHAGUS

The solitary peptic ulcer of the lower esophagus has been described often in the literature (5). It has all the characteristics of a chronic peptic ulcer of the stomach or duodenum, that is, it is round, it penetrates, it bleeds, it obstructs, and it perforates (Fig. 4). It may heal with scarring and, at times, stenosis. It is a rare disease; I have seen only five cases during the past thirty years. However, the literature indicates that it is not such a rare disease. The reason for the discrepancy may be that most of the cases reported in the literature were confused either with the marginal ulceration of the lower esophagus and upper stomach adjacent to a hiatus hernia or with an ulcer occurring in a herniated stomach whose gross appearance, probably due to faulty radiographic technique, resembled the esophagus. This confusion may be avoided if endoscopic biopsies

FIG. 4. Solitary peptic ulcer of the lower Esophagus. Niche with spasm immediately above and below it.

above, at the site of, and below the ulceration are taken. This reveals the fact that most cases diagnosed as solitary peptic ulcers of the esophagus are really hiatus hernia ulcerations usually involving lower esophageal mucosa and contiguous gastric mucosa. Another feature which differentiates these conditions is the fact that the solitary peptic ulcer penetrates, i.e., it goes through the muscularis mucosa and even through the entire thickness of the esophageal wall. Marginal ulceration at the cardia in hiatus hernias, in our experience is in the nature of a flat, superficial ulceration.

The etiology of the penetrating solitary peptic ulcer of the lower esophagus remains obscure. It is not associated with a hiatus hernia. It may be a reflux lesion in an ulcer-susceptible patient, or it may be a lesion in or adjacent to a patch of ectopic gastric secretory tissue. It has been emphasized by Barrett (5) that the solitary penetrating ulcer occurs in a lower esophagus lined with gastric mucosa and that such a lower esophagus is often associated with a hiatus hernia (secondary?). Whether the gastric mucosa in the lower esophagus is ectopic, heterotopic, or metaplastic, must be settled by further studies. These theories are difficult to prove without a careful histologic study of resected specimens.

The therapy is similar to that of peptic esophagitis. However, because of penetration and stenosis, surgical therapy is indicated more frequently.

SUMMARY

I. Of the several varieties of peptic ulceration in the esophagus, three are chosen for presentation here.

II. The first, peptic esophagitis associated with duodenal (or gastric) ulcer, is due to peptic action on a long segment of the lower esophagus. Dysphagia, pain and hemorrhage occur. Stenosis and hemorrhage are the chief complications. Ulcer drug therapy, diet and dilatations usually alleviate the symptoms. Occasionally, surgical therapy is necessary.

III. Peptic marginal ulceration in a short esophagus immediately at the cardia in a sliding hiatus hernia occupies characteristically a short segment (one to two centimeters) of lower esophagus and often adjacent gastric mucosa. The symptoms and therapy are like those in the first group. Repair of the hernia may be considered when the ulceration is healed.

IV. The solitary peptic ulcer of the esophagus is a rare disease. Many cases regarded in the past as solitary peptic ulcers of the esophagus were probably instances of marginal ulceration associated with hiatus hernias and the short esophagus. Reflux of acid contents, heterotopic, ectopic, or metaplastic gastric secretory tissue lining the lower esophagus may be etiologic agents. Surgical therapy may be necessary in severe cases.

V. It is not too difficult to differentiate these three conditions if one utilizes good radiographic technique and expert esophagoscopy with appropriate mucosal biopsies.

VI. These esophageal inflammatory conditions must be differentiated from carcinoma by esophagoscopy with biopsy.

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CONGENITAL ATRESIA OF THE ESOPHAGUS AND TRACHEO-ESOPHAGEAL FISTULA

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Congenital atresia of the esophagus and tracheo-esophageal fistula are associated anomalies of great importance to all physicians who deal with the care of the newborn infant. The increasing number of reports of cases of congenital atresia of the esophagus makes it evident that the abnormality is not rare.

Studies of the embryologic development of the trachea and esophagus reveal that in early fetal life these structures are one tube (1). Between the fourth and twelfth weeks of fetal life this tube becomes divided into two structures by an ingrowth of mesoderm. The lumen of the esophagus becomes obliterated by the proliferation and concrescence of its epithelial lining. Later, this solid cord becomes vacuolated, the vacuoles coalesce, and the lumen is reestablished. An arrest in development, or failure of the mesoderm to separate completely the trachea from the esophagus, results in a tracheo-esophageal fistula, while failure of the vacuoles to coalesce results in an atresia of the esophagus.

These anomalies take a variety of forms, from atresia of the lower two-thirds of the esophagus to a completely patent esophagus with a tracheo-esophageal fistula. In over 90 per cent of the cases the upper portion of the esophagus ends as a blind pouch at the level of the first or second dorsal vertebra, and the lower segment of the esophagus enters the trachea just above its bifurcation, thus forming a tracheo-esophageal fistula (Figs. 1, 2, 3). The upper blind pouch is usually dilated and its walls hypertrophied. This dilatation and hypertrophy are evidently the result of the ineffectual attempts of the fetus to swallow the amniotic fluid. The lower segment of the esophagus, at the cardiac end, is usually of normal size but diminishes in diameter toward its tracheal opening, occasionally being as small as three to four millimeters.

The early recognition of this anomaly is of paramount importance in its successful treatment. This responsibility rests with obstetricians and pediatricians. The symptoms are noted soon after birth. The infant is seen to have an excess of saliva in the mouth. Spells of choking and, usually, some cyanosis occur during aspiration of mucus. When a feeding is given there is immediate regurgitation with aspiration of fluid into the air passages and an increase in the choking and cyanosis. The staff in newborn nurseries should be taught to report these symptoms immediately and not to persist in further attempts at feeding. Examination of the chest often reveals moist rales in the lungs, usually in the right upper lobe.

Roentgenologic examination is of great aid in diagnosis. A small soft rubber catheter is passed down the esophagus. If an obstruction is met about 10 to 12

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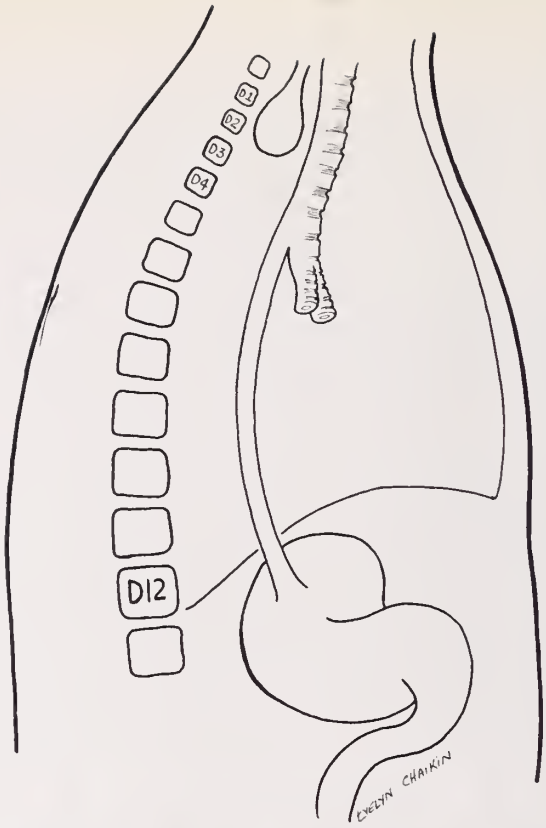

FIG. 1. Drawing illustrating atresia of the esophagus and tracheo-esophageal fistula.

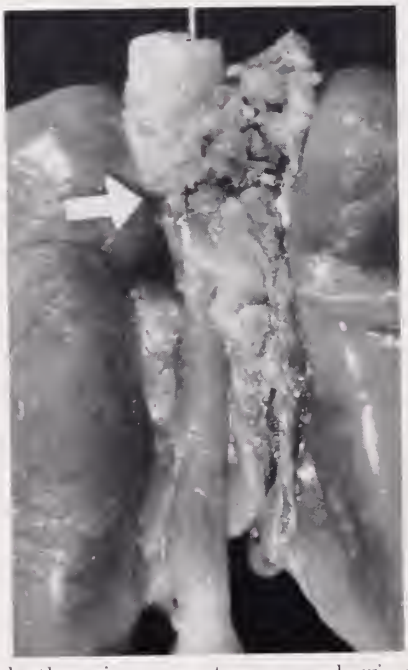

FIG. 2. Photograph of the thoracic organs at necropsy showing the site of the end-to-end anastomosis of the esophagus (arrow).

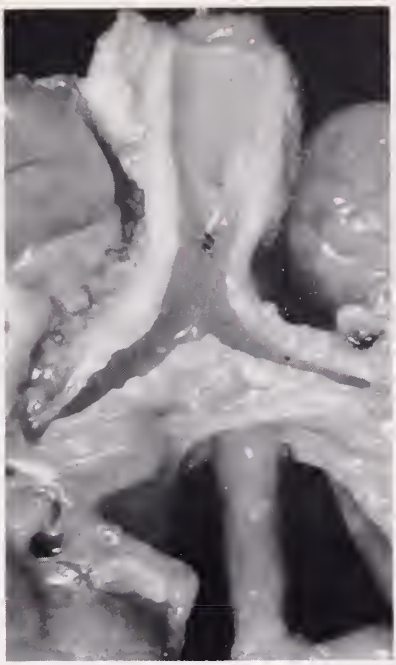

FIG. 3. Photograph of the opened trachea at necropsy showing the site of the closed tracheo-esophageal fistula on the posterior wall.

centimeters from the mouth, a diagnosis of congenital atresia of the esophagus is confirmed. This procedure should be performed under the fluoroscope. If this precaution is not taken, the catheter may be coiled in the proximal pouch of the esophagus, and the examiner may believe that it has passed through the esophagus into the stomach. A roentgenogram with the catheter in place will demonstrate the site of the obstruction. Most authors advise the instillation of 0.5 to 1.0 cc. of iodized oil for roentgenographic demonstration of the condition. This outlines the upper esophageal pouch, but, to my mind, it is unnecessary and gives no important additional information. The roentgenogram should include the abdomen, for the presence of air in the stomach or intestines is indicative of a communication between the lower esophageal segment and the trachea. The absence of air in the stomach or intestines indicates but does not prove the absence of a fistula, for this communication may be very small. The chest film will also supplement the physical examination in estimating the amount of atelectasis or pneumonia, which is usually present in these patients (Figs. 4, 5, 6).

Congenital anomalies of the esophagus are frequently associated with anomalies of other organs of the body, and some of these abnormalities in themselves may be incompatible with life unless corrected surgically. The most frequent of these are abnormalities of the heart and urinary tract, and imperforate anus.

The preoperative care of these infants is important. The baby is kept in an

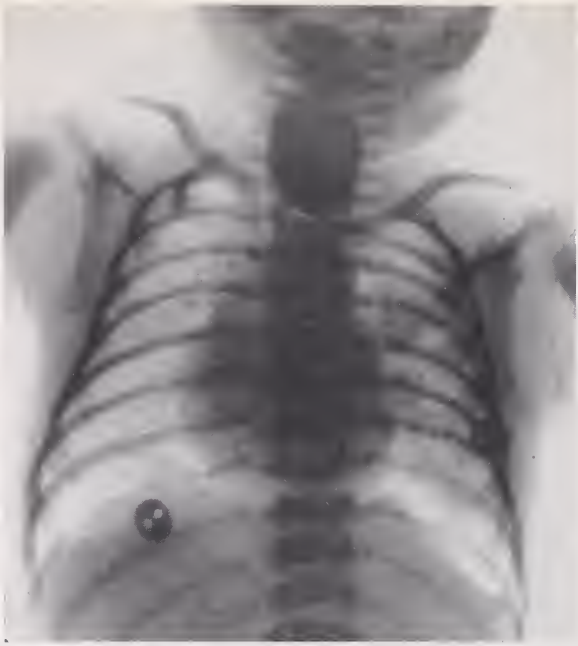

FIG. 4. Roentgenogram of the chest and abdomen (iodized oil administered) showing a dilated upper pouch of esophagus, oil deposits in the lungs, and air in the intestines.

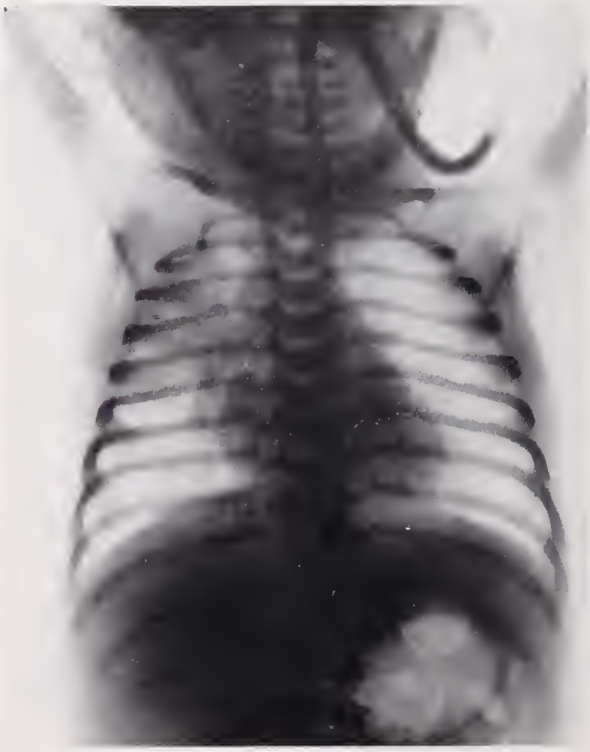

FIG. 5. Roentgenogram of the chest and abdomen (without the use of a contrast medium) showing a catheter in the esophagus obstructed at the superior thoracic aperture, consolidation of the right upper lobe of the lung, and air in the gastrointestinal tract.

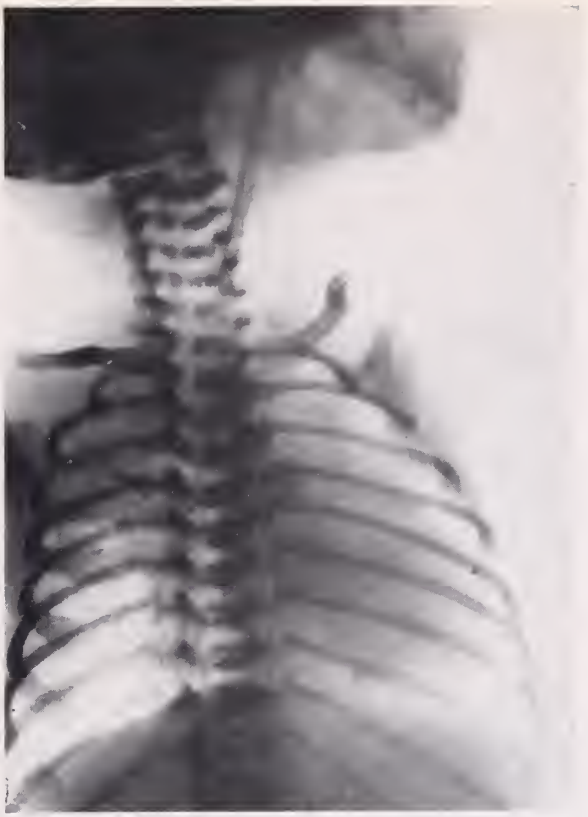

FIG. 6. Roentgenogram of the chest and abdomen (without the use of a contrast medium) showing a catheter in the esophagus obstructed at the level of the seventh cervical vertebra, consolidation of the upper third of the right lung, and absence of air in the gastrointestinal tract.

FIG. 7. Photograph of infant in an incubator following primary anastomosis of the esophagus and division of tracheo-esophageal fistula.

incubator which provides for the influx of desired concentrations of oxygen and temperature and humidity control (Fig. 7). A small soft rubber catheter is introduced into the pharynx and attached to constant gentle suction. A slight Trendelenberg position will facilitate the aspiration of mucus. An ankle vein is exposed through a small incision and a polyethylene catheter inserted for the administration of parenteral fluids. The amount of intravenous fluid must be carefully regulated so as not to exceed 100 cc./Kg./24 hours. The solution used is preferably five per cent dextrose in distilled water. Solutions of sodium chloride should be avoided because of the probability of poor renal excretion of the salt with resultant harmful edema. Most newborn babies have a high concentration of hemoglobin and red blood cells and do not require blood transfusions in this period of preparation. However, blood in the amount of 15 cc./Kg. is routinely administered during operation. Adequate doses of penicillin and streptomycin are immediately started. If these measures are carried out, 24 hours will be sufficient time to obtain the maximal beneficial response from preoperative treatment. Additional time will be needed in infants who have extensive pneumonic consolidation.

Cyclopropane or ether and oxygen, administered through a small, snugly fitting mask, are the anesthetic agents usually used. An endotracheal tube can be of aid, provided the anesthetist is experienced in its use in infants.

Before discussing the plans of surgical treatment, mention should be made of the fact that gastrostomy alone is a procedure to be condemned because the gastrostomy feedings pass upward through the tracheo-esophageal fistula into the lung, and the infant soon dies of aspiration pneumonia. Some encouragement was given to surgeons by the early and few successes of Ladd (2) and Leven (3), who devised multiple-stage procedures. These consisted essentially of extrapleural division and ligation of the tracheo-esophageal fistula, gastrostomy, exteriorization of the upper esophageal pouch into the neck, and construction of an anterior thoracic esophagus. Reestablishment of the continuity of the alimentary tract is a major problem in cases in which multiple-stage operations have been performed. A variety of skin lined tubes and jejunal transplantations have been tried, and although a few successful results have been reported, the technical difficulties have been great, and the periods of hospitalization long and expensive. The first successful primary anastomosis of the esophagus for esophageal atresia reported in 1943 (4) provided the impetus for a renewed attack on the problem.

The operative exposure is in the right posterior superior mediastinum. Surgeons differ as to whether the approach should be retropleural or transpleural; the writer strongly advocates the former. The work of Haight (5), Swenson (6), Leven (7), Potts (8), and Bigger (9) has been pre-eminent in the management of these cases, and the details of the technic of primary anastomosis have been described by them. These authors advise a gastrostomy for feeding purposes 24 hours after operation. This allows oral feedings to be deferred until about the tenth postoperative day. In recent experiences I have not found a gastrostomy necessary. On the fourth postoperative day the continuity and patency of the

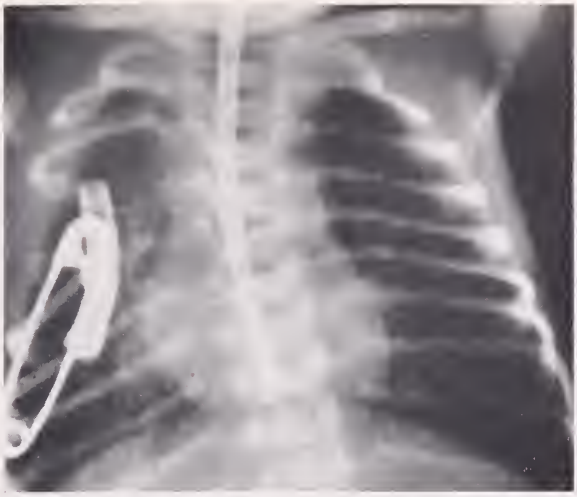

FIG. 8. Roentgenogram of the chest one day after primary anastomosis of the esophagus and division of tracheo-esophageal fistula showing the plexitron tube in the esophagus, resection of fourth right rib at operative site, and drainage tube in superior mediastinum.

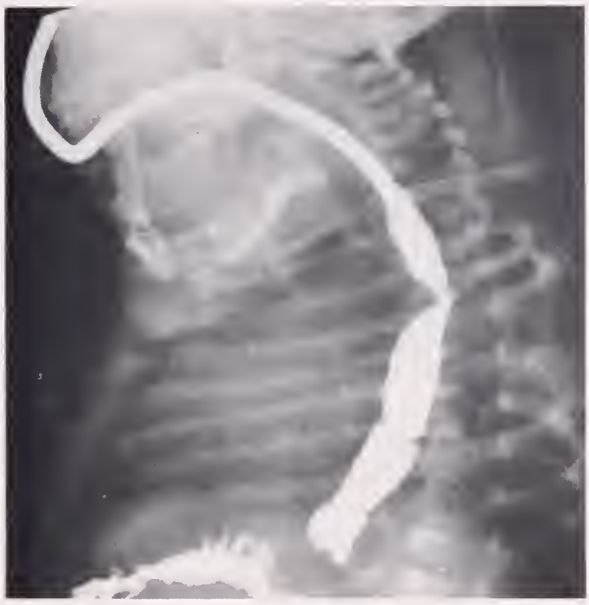

FIG. 9. Roentgenogram of the chest and esophogram one month after primary anastomosis of the esophagus and division of tracheo-esophageal fistula showing slight narrowing at the site of anastomosis, and no obstruction to the passage of contrast medium.

esophagus is studied fluoroscopically by the instillation of a small amount of iodized oil into the upper esophagus. If the lumen of the anastomosis is adequate and no leak is present, oral feedings are started. If a fistula is seen, a plexitron intubation tube is passed into the stomach and feedings administered through

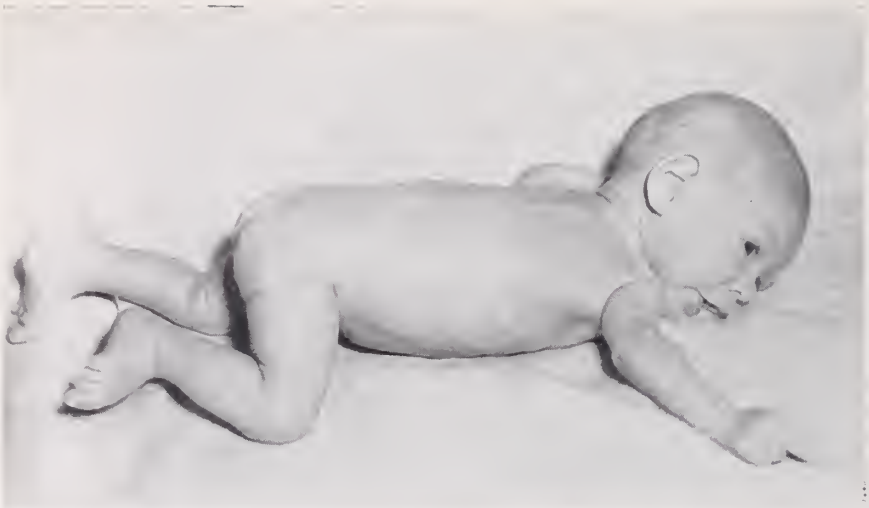

FIG. 10. Photograph of premature infant one month after primary anastomosis of the esophagus and division of tracheo-esophageal fistula.

it. In a few recent cases I have found no reaction to plexitron tubes placed at the time of operation, and starting feedings by the third postoperative day (Fig. 8). External esophageal fistulas from leakage at the site of anastoomsis usually heal without difficulty. Some narrowing of the area of anastomosis is common in the early postoperative days (Fig. 9), but dilatations are rarely necessary.

A marked improvement in the survival rate of infants with atresia of the esophagus has been reported by surgeons experienced in the surgical care of the newborn. In averaging the results of operation by this group, the survival rate is 47 per cent. This is encouraging when one considers that prior to 1939 no infant with this condition survived. The assistance of experienced resident and nursing staffs is invaluable. Once over the trying period of the first postoperative week, these babies usually progress rapidly (Fig. 10). It is not generally known that infants in the first 48 hours of life stand major surgical procedures far better than they do a week or so later. The care of the premature baby (weighing five pounds or less) has always presented a serious problem, and even in these tiny patients with atresia of the esophagus, Gross and Ferguson (10) reported a survival rate of 33 per cent. One of our successes was in a premature who is shown in Figure 10.

SUMMARY

The pathologic and clinical features, and the diagnosis of congenital atresia of the esophagus and tracheo-esophageal fistula are reviewed. The principles of treatment and some personal observations are presented.

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ACHALASIA OF THE ESOPHAGUS

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Cardiospasm, or achalasia, is a disturbance of function of the esophagus, associated with obstruction at the esophagocardiac junction, and dilatation of the organ proximally. Despite the fact that this syndrome was recognized in 1672, the essential cause is still not clearly defined.

Willis (1) described the first case in which difficulty in swallowing and vomiting were present, and in whom dilatation was attempted with a bougie of whale bone. Several workers, including Mikulicz (2) and Einhorn (3) who sought an explanation of this condition, postulated spasm or lack of relaxation of the cardia at the time of swallowing. Hurst (4) championed the theory of failure of relaxation of the cardiac sphincter, believing that a paralysis of the vagal mechanism was present. Rake (5), seeking an anatomical cause pointed out an inflammatory reaction around the ganglia of Auerbach's plexus in the submucosa, which, in later stages, progressed to fibrosis and disintegration of the ganglion cells. Gallinaro (6) was able to duplicate these observations. The dilatation of the esophagus is probably secondary to this reaction, although some workers feel that the degeneration of Auerbach's plexus is secondary to the esophageal dilatation.

PATHOLOGIC PHYSIOLOGY

Sleisenger and his co-workers (7) recently summarized the motor physiology of the esophagus based on their own work and that of others (8, 9). In normal subjects, certain changes, as measured by balloons inserted into the esophagus, occur in the intraluminal pressure on swallowing. There is an initial negative deflection in the tracing followed by a sharp rise in pressure. Subsequent to this, there is a gradual rise in pressure in the distal esophagus, ending in a final strong rise in pressure representing the peak of the entire complex. This climactic positive wave occurs about two seconds after swallowing in the upper esophagus, about five seconds in mid-esophagus, and eight seconds in the distal esophagus.

Sanchez, Kramer, and Ingelfinger (9) emphasized the differences in motility between the body (upper seven eighths) and the distal (lower one eighth) of the esophagus. Their studies would indicate that the extreme lower end of the thoracic esophagus (the vestibule) has a motor function separate from the rest of the gullet. It is in this area that the degeneration, or absence of the ganglion cells of the myenteric plexuses occurs, and in which the motility disturbances of the esophagus in cardiospasm are initiated.

In cardiospasm, the balloon technics of Kramer and Ingelfinger (10) indicate that the motility of the esophagus is abnormal, with irregular, low phasic contractions. Pressure changes occur simultaneously at all levels, with none of the progressive changes seen in the peristalsis of the normal esophagus. In addition,

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the esophagus responds with increased sensitivity to parasympathomimetic agents, such as mecholyl, going into sustained contraction. This finding has been confirmed by Sleisenger (7) and Hightower (11). The sensitivity of the esophagus to mecholyl is explained by Cannon's "law" that end organs deprived of their autonomic nerves react with unusual sensitivity to chemical mediators of nerve transmission.

ETIOLOGY

The cause of cardiospasm is unknown. Vitamin deficiency has been suggested by Etzel (12) who found cardiospasm in a large group of people in Brazil who were suffering from severe malnutrition. The association of cardiospasm (megaesophagus) with Hirschsprung's disease (megacolon) suggests a congenital origin, but the disease is rarely seen before the fourth decade.

A history of emotional trauma preceding the onset of symptoms may be elicited in many cases. One young woman who successfully fought off an attempted rape was treated by us. Achalasia has been reported in patients suffering from severe depression and schizophrenia. Situational conflicts may be related to the development of cardiospasm (13).

Cardiospasm may follow vagotomy. We have noted one patient whose symptoms followed the removal of an esophageal leiomyoma with section of the vagus nerve.

PATHOLOGY

The obstruction is usually confined to a small segment of esophagus about 1.5 centimeters above the cardio-esophageal junction. The esophagus proximal to this is markedly dilated with thickened wall, hypertrophy of the muscle layers, edema, and frequent ulceration of the mucosa. The dilatation may be so extreme as to occupy much of the right thoracic cavity. As the disease progresses, the esophagus elongates and becomes somewhat reduplicated to form the typical S-shaped deformity.

SYMPTOMS

The initial symptoms of cardiospasm may be those of oppression and heaviness in the chest. Patients complain of constriction in the lower posterior chest when under stress, which is frequently relieved by a hot drink. Food causes only slight distress at first, but eventually obstructive symptoms supervene. The patient may regurgitate food eaten the day before.

Symptoms usually increase in severity so that dysphagia and substernal distress are almost constant. Nutritional disturbances may develop as a result of fear of eating, but it is amazing that the vast majority of these patients maintain their nutrition with little weight loss. Recurrent bouts of pneumonia may occur in the long standing cases due to spillover of retained food.

RADIOLOGIC FEATURES OF CARDIOSPASM

Templeton (14) has summarized the radiologic features of achalasia. In the early stages, when barium is ingested, the esophagus may not appear dilated, but a narrowing, about one to two centimeters in length may be demonstrated

at the lower end. This narrowing is the result of spasm which, if persistent, becomes a contributing factor in the subsequent dilatation of the esophagus. Fluoroscopic examination will show secondary esophageal movements with spasmodic contractions of the entire esophagus working to empty itself.

As the disease progresses, dilatation of the esophagus increases, and a smoothly outlined, markedly widened organ develops. Many purposeless contractions are visible without any evidence of emptying of esophageal contents into the stomach.

Dilatation, elongation, and tortuosity of the esophagus are demonstrated, and the final S-shaped deformity of cardiospasm develops. It is of extreme importance to study the cardia of the stomach, since a neoplasm in this area may be the underlying cause of the obstruction (15).

Carcinoma occurs occasionally in individuals suffering from long standing cardiospasm. More commonly, however, the carcinoma has preceded the so-called cardiospasm. Baer and Sicher (16) consider achalasia to be a rare precursor of carcinoma, but Benedict (17) feels that there is only a coincidental relationship. Rake (18) favors an etiological relationship on the basis of irritation of the esophageal mucosa by stagnated food, mucosal ulceration, attempts at repair, islands of epithelial hyperplasia, papillomatous formation, and malignant growth.

ESOPHAGOSCOPY

Endoscopy is mandatory to rule out neoplasm and to obtain information about the condition of the esophageal mucosa. Esophageal lavage is advisable before instrumentation so that a clear view may be obtained. A foul odor is frequently encountered because of putrefaction of retained food. The esophageal mucosa is reddened, inflamed, and frequently ulcerated. The cardia may not be reached because of the elongation and distortion of the organ.

COMPLICATIONS

The most common complication is esophagitis, which can be demonstrated by esophagoscopy. Diverticula may occur as a result of the stasis and dilatation.

Pulmonary complications are not infrequently encountered. The weight of the dilated esophagus may compress the right lung, with resultant localized areas of atalectasis. Pneumonitis may be the result of compression and of continuous aspiration of regurgitated esophageal contents (19). Spontaneous pneumothorax, lung abscesses, pleural effusions, and even an esophago-bronchial fistula have been reported. But these are exceedingly rare chest complications nowadays.

Rheumatoid arthritis has also been noted in association with cardiospasm, but the course of arthritis is apparently uninfluenced by the relief of the cardiospasm.

TREATMENT OF CARDIOSPASM

Many cases of cardiospasm may be managed by a medical regimen, which includes attention to the nutritional state, frequent small meals, the washing

down of meals by hot drinks, and the exhibition of sedative antispasmodic drugs, such as atropine and phenobarbital. The more potent anticholinergic drugs, such as banthine and prantal are not indicated because of their tendency to induce spasm of the cardia.

The majority of patients will require dilatation. The most satisfactory method consists of the use of the Hurst mercury-weighted bougie. A series of rubber tubes varying in size from 28 to 34 French, 31 inches in length are employed. Each tube contains approximately one pound and five ounces of mercury. The tube is passed toward the cardia, and exerts pressure against the obstructed segment. The patient usually experiences considerable relief as the tube passes into the stomach. The tube remains in situ for about fifteen minutes, and successively larger tubes are used in later treatments. The patient can be taught to pass the tube before each meal. As relief is obtained, two or even one dilatation each day may be adequate. It is hazardous to attempt this form of therapy in the S-shaped deformity cases for fear of perforation in the reduplicated portions of the organ. It is in this variety of the disease that surgical therapy is particularly indicated.

Surgical Therapy

(John H. Garlock, M.D.)

The problem of the therapy of cardiospasm or achalasia has always been and still continues to be one of great difficulty. It must be stated emphatically that no final definitive therapy has, as yet, been found which is 100 per cent effective. The history of the treatment of this disease surgically extends back many years. In the early part of this century, numerous procedures were advocated, ranging from the now repopularized Heller operation to various complicated anastomotic operations in order to enlarge the entrance to the stomach. The Heller operation, which is a myotomy of the lower end of the esophagus and the adjacent portion of the stomach performed in the same way as one does a myotomy for congenital hypertrophic pyloric stenosis, fell into disuse over the second 20 years of this century and the operation of anastomosis between the esophagus above and the greater curvature of the stomach below became popular with the advent of the newly described operations by Grundahl and Heyrovsky. This is now known as a Grundahl-Heyrovsky procedure and consists of a lateral anastomosis between the left wall of the esophagus and the adjacent greater curvature of the stomach so as to produce a larger communication above the site of the obstruction. No attention was paid in most of the operations done, according to this technique, to the cardiospastic area itself.

In the early days of esophageal surgery at the Mount Sinai Hospital the Heyrovsky operation was undertaken as the operation of choice. Twenty odd cases were treated by this method and they were carefully followed over a period of years. It became evident that the longer we followed these patients, the greater became the incidence of reflux esophagitis, (up to 40 per cent) with all the serious complications attending this inflammatory reaction in the lower esophagus. The main symptoms were those of severe esophagitis with the subsequent

formation of ulceration and stricture, and severe hemorrhage. A number of the patients bled so extensively over a prolonged period of time that, upon admission to the hospital for further definitive therapy, the hemoglobin was under 7 grams.

A careful appraisal of these results of the anastomosis operation led us to feel that the danger of reflux esophagitis was too great to warrant continuation of the operation. The patients who developed these complications subsequently had to be subjected to a most radical type of operation. This involved excision of the distal portion of the esophagus and the upper two thirds of the stomach, i.e. a proximal subtotal gastectomy, and anastomosis between the esophagus and the remainder of the stomach with a complementary bilateral vagotomy and pyloroplasty through a combined abdomino-thoracic approach. This is an extensive procedure but the results have been excellent. We have not seen any reason for utilizing a segment of jejunum with by-passing of the stomach as recommended by Allison.

Since these results were examined and the anastomosis operation found to be inadequate and subject to late complications, we began to use the long discarded Heller procedure which has been advocated for many years by Graham. This procedure, done through an abdominal incision, entails the mobilization of the lower portion of the esophagus in the posterior mediastinum and a most careful myotomy of the musculature starting about 1.5 inches above the obvious area of constriction and extending downwards through the constriction on to the anterior wall of the stomach for a distance of about two inches. In other words, a myotomy incision averages between three and four inches in length. Graham has always insisted that this is an important feature of the operation and we have followed his admonition consistently in all the cases we have done. It must be observed that there is really very little to see at the time of operation at the point of spasm. The musculature here is certainly not hypertrophied. It is always located about 0.75 to 1.5 centimeters above the exact cardia and extends over a distance of about 1.5 centimeters. In fact, the musculature may be so thin at this site that the lumen of the esophagus may be entered with ease unless extreme care is taken by the surgeon to prevent this complication. However, no great harm results from it if a careful suturing of the mucosa is effected. After the myotomy, there occurs a bulging of the mucosa with lateral separation of the muscle fibers. The operation is effective because the dysphagia is relieved immediately and rarely recurs.

We have done this operation in approximately 15 patients and already we have had three instances of reflux esophagitis. It is true that in only one was it severe enough to warrant further surgery, but the mere development of reflux esophagitis indicates that even the Heller operation which is championed by many surgeons in the United States is not the last word and that we must seriously appraise the results of this operation in the future before accepting it as the operation of choice. I am not convinced from the experience that we have had at the Mount Sinai Hospital that the Heller operation is the only operation for cardiospasm. We are continuing our studies in the therapy of this disease

and it is hoped that from further experience may evolve a procedure which will have greater efficacy and a higher percentage of better long term results than the Heller operation.

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DIVERTICULA OF THE ESOPHAGUS

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It is the purpose of this paper to review the classification of esophageal diverticula, their symptoms, diagnosis, complications and therapy, together with a survey of the recent literature.

CLASSIFICATION

Diverticula of the esophagus may be classified according to their anatomical location or from a pathogenetic point of view.

Anatomical (1)

Extrathoracic. This is most commonly known as Zenker's diverticulum. Zenker and Ziemssen (2) were the first to classify esophageal diverticula into pulsion and traction types and reported 27 autopsied cases in 1877. This type of pouch is also called a *pharyngo-esophageal* or *cervical* diverticulum and is situated at the junction of the pharynx and esophagus proper. About 90 per cent of all esophageal diverticula are of this variety.

Intrathoracic. This category includes **epibronchial** diverticula which arise from the upper and mid-esophagus and **epiphrenic** diverticula which arise from the distal esophagus just above the diaphragm.

Pathogenetic

In 1840, Rokitansky (3) classified diverticula of the esophagus according to their pathogenesis, as follows:

Pulsion type. These develop because of increased intraluminal pressure within the esophagus.

Traction type. These arise because of forces exerting their effects on the extrinsic wall of the esophagus.

A third variety, the *traction-pulsion type*, of which the epiphrenic diverticulum may be used as an example, is described subsequently.

In the remainder of this paper, the extrathoracic Zenker type shall be referred to as *pharyngo-esophageal diverticula* and the intrathoracic epibronchial type as *traction diverticula.*

There are also false or "functional" diverticula, described by Johnstone (4) in 1949, which are usually seen in the lower third of the esophagus. These are areas of apparent pouching of the esophageal wall due to a local hypotonic state of the smooth muscle layers associated with adjacent hypertonic areas or apparent stricture formation. They may disappear in the resting state, become apparent during abnormal peristalsis, and are usually associated with achalasia and "corkscrew" esophagus (5).

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PATHOGENESIS AND ANATOMY

Pharyngo-Esophageal Diverticulum

This is a pulsion type of pouch and, as already mentioned, is the *commonest* type of esophageal diverticula. It usually arises in the posterior midline of the hypopharynx at the pharyngeal "dimple", in the triangle bounded above by the inferior constrictor muscles and below by the cricopharyngeus muscles. On rare occasions, it may arise in other areas between fibers of the constrictor pharyngeus inferior or between the cricopharyngeus and longitudinal esophageal muscles. In one case, the diverticulum was located anteriorly with its orifice situated just below the arytenoid cartilages, a position reminiscent of the ventral air bladder in certain fish (6). Actually, this type of sac is a pharyngeal defect and, as Bockus (7) points out, is due to a herniation of the mucosa and submucosa of the hypo-pharynx. In the majority of cases, it is thus not a true diverticulum. The wall of the sac is made up of mucosa, sub-mucosa and fibrous tissue of varying thickness. Thinned out fibers of muscles of the pharynx envelop the neck of the sac or insert on its proximal portion. A complete muscular coat usually is not present. Despite the fact that this is an anatomic defect, there are only two cases of undoubted congenital origin reported up to now (44). This would tend to contradict the *congenital* origin of these particular diverticula and would favor the theory of an *acquired* lesion. According to Johannson and Michas (1), these extrathoracic diverticula are seen almost exclusively in people over 50 years of age. King (8) has observed none in patients below the age of 15 years. Cortesi (9) observed from several autopsy studies that one third of all subjects of all ages showed poorly developed constrictor musculature. This constitutional weakness plus the changes caused by aging might then explain why extrathoracic diverticula are more common in later life. There are other explanations as to the origin of these sacs, such as *ossification of the cricoid cartilage* pressing the esophagus against the vertebral column (10) or thinning of the inferior constrictor muscle caused by repeated *pressure* exerted by the lower border of the cricoid cartilage against the anterior surface of the cervical vertebrae (8). According to Jackson (11), neuromuscular incoordination during the act of deglutition causes an abnormally elevated intraluminal pressure with a tendency to herniate via the pharyngeal "dimple". As a result of an organizing peridiverticulitis, a secondary traction factor might be superimposed on a pulsion effect, according to Liebow (12). Muscular deficiency at the hernial site is felt to be the chief factor in the etiology of these sacs, according to Harrington (13).

No matter what the primary cause may be, the important fact remains that these diverticula become more and more enlarged as a result of repeated distention by swallowed food. As it develops, the sac of mucous membrane presents posteriorly behind the esophagus and in front of the prevertebral fascia and eventually projects to the left of the esophagus. When very much enlarged, the pouch may enter the mediastinum with only a very small transverse opening into the esophagus. The tendency for the diverticulum to increase in size may also be due to the fact that there is no fascial barrier to limit extension into the

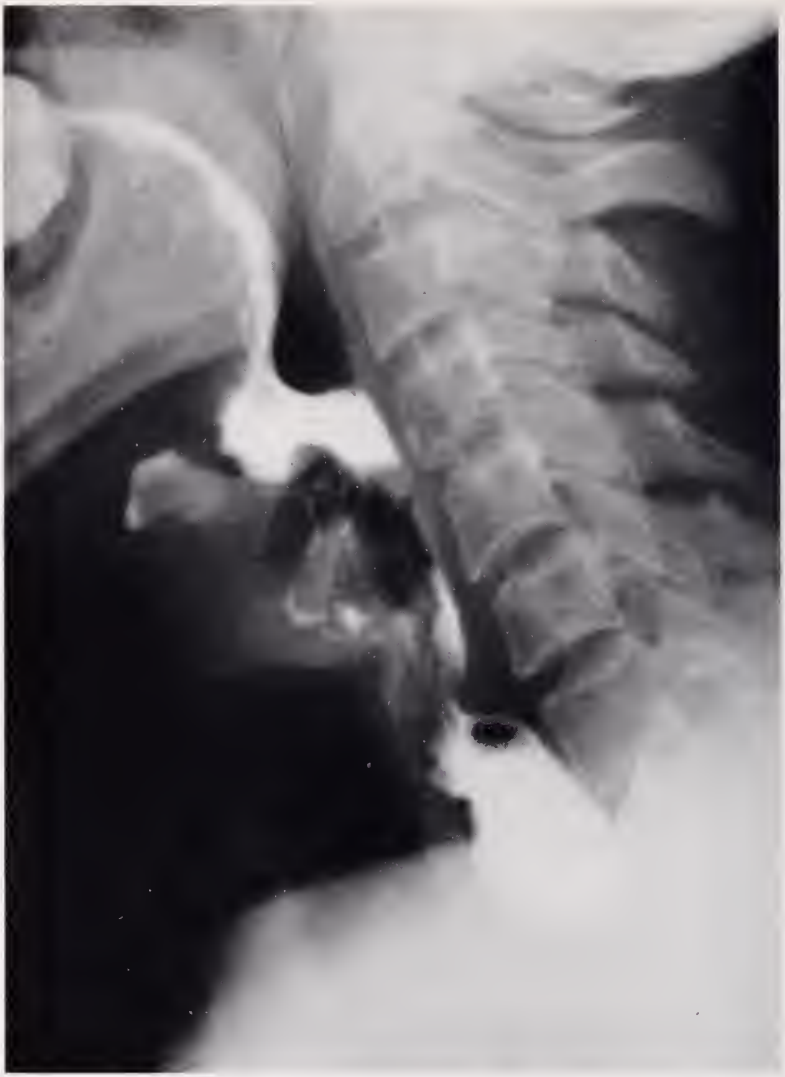

FIG. 1. Pharyngo-esophageal diverticulum. The pouch projects posteriorly and contains an air pocket.

superior mediastinum. In addition, food and secretions enter the sac before going into the esophagus, thereby tending to make the pouch grow larger.

Traction Diverticulum

This type of diverticulum is seen in the midesophagus near the left main bronchus or opposite the bifurcation of the trachea. When a mediastinal infection becomes organized, fibrotic traction is exerted on the adherent esophageal wall. The most common cause is tuberculosis of the tracheobronchial lymph nodes (7). Occasionally, a diseased vertebra, as in Pott's disease, may give rise

FIG. 2

FIG 3

FIG. 2. Multiple esophageal diverticula. Traction diverticula in the pulmonary hilar region.

FIG. 3. Traction-diverticulum. The pouch is situated at the level of the tracheal bifurcation and projects anteriorly from the esophagus.

to a traction diverticulum. Such a pouch rarely attains great size and is usually not larger than 1 or 2 centimeters. They almost invariably extend in a transverse direction. The growth of the sac cannot be rapid because the mouth of the sac is usually at a *lower* level than the fundus so that the retention of secretions, food and foreign bodies is at a minimum. These diverticula fill and empty easily because each has a wide mouth and no neck. In rare instances, the sac ultimately may become larger as a result of pulsion effects. The pouch usually develops on the anterior or anterolateral wall of the esophagus. As would be expected from the mechanism of its origin, the traction type is a *true* diverticulum and is made up of all the coats of the esophagus with mucosa, submucosa and muscularis. Myomata or other benign mural tumors also can exert traction effects as they grow, resulting in diverticula that can occur anywhere in the esophagus. This type of diverticulum is shown in figures 2 and 3.

FIG. 4. Epiphrenic diverticulum. Large epiphrenal diverticulum with an air pocket. The left oblique view shows its origin from the esophagus.

Epiphrenic Diverticulum

This is probably the rarest of the three main types of diverticula. Until 1951, only 126 cases had been reported in the literature (33). Only four cases were so diagnosed between 1942 and 1953 at the New Haven Hospital. Its mode of origin is not well known. According to Raven (14), some form of esophageal obstruction distally results in increased intraluminal pressures and herniation through areas weakened by local esophagitis. A similar theory has been presented by Kay (15), who excluded the need for esophagitis as an additional factor. There may not always be an element of traction present, the diverticulum being purely of the pulsion variety. The obstructive theory of origin is supported by the fact that cardiospasm is associated with about half the cases of distal epiphrenic diverticulum. However, cardiospasm may be the *effect* rather than the cause. Bockus (7) states that this diverticulum is a true diverticulum, all the coats of the esophagus being present in the sac. However, Lindskog and Stern (6) argue that as in the case of pharyngo-esophageal diverticula, the sac wall usually consists of mucosa, submucosa and an outer fibrous covering of variable thickness. The diverticulum usually projects from the right side of the anterior wall of the esophagus and although often of small size, may grow to three inches in diameter. The sac fills and empties readily because of its wide mouth. Figures 4 and 5 illustrate this type of diverticulum.

CLINICAL PICTURE

Pharyngo-esophageal Diverticulum

This is the only type of esophageal diverticula which commonly cause symptoms and yet, as MacMillan (16) has pointed out, it accounts for only two per

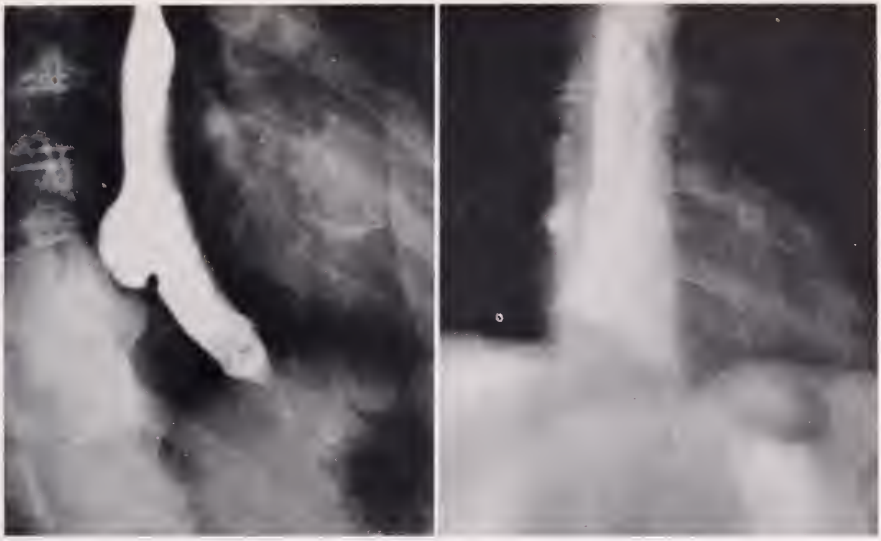

FIG. 5. Epiphrenic diverticulum. This large pouch projects posteriorly from the esophagus and has a wide orifice.

cent of the patients in his study of 1,000 cases with dysphagia. Males account for 80–90 per cent of the cases. The average age of the patients developing esophageal diverticula is 60 years. Lotheissen (17) collected 616 cases of this type of diverticulum and 79 per cent were in men. Lindskog and Stern (6) report 15 cases; twelve were males and three were females; the mean age was 56 years at the time of admission for surgery, with the extremes of 41 and 75 years.

Clinically, these diverticula may manifest themselves in three stages (7). There may be an initial stage of *throat irritation* with excessive mucus or the sensation of the presence of a foreign body on swallowing. However, *dysphagia* of insidious onset is usually the first symptom although sometimes the symptoms come on suddenly and become rapidly severe. At times, there may be an irritative type of cough or a gurgle or croaking noise may be heard upon swallowing liquids. There may be regurgitation of undigested food and mucus even several hours after ingestion, especially when the patient lies down or bends over. Regurgitation occurs after the pouch has become large and, as a rule, the food that is regurgitated is the same in taste and odor as that which was swallowed. There may be distaste for food, resulting in nausea. A bad odor in the mouth may also occur as a result of bacterial action on the contents of the pouch. There may be siallorrhea, hoarseness or dyspnea due to tracheal compression by a large diverticulum.

Obstruction of the esophagus which can become almost complete, may develop eventually, with the resultant sequelae of marked weight loss and emaciation.

Physical examination may reveal some asymmetry of the neck with a fullness palpable beneath the lower part of the sternomastoid. A muscle mass is seldom felt unless a malignancy, abscess or granuloma is associated with the diverticulum (6). By pressing on the side of the neck, one may be able to produce some regurgitation or an audible gurgling sound. One may be able to demonstrate a suc-

cession of splashing sounds by auscultation of the neck during the swallowing of liquids.

The duration of symptoms may be from a few months to many years. They usually come on gradually and develop insidiously. Proper x-ray examinations are essential for diagnosis and present the only means of ascertaining the exact location of the diverticulum, degree of retention and size of the pouch. Prior to giving the barium meal, lateral views taken in the erect position frequently reveal the presence of air in the upper part of the pouch. Sometimes, evacuation of the contents may be necessary before satisfactory x-ray studies can be made since barium may not enter the pouch because of retained secretions and food or because of the small mouth and neck of the sac. A thin mixture of the barium swallowed with the patient in the recumbent position may fill the sac more easily. The diverticulum is usually symmetrical and regular in outline and frequently a fluid level can be seen in the pouches of larger size. (Fig. 1). The esophagus is often pushed anteriorly even with small pouches. Any irregularity in the outline of the sac when filled with barium should suggest the possibility of malignant tumor within the sac. Despite its rarity, the surgeon is better prepared to treat such a lesion radically if the correct diagnosis is made preoperatively, than in the case of removal of a *benign* diverticulum.

Endoscopy will locate the orifice of the sac. When a large pharyngo-esophageal diverticulum causes obstruction, the opening is directed downward and the opening into the esophagus is lateral, making both the entry of food or of an esophagoscope into this lateral opening difficult. Esophagoscopy, however, is not necessary to establish the diagnosis.

Traction Diverticulum

These diverticula cause symptoms infrequently because there is seldom retention of food in the sac. They often are not diagnosed clinically for this reason. They usually arise opposite the pulmonary hila and frequently are multiple (Fig. 2). Most of these diverticula are discovered during routine fluoroscopy of the gastrointestinal tract or as an incidental postmortem finding. Six to ten per cent of the cases at post mortem have traction diverticula of the esophagus according to Kragh (18). Engler (19) states that 73 per cent of these diverticula show histologic evidence of tuberculosis. If dysphagia does occur, it is usually due to mediastinal inflammation and fibrosis, strictures or a malignancy of the esophagus. According to Wallace (2), over one third of his 40 cases with roentgenographic evidence of traction diverticula had symptoms as a direct result of the lesion. These symptoms consisted of dysphagia and substernal distress (pain, heaviness and burning). Three patients had gross hemorrhage, one having a hematemesis of about 500 cc. According to Palmer (21), hemorrhage is uncommon. Cases have been reported with myomata causing diverticula but these are apparently asymptomatic.

When a traction diverticulum happens to cause partial esophageal obstruction, a pulsion element may also enter into increased development of the sac and it

may then be called a "traction-pulsion diverticulum". Such a pouch usually causes symptoms when situated in the midesophagus.

Traction diverticula occur equally among men and women and there is no particular age at which they are discovered. Wheeler (22) found only six cases in the course of 20,000 upper gastrointestinal x-ray examinations. MacMillan (16) found traction pouches to be the cause of symptoms in four of 1,000 patients complaining of dysphagia.

On x-ray examination, the barium-filled outline of the traction diverticulum assumes a fusiform, cone, tent, or funnel shape. Careful technique may be needed to demonstrate the smaller pouches by x-ray. Premedication with barbiturates and atropine and use of an effervescent barium mixture are advocated to expedite entry of the mixture into the sac so as to produce a clearly defined gas bubble with a fluid level. As would be expected, traction diverticula do not present positive physical findings unless there are complications.

Epiphrenic Diverticulum

Since so many of these diverticula are associated with cardiospasm, it is often difficult to decide whether or not the epiphrenic diverticula are *directly* responsible for symptoms (6). The latter may consist of substernal or epigastric pain, regurgitation, eructation or vomiting after meals, hiccough, mild dyspepsia, some loss of weight or dysphagia. Generally, these diverticula probably cause symptoms by themselves; thus, Lahey and Harrington (27) reported that this lesion made up four per cent of all types of pharyngeal and esophageal sacs requiring surgical intervention. The rarity of such pouches is also attested by the fact that Wheeler (22) found only three cases in 20,000 radiologic examinations. Symptoms usually do not become apparent until the fifth or sixth decade unless complications have occurred. Thus, if there are pulmonary complications, epiphrenic diverticula may be found even in childhood. About 80 per cent of patients with this type of pouch are males.

At times, it may be very difficult to differentiate between a large, penetrating lower esophageal peptic ulcer, hiatus hernia or a diverticulum in this location (7). The diagnosis can be made by esophagoscopy whenever the roentgenographic examination is unsuccessful. There are no pathognomonic physical signs for epiphrenic diverticula. Radiographic study reveals these diverticula to take the form of a spherical pouch with some narrowing at the neck. They may grow to a considerable size but do so by slow expansion and are probably self-limited in extent.

Of 12 cases reported by Dessecker (23), nine presented to the right of the esophagus, two directly posteriorly and one to the left. Esophagoscopic examination reveals a pouch that is folded with a pale interior that rarely contains food or secretion since it is not in a dependent position and since it can be emptied by the "massaging" action of the lungs, heart and diaphragm. Bensaude et al. (24) have described the opening and closing of the cavity with respiratory action, with a rhythmic filling and emptying of the sac, as seen through the esophagoscope.

COMPLICATIONS

Pharyngo-esophageal Diverticulum

A foreign body may enter one of these pouches, usually a chicken bone, and perforate the sac thereby producing an acute para-esophageal abscess which can then extend quickly into the mediastinum. On the other hand, only a localized phlegmon or a solid granulomatous mass may develop and may be felt as a somewhat tender deep seated cervical mass. Even without a foreign body, mechanical and chemical irrigation caused by distention of the sac with secretions and decomposed retained food may lead to a localized esophagitis, but this rarely causes a perforation.

The most important complications occur in the bronchi and lungs. Aspiration pneumonia, bronchiectasis, lung abscess and empyema may occur especially when the contents of the diverticula spill over into the air passages when the patient is supine or asleep and has weakened pharyngeal reflexes. In far advanced cases, one encounters hypochromic anemia, hypoproteinemia, avitaminoses, and inanition. At present, these far advanced cases are seen rarely. Obstruction, malignancy and trauma as a result of esophagoscopy are other complications to be noted. The carcinomas associated with pharyngo-esophageal diverticula usually are of the well differentiated epidermoid variety (6, 35). Another complication is hoarseness resulting from involvement of the recurrent laryngeal nerve by inflammation.

Traction Diverticulum

Since traction diverticula rarely produce clinical symptoms, they are of importance only because of their tendency to cause complications which may be serious. Histologically, the muscle layer of this type of sac is well developed and normal in amount in contrast to epiphrenal diverticula (vide infra). In rare instances, such a pouch, if abscessed and growing, may ulcerate or perforate into the trachea, bronchi, lung, mediastinum, aorta or esophagus, accouting for the formation of an esophago-bronchial fistula or mediastinal abscess. Nash and Palmer (25) state that five per cent of all esophagobroncho-tracheal fistulae arise from traction diverticula. The bronchi are the most frequent sites of invasion and hemorrhage may rarely be the first symptom. Perforation may occur. If this takes place, the mediastinal infection tends to remain localized since the abscess in the diverticulum itself is usually of long standing and allows time for some walling-off to take place.

These midthoracic diverticula are frequently associated with cardiospasm. Achalasia has been reported in from one third to more than one half of cases with diverticula but the symptoms in these cases are apparently caused by the cardiospasm rather than the diverticulum. A localized esophagitis with obstruction of the orifice of the pouch may occur at times and the esophagitis may also extend into the pouch and cause a diverticulitis. Schick and Yesner (26) report the first case of chronic and fatal hemorrhage as a complication of a traction diverticulum which developed diverticulitis.

Epiphrenal Diverticulum

These diverticula are potentially dangerous, because of their possible serious complications. The infected contents of such pouches may lead to ulceration of the walls and perforation resulting in broncho-pulmonary complications. Histologically, all layers of the esophagus can usually be seen, but the muscle layer is thin, resulting in weakness in this area. At times there is edema and hemorrhage in the stoma. Disturbance of the sympathetic nerve ganglia has been said to be a contributory factor in the etiology of epiphrenal diverticulum but in three surgical specimens studied by Putney and Clerf (27), intact normal ganglia were found.

Mondiere (28), in 1833, suggested three possible explanations for the weakness of the muscular layer: (a) separation of the muscle fibers—probably congenital; (b) prolonged sojourn of a foreign body; and, (c) any obstacle whatever to the passage of food. Despite these and other theories, there is no adequate explanation for the origin of an epiphrenal diverticulum when there is no obstructing lesion.

Perforation is more apt to occur in diverticula projecting to the right of the esophagus than in those appearing to the left, according to the French literature. For example, in three cases with esophagobronchial fistula reported by Monod (29), all presented to the right side.

Cardiospasm may accompany these diverticula. Kausel and Lindskog (30) found as much evidence to consider achalasia secondary to diverticulum as the reverse. In Granet's series (31) of 31 cases, eight had associated cardiospasm and in Vinson's series (32), eight of 42 had associated achalasia. In Goodman and Parnes' series (33), 65 per cent were associated with achalasia. Dessecker (23) found the two combined conditions in five of eight cases of diverticulum. On the other hand, Johnstone (4) studied 200 cases of achalasia without finding a diverticulum in this location. Of eight cases of epiphrenal diverticula reported by Holinger (34), six were associated with hiatal hernia. In one case reported by Putney and Clerf (27), there were co-existing traction and pharyngo-esophageal pulsion diverticula. Another had an associated achalasia and hiatal hernia.

Aspiration of the sac contents, especially at night, may lead to chronic bronchitis, bronchiectasis or pulmonary abscess. Carcinomas have been known to develop within epiphrenic pouches (6, 35). The diverticular mucosa also may contain gastric mucosal and pancreatic rests which may become the sites of peptic ulceration. However, most ulcerations in these sacs are produced by foreign bodies.

Julian (36) recently reported a case of epiphrenal diverticulum with precordial pain and T wave inversions in leads I and V4 of the electrocardiogram. Precordial pain and cardiographic evidence of coronary insufficiency were present before but not after resection of the diverticulum. The coronary spasm could have been brought about by reflex vagal spasm or by direct pressure. The former seemed the more probable explanation in view of the position and size of the sac in this case. There was no clinical evidence of coronary artery disease post-

operatively and the electrocardiogram then showed only a left axis deviation, unaffected by anoxemia or exercise.

Leger and Pichon (37) and Dohn and Jacoby (38) have reported pain resembling that of myocardial infarction. Duval (39) published the history of a patient with a diverticulum and coronary artery disease in which surgery cured the symptoms in part.

TREATMENT

Pharyngo-esophageal Divertieulum

Medical therapy is palliative, consisting of a bland diet, proper and thorough mastication and drinking a full glass of water post-cibum to wash out the sac. Dilatation of the subdiverticular opening by esophagoscopy may relieve symptoms caused by a very small sac (40). A small rubber tube inserted into the sac before retiring and evacuation of the retained food may help prevent nocturnal regurgitation and aspiration of food into the lungs. The only complete cure is through surgical intervention.

The first successful diverticulectomy carried out for this type of pouch in a single stage procedure was performed in 1891 by Von Bergmann (41). However, leakage via the esophageal suture line led to a high incidence of septic mediastinitis or patients died of pneumonia. Goldmann in 1909 reported a two-stage procedure which was safer. In the first stage, the diverticulum was freed and suspended by suturing it to the cervical fascia. The second stage consisted of excising the pouch through an area which had theoretically been safely walled off by adhesions. Bevan (42) in 1921 reported a method for invaginating smaller sacs, thus doing away with the necessity of an esophageal suture line. The modified two stage procedure has been strongly advocated by Lahey (43) who believes Goldmann's method is unsound in principle since it results in sloughing, perforation, leakage and contamination of the fascial planes and possibly the mediastinum. However, the one stage method seems to be the one preferred by most surgeons the world over. There is a lower recurrence rate, shorter hospital stay, lowered morbidity and rarely any serious infection, (especially since the use of antibiotics), when the one-stage technic is employed. Lahey (43) still favors the two-stage procedure which requires less time in the hospital than formerly since the second stage is now done on the seventh day.

If the patient is markedly undernourished, anemic and has signs of vitamin deficiency, he should receive proper preoperative preparation with parenteral therapy.

In any surgery performed in this area, the danger of cerebral vacular accidents can be minimized by avoiding heavy retraction on the carotid blood vessels. Recurrent laryngeal nerve paralysis can also be avoided by following the nerve from the inferior thyroid pole upwards and protecting it as the surgical dissection proceeds. Although permanent hoarseness may result, it is as a rule temporary, because the trauma to the nerve is usually caused by traction and not by transection. Follow-up study in Lahey's 250 cases (43) revealed recurrent laryngeal nerve injury in 12 cases.

Post-operative fistulae rarely occur and can be avoided by attention to proper technic. In preantibiotic days, leakage from the suture line was a serious complication, but nowadays, the judicious use of antibiotics and drainage of the operative wound will usually result in speedy recovery.

Experienced surgeons caution not to perform excessive resections, especially in very small pouches, as stricture of the esophagus may result from overextended excisions at the neck of the diverticulum. On the other hand, inadequate removal of a diverticulum may lead to a recurrence. Leaving the smallest bit of sac creates conditions for regrowth, since surgery does not eliminate the etiologic factor. Relief of symptoms post-operatively does not guarantee against freedom of recurrence (1). After removal of the sac, radiography may show certain changes which bear some resemblance to recurrence of the diverticulum for some time. These should not be confused with the permanent bulges in the esophageal wall in which barium is retained for quite a long time after surgery (1).

Traction Diverticulum

According to Lahey (43), these diverticula rarely require surgery, and their management is largely conservative. Operation becomes indicated for the rare complications, such as perforation with abscess or with broncho-esophageal fistula. When traction diverticula are associated with symptoms other than obstruction, they may be treated in the majority of cases satisfactorily by dilatation.

Epiphrenic Diverticulum

Symptomatic epiphrenic diverticula are best treated by a direct transthoracic excision. According to Putney and Clerf (27), experience has shown that when there has been any surgical interference with the esophago-gastric junction, there were complications, the most serious of which has been severe and repeated hemorrhage. Esophagitis was almost invariably found on esophagoscopy. They conclude from these findings that surgical procedures which disturb this relationship appear contraindicated in uncomplicated cases. Thus, surgical excision of the sac is preferred over resection of the lower esophagus and esophagogastrostomy in order to avoid post-operative esophagitis and dilatation of the esophagus.

RESULTS OF SURGICAL TREATMENT

Pharyngo-esophageal Diverticulum

In the hands of competent surgeons, the two-stage operation has a mortality of two to four per cent. In 1954 Lahey and Warren (43) reported a series of 365 patients operated upon for pharyngo-esophageal diverticula with but two deaths. There was a recurrence rate of 4.8 per cent, there being twelve recurrences in 250 cases, with a minimum follow-up of 2½ years. The number of recurrences may be lessened by post-operative dilatation of the pharyngo-esophageal junction.

A large series of cases using the one-stage operation have been reported by Jackson and his associates (7) without mortality or serious complications. Johannson and Michas (1) reported ten cases of pharyngo-esophageal diverticula

excised through a cervical incision without a fatality, but one patient developed paralysis of the recurrent pharyngeal nerve. Another developed a fistula on the fourteenth post-operative day and in repairing this the recurrent laryngeal nerve was injured, resulting in permanent paralysis. There were recurrences of the diverticular sac in four patients. In fifteen cases of pharyngo-esophageal diverticulum operated upon between 1942 and 1953, and reported by Lindskog and Stern (6), there were no deaths.

Traction Diverticulum

Johannson and Michas (1) operated upon seven cases of this type in the mid-esophagus without a mortality.

Epiphrenal Diverticulum

Lahey's operated series (43) include nine cases of this type of diverticulum without any mortality and with satisfactory follow-up results in all. One case of epiphrenal diverticulum was operated upon in the series reported by Lindskog and Stern (6) because of epigastric pain, dysphagia and weight loss.

SUMMARY

1). The various types of diverticula of the esophagus have been described according to their anatomy, pathogenesis, signs, symptoms and diagnosis.

2). The complications arising from esophageal diverticula and the various methods of medical and surgical therapy and results are outlined.

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Surgical Considerations

(John H. Garlock, M.D.)

Dr. Cornell has covered the subject of the surgical treatment of diverticulum of the esophagus so well that very little remains for me to add. However, there are a number of points that deserve special emphasis.

The operation for diverticulum of the cervical esophagus, the so-called Zenker's diverticulum or pharyngo-esophageal diverticulum, has progressed now to the stage where most surgeons do the operation in one stage. Lahey was the great protagonist of the two stage operation and he deserves a great deal of credit for claryifying the surgical therapy of this rather frequent disease of the esophagus. When he originally proposed the two stage operation, antibiotics were not available and not infrequently leakage from the suture line occurred. He, therefore, proposed the two stage procedure in order to obviate any possible mediastinal infectious complications. The first stage consisted of a dissection of the sac up to its exact origin at its neck at the point of weakness between the cricopharyngeus muscle and the upper edge of the esophagus in the midline posteriorly, and elevation of the diverticulum from a dependent position to a reverse upright position so that it would drain through its opening into the esophagus. The sac was suspended in the neck wound and sutured to the sternomastoid muscle and the wound was closed after the posterior mediastinum was packed with gauze. At a subsequent stage, seven to ten days later, the wound was reopened, the sac, now greatly diminished in size, was isolated and excised with careful repair of the opening in the esophagus using two layers.

In recent years this two stage operation has been given up by most surgeons. Lahey, however, up to the time of his death persistently advocated the two stage procedure. The one stage operation is now the operation of choice in most clinics. It consists of a careful dissection of the sac, isolation of the point of origin from the opening in the esophagus and a careful two layer repair of the opening with interrupted sutures of silk for the mucosa and a firm repair of the defect in the musculature. When this operation is done carefully, the recurrence rate is extremely low and the mortality should be almost zero. In our series, which is quite considerable, we have had no mortality and a $3\frac{1}{2}$ per cent recurrence rate. There were two instances of recurrent nerve injury. In one, there was complete recovery and in the other, the recurrent nerve remained permanently paralyzed but the opposite intact vocal cord took over the function of the one that was disturbed by the recurrent nerve palsy.

There is no indication for surgical intervention for traction diverticula of the middle third of the esophagus. Rarely, with complications such as perforation with mediastinal abscess or with a penetration into the neighboring bronchus or trachea does surgery become indicated. This is a complicated procedure and fortunately is not necessary often.

With respect to the epiphrenic diverticulum, it might be said that most of these occur in individuals who are quite elderly. Of the three examples in our series that have been subject to operation, two of them, on histological examination,

disclosed brown atrophy of the thin musculature covering the diverticulum which was excised. This may be a feature in the pathogenesis of the so-called epiphrenic diverticulum which lies almost on the superior surface of the diaphragm and usually projects toward the right side. Many operations have been recommended for its treatment in the past but with the advent of modern surgery and antibiotics, surgeons have now no compunction in entering the left chest for a direct attack on the diverticulum, effecting a complete excision and an accurate repair of the opening in the esophageal wall. The follow-up results in the three cases in our series have been excellent.

It has always been considered that epiphrenic diverticulum may be a disturbance of the esophagus secondary to cardiospasm. However, in the three cases cited, there was no evidence of cardiospasm and relief of symptoms followed excision of the sac.

ENDOSCOPY IN DIAGNOSIS AND TREATMENT OF DISEASES OF THE ESOPHAGUS

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In the diagnosis and treatment of diseases of the esophagus, the endoscopist has become recognized as an indispensable member of a medical team which includes the gastroenterologist, roentgenologist and the surgeon.

Through the generalized use of endoscopic procedures the interior of the esophagus has become one of the most readily examined areas of the body. Direct visualization of the esophagus permits the detection of incipient as well as advanced pathology as it appears in the living. In combination with the roentgenologist, the esophagoscopist has contributed much to clarify some important aspects of esophageal physiology. In addition, changes in the esophagus resulting from generalized medical diseases have been studied and confirmed by endoscopy.

In actual clinical practise, the role of the endoscopist is a most important one in the diagnosis of esophageal disease. No matter how classical the roentgen findings and clinical history may appear, final confirmation by direct visualization and biopsy is most desirable. In instances of neoplastic invasion, the exact site of the tumor and the condition of the proximal muscosa can best be ascertained by endoscopy.

It is well known that in any endoscopic procedure, there is an inherent danger depending on the skill and the experience of the operator. Except in instances of severe debility, marked cervical kyphosis, or inability to open the mouth widely as in dermatomyositis, this minimal risk should not deter one from esophagoscopic examination. In discussing the more common lesions of the esophagus, stress will be placed on the local finding and the scope of endoscopic therapy.

NORMAL ESOPHAGOSCOPIC FINDINGS

In order to appreciate the endoscopic changes incident to diseases of the esophagus, one should first review the normal esophagoscopic findings and then note the altered appearances in various conditions.

The normal esophageal mucosa is smooth, glistening and has a yellowish pink color. The intensity of the yellow is dependent upon the character of the illumination. Nevertheless, both with distal and proximal lighting the esophageal mucosa has a distinctive appearance and can readily be distinguished from the crimson rugae of the gastric mucosa. Routinely, we have employed a 12 mm. external diameter Killian or Yankauer esophagoscope.

On the introduction of the endoscopic tube through the thoracic esophagus, one sees the lumen slightly expanding with deep inspiration and contracting with expiration. As the esophagoscope is further advanced and directed to the left

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and anteriorly, the region of the gastro-esophageal junction is encountered. The passage between the resting esophagus and stomach is not normally patent. In addition to the protection afforded by the angular insertion of the tubular esophagus into the stomach distally, a muscular closure in the terminal segment of the esophagus aids in preventing reflux of gastric juice. This sphincteric mechanism is recognized on esophagoscopy at a distance of 38 to 39 centimeters from the upper incisor teeth as a spastic group of smooth vertical mucosal folds forming a rosette and terminating in a dimple (Fig. 1). This rosette corresponds to the proximal portion of the cardiac or sphincteric canal leading to the stomach proper.

Except under conditions of vomiting, this closing mechanism is in tonic contraction and represents a bar between the negative pressure of the esophagus and the positive pressure of the stomach. Until the tube is introduced beyond this mechanism, gastric reflux is not obtained.

After the rosette has been encountered, gentle pressure of the tube in the direction of the dimple will cause the folds to yield or relax and permit the esophagoscope to glide into the sphincteric canal. The proximal one to one and a half centimeters of this canal is lined by esophageal mucosa and just distal to this, the Z line or actual juncture of gastric and esophageal mucosa is recognized (Fig. 2). This juncture can be determined more readily by esophagoscopy than by roentgenology. The entrance of the tube beyond the Z line is heralded by the escape of gastric juice and the appearance of the crimson gastric rugae. About one to two centimeters more distally, the widened pouch of the stomach proper is identified. On rare occasions, an altered, flat mucosa proximal to the gastric folds may be encountered which cannot be definitely recognized as being esophageal or gastric.

Fig. 1

Fig. 2

Fig. 1. Endoscopic appearance of the rosette which is formed by closure of the inferior esophageal sphincter.

Fig. 2. Endoscopic view of the sphincteric canal at the Z line or gastro-esophageal juncture. E. Squamous epithelium of esophagus. R. Gastric rugae.

PEPTIC ESOPHAGITIS

While the color of the esophageal mucosa in any single patient is partially determined by the character of the illumination and other individual factors, the hue is uniform throughout the entire length. However, in peptic esophagitis, the change in color of the lower segment of esophagus is striking and a valuable diagnostic aid. The transition from the yellow pink color of the proximal esophagus to the red, hyperemic color of the distal portion is characteristic of the esophagitis.

Peptic esophagitis may occur with the sliding type of hiatal hernia and in association with duodenal or gastric ulcer. It may result from persistent vomiting or the prolonged use of an indwelling feeding tube. In such instances, an ulcerative inflammatory process usually involves a long segment of the distal esophageal mucosa. Multiple erosions and areas of intense hyperemia interspersed with minute irregular ulcerations may extend along the distal ten centimeters of the esophagus (Fig. 3). Throughout this area of esophagitis, a uniform narrowing of the esophageal lumen is encountered terminating at the gastro-esophageal junction. There may or may not be regurgitation at the time of esophagoscopy and the rosette is apt to be two to three centimeters above the diaphragm. In these cases, the peptic esophagitis always occurs in esophageal mucosa proximal to the gastro-esophageal junction. Should spontaneous healing occur, a smooth, fibrotic stenosis just above the gastro-esophageal juncture may result.

SHORT ESOPHAGUS WITH MARGINAL ULCERATION

There is another type of peptic ulceration occuring in association with a hiatal hernia which is of the traction type and which does not have the appearance of a typical sliding hernia. In these cases, heterotopic gastric epithelium may or

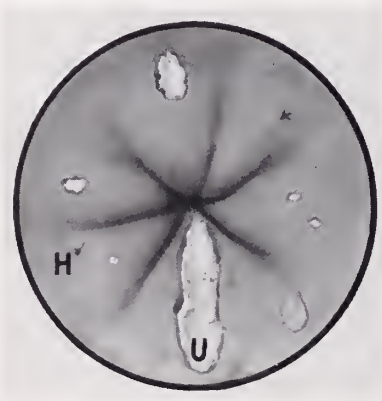

FIG. 3

FIG. 4

FIG. 3. Endoscopic appearance of peptic esophagitis. U. Multiple superficial erosions. H. Submucosal hemorrhage and areas of intense hyperemia.

FIG. 4. Endoscopic appearance of marginal ulcer. J. Reflux of gastric juice through patent gastro-esophageal juncture. U. Ulcer partially surrounding distal esophageal segment.

may not exist in the terminal segment of the esophagus. These cases of short esophagus with marginal ulceration are more apt to produce fibrotic stenosis.

Whereas normally, gastric juice is not obtained until the gastric lined portion of the cardiac canal is entered, gastric regurgitation is a constant feature of short esophagus with marginal ulceration. Reflux is encountered as soon as the tube enters the upper esophagus and requires continuous aspiration for proper visualization and the further passage of the tube. In short esophagus with marginal perforation, the gastric juice can be seen to well up from below through the patent gastro-esophageal juncture at the distal ulcer margin. The characteristic feature of the lumen at this point is its constant patency.

In the absence of gastric reflux, one rarely encounters significant endoscopic evidence of peptic esophagitis. Certainly, most patients with short esophagus and uncomplicated hiatal hernia show little evidence of esophagitis. When the gastro-esophageal junction is competent, the esophageal mucosa appears grossly normal. Should incompetence develop at a later date and symptoms result, then the classical picture of peptic esophagitis is to be expected. In our experience in the patients who came to endoscopy merely because of the roentgen finding of hiatal hernia, little evidence of esophagitis was found unless heartburn or other symptoms of regurgitation were present. After thorough aspiration of the regurgitated esophageal contents, one can recognize the inflammatory changes in the lower esophagus with the erosion or ulceration, distally.

The ulcerated area is covered by yellow-grey membrane or slough which can be readily removed by grasping forceps (Fig. 4). Occasionally, the attachment of this fibrinous cast is so tenuous that mere suction is sufficient to remove it with very little bleeding. A reddened, granular base is now visible. This is rather uneven, due to the presence of exuberant granulation tissue. A true ulcer crater with undermined edges and a necrotic base is rarely encountered. Rather is the erosion superficial and the proximal edges less distinct than the distal which always borders on the gastric mucosa. Heterotopic gastric mucosa may be present laterally.

The lesion is frequently elongated and somewhat irregular with a tendency for encirclement of the distal centimeter or two of the esophagus. Not always is the yellow gray membrane present at both the initial and subsequent endoscopies. In such cases, the bed of the superficial erosion can be detected as an uneven, granular, reddish surface lacking the smooth epithelial covering of the normal esophagus. Minute mounds or elevations can be seen resulting from varying loss of mucosal covering interspersed throughout the granulating surface.

Mucosal changes, proximal to the ulcer are common and constitute the varying degrees of peptic esophagitis. Localized inflammation, congestion and edema with spotty, superficial erosions and hemorrhage occur. A narrow zone of hyperemia consistently surrounds the borders of the marginal ulcer and extends proximally up the esophagus for a variable distance. Although the appearance is quite characteristic, a routine biopsy must be done to exclude tumor.

The ulcerative phase is invariably accompanied by segmental spasm of the esophagus so that a visible narrowing of the esophageal lumen is encountered

at the upper level of the esophagitis. This spasm is however, usually overcome by the mere passage of the esophagoscopic tube. At the proximal margin of the ulceration, greater difficulty in the further introduction of the tube may be experienced due either to the presence of increased spasm or of a periosophagitis with fibrosis. The point of maximum narrowing is always at the gastro-esophageal juncture in these instances. When fibrotic stenosis does occur, except in the rare case, the esophagoscope can push the narrowed gastro-esophageal juncture for a distance of three centimeters distally, thereby elongating the shortened esophagus. Gradual dilatation with graded bougies may be necessary before the tube can be finally introduced into the gastric pouch. Repeated esophagoscopic examinations in the same patient have demonstrated varying stages of the healing of the ulcer with occasional recrudesence. The gastric reflux which is the cause of the ulceration, should be increased by the endoscopic dilatation. Paradoxically, however, the ulcer seems to improve by relief of the stenosis. If the lumen can be adequately maintained, (non-obstructive phase) and the acidity controlled by antacids and anticholinergic drugs, there is a tendency for spontaneous healing. However, in marginal ulceration with hiatal hernia, healing is apt to be accompanied by fibrosis and contracture which may lead to varying degrees of stenosis and stricture formation. In one recent case, complete obliteration of the esophageal lumen resulted. In well advanced stenosis, the lumen may be constricted to two to three millimeters as measured by the caliber of the bougie it can accommmodate.

The diagnosis of peptic esophagitis and ulcer must be confirmed by endoscopic visualization and biopsy. Esophageal shortening as a result of spasm and fibrosis accompanying the ulcer occasionally occurs. Obstruction with marginal ulcer results either from segmental spasm during the acute phase, or from cicatricial stenosis after healing.

Most peptic stenoses of the distal esophagus are associated with short esophagus and hiatal hernia and result from previous ulceration. Narrowing of the esophagus is a relative term and must be evaluated by comparison with the average lumen of the esophagus. In the normal adult, an esophagoscopic tube with outside diameter of twelve millimeters is employed and is readily accommodated within the lumen, although the sixteen millimeter tubes may be tolerated. When the twelve millimeter tube encounters a narrowing or stenosis, it simply implies that the diameter of the stricture is narrower than that of the tube. A relative stenosis can be said to be present when a twelve millimeter tube cannot be passed except after preliminary dilatation with a Jackson bougie. Under such circumstances, a constriction as compared to the normal diameter of the esophagus certainly exists. Such findings on endoscopy can explain the occasional narrowing of the esophageal lumen, demonstrable by roentgen film in a patient who experiences no difficulty in swallowing a routine daily diet. Occasionally, a large bolus of food becomes embedded into the narrowed segment and may require esophagoscopy for removal. On the other hand, the endoscopist may encounter a band in a patient whose x-ray seemed within normal limits because the barium passed promptly into the stomach without any demonstrable

delay. Direct visualization is the most important means of confirming the diagnosis.

PEPTIC ULCER IN AN ESOPHAGUS LINED BY GASTRIC MUCOSA

Whereas superficial erosions and ulceration of the esophagus are not uncommon, true isolated peptic ulcer is rare. Peptic ulcer of the esophagus occasionally occurs in instances of gastric mucosa lined esophagus. The flat, heterotopic epithelium which surrounds the ulcer may not be distinguishable from the squamous epithelium except by biopsy. In one recent case, a penetrating ulcer of the esophagus was encountered in an elderly individual. The ulcer was surrounded by a wide segment of velvety heterotopic gastric mucosa on the esophageal side and gastric rugae distally (Fig. 5). The proximal margin of the ulcer was very stenotic and could be dilated only with extreme difficulty. Multiple biopsy of the esophagus above the stenosis revealed heterotopic gastric mucosa. This is an example of a Barrett type of ulcer.

In another indolent, peptic ulcer of the lower esophagus, a marked stenosis at the proximal margin made dilatation very difficult and hence visualization of the ulcer impossible. The ulcer was surrounded by squamous epithelium except at the lateral margins where gastric mucosa was in contact with it (Fig. 6). The

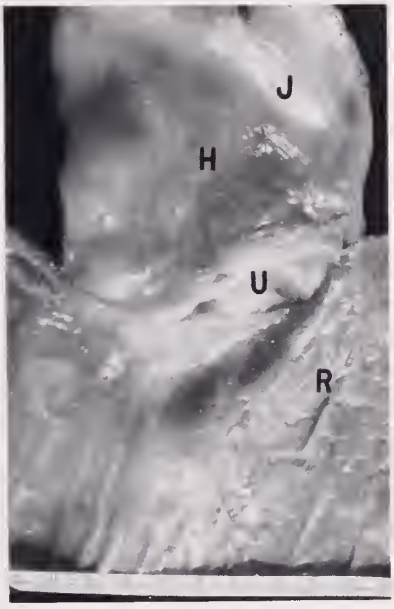

FIG. 5

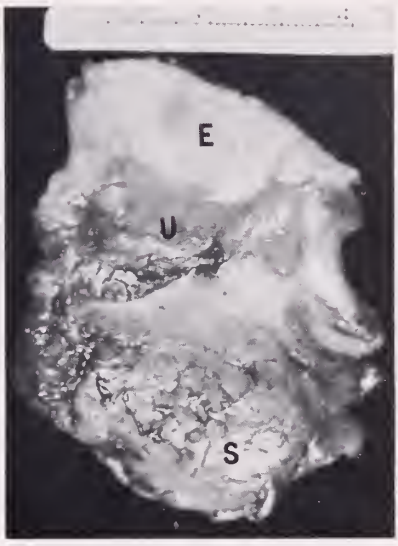

FIG. 6

FIG. 5. Peptic ulcer in an esophagus lined by heterotopic gastric mucosa. U. Ulcer bed penetrating through muscular wall. R. Gastric rugae. H. Heterotopic gastric mucosa surrounds the ulcer proximally. J. Juncture of squamous epithelium and heterotopic mucosa.

FIG. 6. Peptic ulcer of esophagus. U. The indolent ulcer was distal to a stenosis in the terminal esophagus. E. Squamous epithelium almost encircles the ulcer G. Gastric mucosa at margin of ulcer. S. Stomach

true peptic ulcer is more apt to be associated with stenosis at the proximal end of the lesion. This organic narrowing usually prevents proper visualization of the ulcer bed because of inability to insert the esophagoscope beyond the stenosis. A biopsy taken deeply within the lumen of the stenosis may reveal the presence of necrosis, characteristic of the ulcer bed. The specimen of the surrounding mucosa usually shows an altered or heterotopic gastric mucosa. The endoscopic appearance in these cases may be that of a smooth cone-like narrowing with or without a superficial erosion proximally. The ulcer may occur at the juncture of the heterotopic gastric mucosa in the lower esophagus with gastric rugae or may occur proximally at the juncture of squamous epithelium with the heterotopic mucosa.

The narrowing proximal to the ulceration is due to submucosal fibrosis which encircles the lumen of the esophagus and produces stenosis. In marginal ulceration or peptic esophagitis, the stenosis produced is more apt to involve a shorter segment of the terminal esophagus. With deeper ulcers, especially of the Barrett type, the fibrotic stenosis may involve a much longer segment of the lower esophagus. On esophagoscopy, a healed peptic stenosis has a smooth, conical appearance tapering distally. The lumen may be as minute as one to two millimeters on the first examination; usually dilatation can be accomplished with Jackson bougies through the esophagoscope up to 28 French. Further dilatation over a previously swallowed string can then be continued until a 40 French lumen is obtained. With ascending fibrosis of the esophagus, more likely associated with deep ulcer, the segment of esophagus involved in the stenosis is larger and bouginage is less effective.

STENOSIS FOLLOWING GASTROESOPHAGEAL SURGERY

Cicatricial stenosis following gastro-esophageal surgery is occasionally encountered at the suture line. Since reflux of gastric juice is unavoidable after by-passing or resection of the cardia, peptic erosion may result when acidity persists. Indeed, after such procedures, as esophagogastrostomy or ablation of the cardia for achalasia, peptic erosion has occurred so frequently as to make these procedures unpopular.

Marginal ulceration is said to follow limited resection of the stomach and esophagus for a carcinoma of the cardia. This is a rare complication of esophagogastrectomy for carcinoma in our experience at the Mount Sinai Hospital. More commonly, stenosis at the suture line may be associated with what may be referred to as a "silk granuloma". The esophageal mucosa at the site of the silk suture becomes edematous and protrudes into the lumen of the gastroesophageal juncture. On endoscopy, the black silk suture can be seen between the folds of the inflamed redundant mucosa. After cutting the silk with a punch biopsy forceps and extraction of the suture, the condition promptly improves. Nevertheless, the edematous mucosa is removed with forceps and examined for evidence of recurrence of neoplasm.

Two instances of peptic stenosis following the Heller operation for cardiospasm have been encountered. Gastric reflux and marginal ulceration resulted after

incision of the esophageal and gastric musculature down to the mucosa. Incompetence of the esophageal sphincter with regurgitation is much more apt to occur after the Heller operation in the presence of an hiatal hernia with achalasia.

INFLAMMATORY DISEASE OF THE ESOPHAGUS

Non-specific inflammatory disease of the esophagus occurs most often in the region of the cricopharyngeus muscle which constitutes the proximal sphincter. The more common lesions in this location are foreign bodies, traumatic perforation, chronic hypopharyngitis and decubitus ulcer.

The subject of the endoscopic removal of foreign bodies of the esophagus requires no further elucidation. Suffice it to say that the history of sudden retching, while eating, followed by a sticking sensation and persistent dysphagia warrants esophagoscopy. The presence of localized cervical tenderness and the roentgen evidence of either a radio-opaque substance, air in the soft tissue or widening of the prevertebral area would confirm this diagnosis. The danger of foreign bodies either becoming embedded and leading to stricture formation or producing a mediastinitis are too great to postpone endoscopic examination.

Instrumental perforation of the esophagus is most frequent in the hypopharynx. In most instances, the esophagoscopist is immediately aware of having produced a tear or false passage. Brisk bleeding and the loss of normal landmarks should arouse the suspicion of a perforation. The administration of large doses of antibiotic therapy, sedation and parenteral feeding will usually prevent a descending mediastinitis. After a short interval, the classical syndrome of fever, dysphagia, creptitation, severe interscapular pain and x-ray evidence of subcutaneous emphysema establishes the diagnosis. Experience has proven that conservative therapy as outlined will prevent further complications in the great majority of cases. Occasionally, cervical drainage of a localized peri-esophageal abscess will be required. Esophagoscopic manipulation is contraindicated.

On rare occasions, the signs of perforation and a peri-esophageal infection may not become manifest until several days after endoscopy. This is especially prone to happen in elderly patients with cervico-dorsal kyphosis or where the patient is unable to open the mouth widely because of fixed bridge work. Prolonged pressure of the metal tube against the esophageal mucosa overlying a prominent cervical spine or spur may be sufficient to cause a pinpoint area of necrosis and subsequent perforation. Such pressure may inadvertently result from an attempt to expose the cardia by depressing the head and directing the esophagoscope anteriorly. Because of the slight inherent risk of such complications all patients who are esophagoscoped are given antibiotics for one or two days after the examination.

In recent years, Schindler has developed a new optical esophagoscope which has proved to be safer and easier to use. A rubber tipped obdurator permits the introduction of the instrument without risk of injury to the hypopharynx. A telescopic system similar to the gastroscope is employed.

The limitation of the use of this optical esophagoscope is that the upper third of the esophagus cannot be visualized and endoscopic manipulation cannot be

performed satisfactorily. The use of this instrument in lesions proximal to the aortic arch is therefore contraindicated. However, the relative safety and ease with which the Schindler esophagoscope can be introduced may prove to make it a most useful instrument. This should stimulate the more extensive use of diagnostic endoscopy in lesions of the lower esophagus where, in addition to x-ray, direct visualization is so essential in the diagnosis of varices, hiatus hernia and esophagitis.

Chronic hypopharyngitis is often associated with hypochromic anemia, glossitis, achlorhydria and iron deficiency. This Plummer-Vincon syndrome occurs predominately in females and is frequently accompanied by dysphagia. The difficulty in swallowing may result from the formation of a narrow stricture or web at the opening of the esophagus. The web is formed by a thin layer of chronically inflamed mucosa and can easily be dilated by the passage of a bougie or an esophagoscope. Such dilatation not only gives prompt relief of the dysphagia but marked improvement in the general condition of the patient.

Decubitus ulcer of the post-ericoid region may result from the prolonged use of a naso-gastric feeding tube. Such tubes have frequently been employed in cases of extensive gastrointestinal surgery requiring prolonged bed rest. With the patient in the reclining position, the pressure of the overlying cricoid cartilage against the rubber tube may cause ulceration of the hypopharyngeal or esophageal mucosa. In one specific instance of a four year old child, a naso-gastric tube had been allowed to remain in situ for four weeks. An ulceration of the posterior surface of the cricoid cartilage resulted in a slough into the larynx. In most instances, the symptoms of dysphagia and pain occur four to six weeks after withdrawal of the tube. By this time the patient has developed a stricture. At endoscopy, a pinpoint lumen may be encountered surrounded by a fibrotic stricture which requires repeated dilatations.

STRICTURE

Congenital stricture of the esophagus may be single or multiple and may involve a larger or smaller segment of the lower esophagus. Often such incomplete or partial stenosis may not become manifest until solids are added to the child's diet. A bolus of unmasticated food may become embedded in the narrowed lumen and produce complete esophageal obstruction. A non-specific esophagitis may accompany such stenosis. Gradual dilatation with graded bougies is the treatment of choice. Usually a rather wide segment of the lower esophagus is involved in congenital stricture.

CICATRICIAL STENOSIS

The accidental swallowing of caustics is the most frequent cause of cicatricial stenosis. Less common causes are specific ulcer of the esophagus, embedded foreign bodies and healed peptic ulcerations. The cicatricial stenosis is the result of fibrotic replacement of the deficient mucosal surface. The deeper the ulcer, the more pronounced will be the resulting fibrosis. In such instances, the epithelial surface may regenerate and the only suggestion of previous ulceration is the

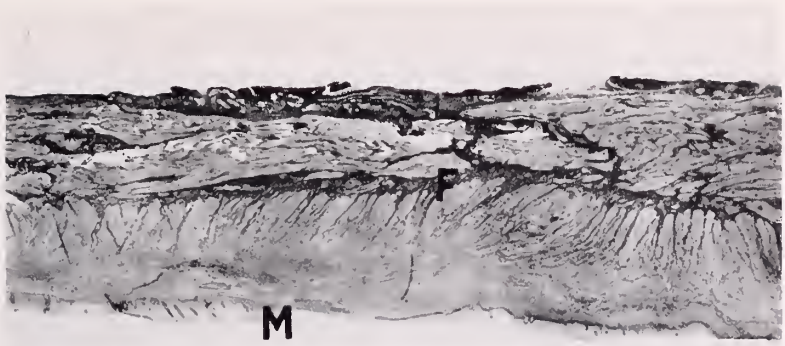

FIG. 7. Low power section of ascending fibrosis of esophagus-stained with Van Gieson. M. The mucosa is intact throughout. F. Fibrosis involves entire wall of esophagus and produces the wide segment of stenosis.

FIG. 8. Endoscopic appearance of cicatricial stenosis.

clinical history (Fig. 7). Endoscopically, the cicatricial area has a paler color than the normal mucosa (Fig. 8). The narrowed lumen is most often eccentrically placed and that part of the circumference of the mucosa involved in the cicatrix seems white. If the stenosed segment is short, it may be possible to look beyond into the distal esophagus. When the mucosal surface is intact, one must consider caustic stricture, healed peptic stenosis, scleroderma or external compressive stenosis as diagnostic possibilities.

The immediate treatment of caustic burns consists of neutralization of the swallowed chemical and supportive measures. After the initial acute phase has been overcome, it may be possible to prevent cicatrization by early passage of the Hurst mercury weighted tube in graduated sizes. The swallowing of the soft rubber tube can be started on the third or fourth day after the chemical burn. Progressively larger tubes can be employed daily as tolerated. On or about the tenth day, a thorough inspection of the entire esophagus with an evaluation of the damage sustained should be made by peroral endoscopy. A search for areas

of ulceration and narrowing will yield necessary information as to the sites of future strictures which may require treatment. The Hurst tube may aid in preventing stricture formation but is inadequate for dilatation of a fibrotic stricture. After ascertaining the location and extent of the stenotic strictures, dilatation therapy should be instituted promptly.

The degree of success of dilatation which is possible is dependent largely upon the extent of the stenotic segment involved and the character of the fibrosis. In ascending fibrosis of the esophagus and in congenital stenosis a rather long segment of the lower esophagus is fibrotic and dilatation becomes an arduous procedure with less promise of success. Conversely, in early lye stricture and peptic ulceration, an adequate lumen can be readily obtained in most cases by a few dilatations. The simplest type of stricture to treat is that which involves only the mucosa and submucosa of the esophagus and stretches across the lumen of the esophagus like a membrane. This applies particularly to the so-called web of the mouth of the esophagus associated with glossitis and secondary anemia. The mere introduction of the bougie beyond the web often produces a cure.

VARICES OF THE ESOPHAGUS

Varicose veins of the esophagus, associated with portal hypertension or obstruction of the splenic veins, can be more easily diagnosed by endoscopy than by radiography. The dilated varices distend the mucosa and can be easily detected under direct vision. They are much more common in the lower third of the esophagus but may extend throughout the entire length of the organ. Routine esophagoscopy with the rigid esophagoscope for detection of varices which do not cause symptoms is not recommended. Varicose distention and distortion of the gastric veins also may be demonstrated occasionally. It is most important to stress that erosion of the overlying mucosa and other evidences of recent hemorrhage such as adherent blood clot may be ascertained only by endoscopy. This, of course, cannot be shown roentgenologically. As a matter of fact, the x-ray can be relied upon to diagnose at best 40 per cent of the advanced cases of esophageal varices and early cases may be missed entirely.

In the proximal half of the esophagus the varices often appear as isolated, bluish spheres surrounded by congested mucosa. In the distal third and, more particularly, around the gastro-esophageal juncture they may occur as clusters of soft bluish red tortuosities, protruding into the lumen. The varicosities are easily compressible and offer no resistance to the further passage of the esophagoscope. Erosion of the superficial mucosa with adherence of old blood clot usually signifies the site of recent hemorrhage. The collapsibility of the varices may explain the difficulty in their demonstration by contrast media.

Esophagoscopy should be employed to corroborate the clinical or roentgen diagnosis of esophageal varices in patients with a history of recurrent hematemesis. The risk of initiating profuse bleeding from the varices is negligible, provided of course, care is exercised. When varices are found in the esophagus, a search should then be made for gastric varicosities since the type of therapy may be modified by the knowledge of their existence.

The treatment of esophageal varices by the injection of sclerosing solution has met with very limited success. The thrombosis of this important esophageal collateral circulation increases the portal hypertension and may favor the formation of gastric varices. When gastric varices coexist with esophageal varicosities, the injection treatment is contraindicated. Occasionally, however, the injection treatment has proven valuable following unsuccessful shunt procedures and splenectomy. Also a patient whose general physical condition does not permit major surgery should be considered for injection therapy.

During episodes of uncontrollable, active bleeding, esophagoscopy may be performed as an emergency diagnostic or therapeutic procedure. Supportive therapy cannot always be relied upon to carry the patient through until hemorrhage ceases spontaneously.

Tamponade for the immediate control of esophageal bleeding has proven relatively effective in some instances. The Sengstaken tube provides occluding pressure against the veins of the gastric cardia as well as those of the lower half of the esophagus. This consists of a triple lumen tube, with the larger central channel used for gastric suction. The other two are used for inflation of the small spheroid gastric balloon and the larger cylindrical esophageal balloon. The tube is swallowed and introduced into the stomach. After the distal cardiac balloon has been inflated with about 100 cc. of air, the tube is withdrawn until the cardiac balloon impinges against the cardia. The esophageal balloon is now inflated to obtain even pressure against the esophageal varices, which maneuver also prevents dislodgement of the tube.

It is suggested that esophagoscopic examination of any patient with unexplained hemorrhage from the upper gastrointestinal tract become a routine procedure, to exclude esophageal varices. If bleeding varices are encountered, the hemorrhage may be temporarily controlled by pneumatic pressure with a balloon.

The problem becomes more pressing if the hemorrhage persists in spite of pneumatic pressure or recurs after withdrawal of the Sengstaken tube. The tube may be allowed to remain in situ for two to three days, during which time frequent aspiration of stomach contents must be carried out. If the hemorrhage is uncontrolled after pneumatic pressure and supportive therapy, direct examination for the source of bleeding becomes imperative. The larynx should be intubated with a cuff, preferably under general anesthesia, in order to prevent spillover of blood into the trachea. An esophagoscope is then inserted, with the intratracheal tube in situ, and the contents of the esophagus are aspirated. If no varices of the esophagus are encountered, it can be stated that the bleeding is not esophageal in origin and that a gastric lesion probably exists.

CARDIOSPASM OR ACHALASIA

Esophagoscopy should always be performed at least once in every suspected case of cardiospasm. No matter how characteristic the clinical history and roentgen findings may seem to be, diagnostic endoscopy is indicated for confirmation. Differentiation from peptic ulceration, cicatricial stenosis and carcinoma often is impossible without direct visualization.

In cardiospasm, the findings on endoscopy vary with the stage of the disease. In the early phase with slight, intermittent obstruction, mild dilatation with small amounts of retained food particles is encountered. In advanced cases, large amounts of stagnant material may be found. The esophageal lumen is apt to be dilated markedly with its diameter distended by pints of undigested material. In such instances, a satisfactory examination is impossible and it is advisable to postpone endoscopy until after the esophagus has been thoroughly lavaged. A large stomach tube with large quantities of warm solution of weak sodium bicarbonate is used for irrigation. After such preliminary cleansing, esophagoscopy will reveal a markedly, dilated tortuous lumen lined by a mildly inflamed mucosa. In the distal portion, the inspissated food particles often are found to be adherent to a thickened mucosa with areas of leukoplakia. After removal of such debris by suction of forceps, small bleeding areas may be visible.

While cardiospasm usually causes a degree of dilatation not seem in benign stricture or neoplasm, cases of marked dilatation similar to cardiospasm have been encountered in adenocarcinoma of the cardia invading the lower esophagus.

In most cases of advanced achalasia, the esophagus is not only markedly dilated but considerably elongated as well. The appreciation of this fact is important when an attempt is made to locate the rosette leading to the cardiac orifice. The ordinary 45 centimeter esophagoscope is often inadequate to reach and explore the esophageal sphincter and a longer tube of 53 centimeters is necessary. The tortuosity of the esophagus especially in its terminal portion may render identification of the rosette very difficult but this should not deter the endoscopist. In every instance of achalasia, it is possible to insert the tube beyond the sphincter into the stomach proper. This maneuver is essential to rule out neoplastic submucosal invasion of the esophagus from an adenocarcinoma of the cardia. In bringing the cardia into view it is helpful often to place the patient's head at a considerably lower level and direct the esophagoscope anteriorly and to the left. When the region of the sphincter is encountered the patient frequently develops a spasmodic cough reflex. It should be pointed out that the dilated portion of the esophagus does not actually reach the cardio-esophageal juncture or the Z line but that a small segment of normal esophageal mucosa separates the rosette from the cardiac mucosa. In the extreme terminal portion of the elongated esophagus, the mucosa may be thrown into longitudinal folds which strongly resemble gastric rugae, especially if inflammatory changes are present. An excellent indication that one is beyond the sphincter is the appearance of gastric juice. The endoscopist should not be content with his examination and with the tentative diagnosis of cardiospasm until he has actually entered the stomach and not only recognized gastric rugae but obtained gastric juice.

The introduction of a Jackson pathfinder tube bougie into the rosette will promptly permit further introduction of the esophagoscope into the stomach. The rosette may not be encountered even at a distance of 48 centimeters from the upper incisor teeth. On several occasions when the operator believed the esophagoscope was in the stomach, biopsies showed esophageal mucosa. When the rosette has been definitely identified, inability to advance the esophagoscope

beyond the sphincter should raise the suspicion of organic obstruction on the basis of carcinoma. Under such circumstances, gentle dilatation with the bougie, followed by introduction of the forceps in the path of the bougie will indicate the diagnosis of malignancy or peptic stenosis.

In early cases of cardiospasm the dilatation of the esophagus may not be as prominent as its elongation. The localization of the rosette at a distance of 44 to 45 centimeters from the upper incisor teeth may suggest cardiospasm. Biopsy will indicate the presence or absence of organic obstruction.

Endoscopic treatment of cardiospasm consists of either passive dilatation with the Hurst mercury weighted tube or active dilatation with the pneumatic or hydrostatic dilating bag.

The dangers of dilatation are obvious but serious accidents are rare and insufficient to preclude this form of therapy. Actually, minute splitting of the mucosa and tear of the underlying musculature must take place to some degree. These injuries are accompanied by pain under the xiphoid, elevation of temperature and occasional chilly sensations. Radiographic examination of the abdomen and chest may show a thin column of air under each leaf of the diaphragm. This would indicate an escape of air through a small rupture. Nevertheless, with antibiotic therapy and intravenous feeding, these patients seem to do well. Hospitalization for several days after active dilatation is mandatory.

The immediate results of active dilatation have been promising but cure is seldom obtained. Several dilatations may be necessary because of return of symptoms. It is important to emphasize that the dilatation of the esophagus is not altered even in successfully treated cases.

DIVERTICULUM

Pulsion diverticula most often occur posterior to the hypopharyngeal opening of the esophagus. The defect in the cricopharyngeal musculature permits the pharyngeal mucosa to herniate and form a pouch along side the esophagus proper. On esophagoscopy, the mouth of this pouch is easily entered. The mucosa of the diverticulum is visualized and can be seen to end blindly at the distal portion of the pouch. The normal opening of the esophagus is so displaced anteriorly and kinked by the diverticulum that it is very difficult to enter it with the esophagoscopic tube. The scope invariably passes into the diverticulum.

An epidiaphragmatic diverticulum can be visualized endoscopically as a slit like ostium in communication with the lumen of the esophagus. The mouth of the diverticulum and the esophagus have a common wall which appears like a shelf. The pouch can be readily entered and traced to its limits. The lowermost portion of the esophagus can also be easily examined until the stomach is entered.

Traction diverticula of the esophagus are of little clinical significance and may or may not be detected endoscopically as an out-pocketing of the esophageal mucosa.

BENIGN TUMORS OF THE ESOPHAGUS

Non-malignant tumors of the esophagus are indeed rare and are almost invariably non-epithelial in origin. Benign tumors may be classified as two types:

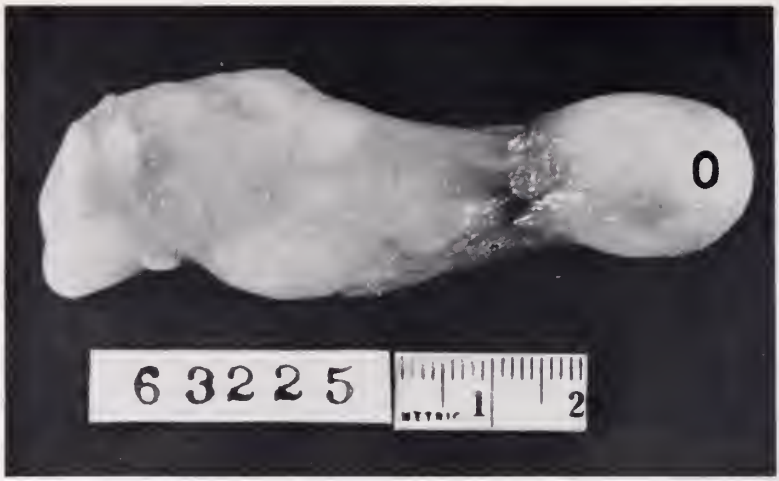

FIG. 9. Surgical specimen of fibro-lipoma removed from upper esophagus. O. Rounded end represents the most dependent portion of tumor which was suspended in the esophageal lumen.

(a) the intraluminal, including the fibrolipoma and the fibromyxoma; (b) the intramural comprise the various leiomyomas.

The fibrolipomata most often arise at the opening of the esophagus by a limited attachment or pedicle and become suspended in the lumen of the upper esophagus. They may attain a rather large size, seven to ten centimeters in length, but are always covered by intact mucosa (Fig. 9). They have been known to become dislodged into the pharynx following an eructation and obstruct the laryngeal vestibule causing severe dyspnea.

On hypopharyngoscopy, a round smooth mass, covered by intact mucosa, may be seen attached to the post-cricoid region. The tumor is freely movable and can be grasped easily and displaced into the pharynx. The best method of removal is by suspension laryngoscopy (Fig. 10). By this procedure an excellent exposure is obtained and both hands are rendered free to extirpate the neoplasm by dissection and coagulating snare. In a recent case, a fibrolipoma was located in the lower half of the esophagus.

The intramural leiomyomas are more often located in the lower third of the esophagus. In a few instances the myomas also extend into the stomach. These tumors are not pedunculated. They have a firm consistency and are always covered by intact mucosa. They appear as oval or round submucosal masses which occasionally encircle the esophagus in the form of a U.

On endoscopy, the lumen of the esophagus seems to be compromised by an extra-esophageal mass. Occasionally, the tube cannot be passed beyond the proximal bulge of the tumor. More often, with diligent care the main lumen of the esophagus can be recognized at an acute angulation. The tumor mass can be displaced by the esophagoscope and the remainder of the esophagus visualized. These intramural tumors are always covered by an intact mucosa. When the diagnosis of a leiomyoma is entertained by the roentgenologist and the findings

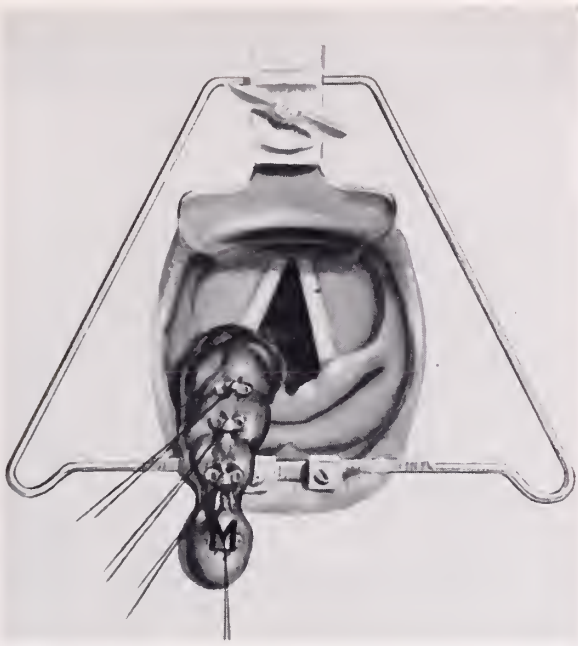

FIG. 10. Removal by suspension laryngoscopy. The pedunculated tumor has been dislodged into the oropharynx. M. Michel clips fastened to tumor give necessary traction so that fibro-lipoma can be ablated by diathermy snare.

on endoscopy, as described above support this view, a biopsy is not necessary. As a matter of fact, a biopsy will not be satisfactory unless taken deep to the mucosa. The resultant ulceration of the mucosa may render subsequent enucleation of the tumor by the surgeon more difficult. Should ulceration of the mucosa be present at the initial esophagoscopy, then the likelihood of malignancy or leiomyosarcoma exists and a biopsy is indicated.

MALIGNANT TUMORS OF THE ESOPHAGUS

Further progress in the study of cancer of the esophagus will follow the development of improved methods for establishing earlier diagnosis. Two essential methods are utilized nowadays to establish the diagnosis of carcinoma of the esophagus; roentgenology and endoscopy. There is little doubt but that the earliest lesion can best be diagnosed by endoscopy. It should be remembered however, that in the majority of instances only the most proximal portion of the esophageal carcinoma can be seen by the endoscopist. The full limits of extension of the tumor are best determined by x-ray.

Carcinoma occasionally develops in the presence of benign lesions of the esophagus, such as stricture, cardiospasm, peptic ulcer and hiatal hernia. An adequate biopsy will indicate the diagnosis.

Carcinoma of the upper esophagus most frequently occurs in the post-cricoid region and at the mouth of the gullet. The incidence of post-cricoid carcinoma is far greater in women than men: a ratio of eight to one. There seems little doubt

that carcinoma in this location is definitely related to the Plummer-Vinson syndrome. Chronic hypopharyngitis seems to be the precursor of this malignant change. The history of progressive dysphagia accompanied by discomfort or pain in the ear on swallowing is suggestive of a lesion at the post-cricoid region.

Indirect laryngoscopy usually reveals a normal larynx. In advanced cases, the upward extension of the neoplasm may be visible in the depths of the pyriform fossa or an unexplained vocal cord paralysis may be detected.

Direct visualization by esophagoscopy is essential for diagnosis. The lesion may be encountered just above the cricopharyngeus in the post-cricoid region where ulceration or nodular thickening may be seen (Fig. 11). Often the sphincter at the cricopharyngeus is visualized but the esophagoscopic tube cannot be passed because of the infiltration and stenosis (Fig. 12). A small bougie might be accommodated but no attempt should be made to force the esophagoscope through the stenosis lest a perforation result.

During the past several years, ten cases of post-cricoid carcinoma have been observed where the evidence seemed to suggest that the lesions developed subsequent to radiotherapy administered fifteen to twenty five years previously.

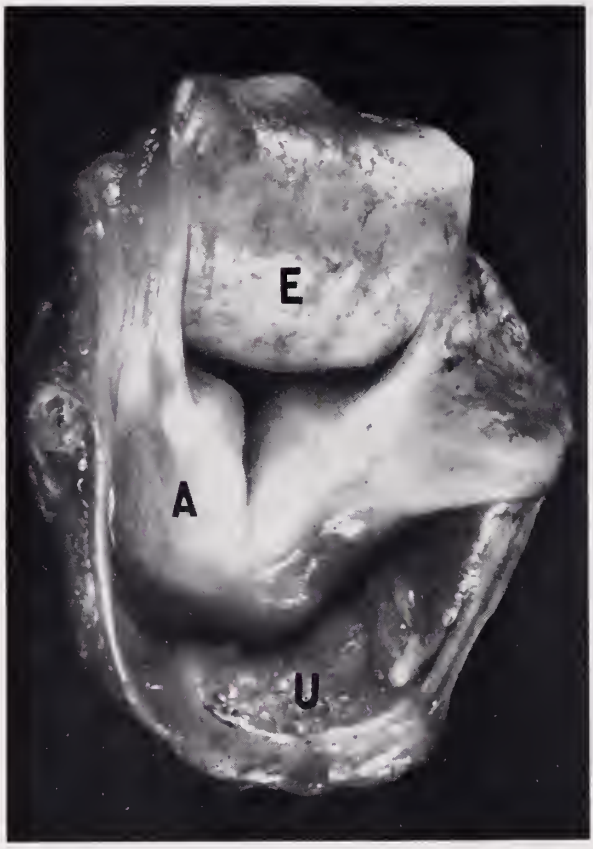

FIG. 11. Surgical specimen of resected carcinoma of upper esophagus. E. Epiglottis. A. Arytenoid. U. Ulcerating tumor on the posterior wall.

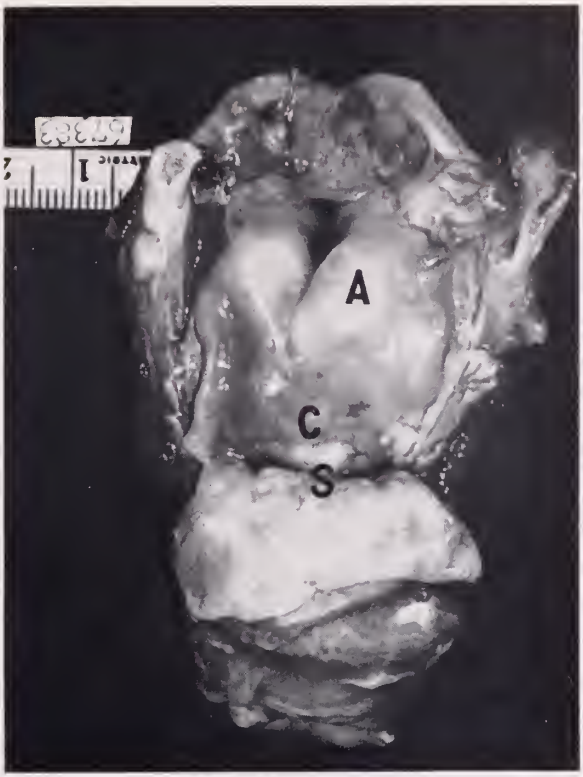

FIG. 12. Surgical specimen of resected carcinoma of upper esophagus. A. Arytenoid. C. Cricoid. S. Carcinomatous stenosis at upper esophagus.

These patients had been treated by radiation either for hyperthyroidism, tuberculous lymph nodes or carcinoma of the vocal cord. There is considerable evidence to substantiate the opinion that malignant transformation of mucosal surface can occur after radiation therapy.

Carcinoma of the middle or lower third of the esophagus may present the same endoscopic appearance. The x-ray film usually discloses the site of the suspected lesion. On esophagoscopy, there may be seen some inflammatory or hyperplastic mucosal changes proximal to the tumor. Care should be exercised to introduce the esophagoscope beyond this area until the lesion itself is identified, otherwise the biopsy may not include the neoplastic tissue. The tumor may present itself as an ulcerative, polypoid, or infiltrative lesion usually producing some obstruction. Occasionally with large polypoid tumors of the middle third, the esophagoscope may be passed beyond the distal limit of the neoplasm.

The lower third of the esophagus is the most common site for carcinoma of the esophagus. In this location the malignant tumor must be differentiated from marginal ulceration, alchalasia and peptic stenosis.

Adenocarcinoma of the cardia may extend proximally to involve the lower esophagus. Such lesions frequently produce organic stenosis of the lower esopha-

gus by submucosal infiltration. The overlying mucosa appears puckered or nodular and the lumen becomes conically narrower with the tapered end toward the stomach. The rosette may appear infiltrated and will not yield to the pressure of the distal end of the esophagoscope. Such resistance to passage may differentiate malignant infiltration of the sphincteric canal with proximal dilatation of the esophagus from dilatation due to true cardiospasm. A specimen from the narrowed lumen of the rosette or a deep biopsy may show submucosal adenocarcinoma extending from the cardia. A microscopic diagnosis of adenocarcinoma almost invariably indicates a neoplasm of the cardia except in the very rare instance of primary adenocarcinoma of the esophagus. In the latter, the lesion originating from submucosal esophageal glands, must be completely surrounded by esophageal mucosa in order to be considered primary. The cardia must be free of neoplasm.

It should be stressed that a single negative biopsy may not be sufficient. When the clinical and roentgen evidence strongly suggest malignancy, the examination and biopsy should be repeated. This is especially true of cardial cancer.

In advanced carcinoma of the esophagus with malnutrition, it may be necessary to pass a naso-gastric tube for alimentation especially during the administration of radiotherapy. In such instances, the stenosed segment might be traversed with a narrow esophagoscope and then the rubber or plastic feeding tube can be fed through the scope into the stomach.

Rarely, other malignant neoplasms involve the esophagus and may be diagnosed by biopsy. Recently, a polypoid primary malignant melanoma was encountered and subsequently successfully resected. Lymphosarcomatous invasion of the stomach produces prominent greyish rugae from which a biopsy may prove the diagnosis. Hodgkin's disease may invade the esophageal wall and elevate the mucosa to permit a biopsy.

In scleroderma and occasionally in dermatomyositis a smooth narrowing of the lower esophagus may be encountered with atrophic mucosa and a rigid wall. If the disease has involved the sphincter mechanism at the lower end of the esophagus, peptic reflux with marginal ulceration may be present.

Finally, all patients with persistent dysphagia not explained on a neurological basis should be esophagoscoped.

THE ROENTGEN FINDINGS OF BENIGN AND MALIGNANT TUMORS OF THE ESOPHAGUS

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It is well recognized that alterations in the anatomy of the esophagus frequently plague the radiologist. Lack of definite information concerning the anatomy and physiology of this organ are part of the difficulty. In the case of tumors, however, this problem is not often encountered and their recognition is somewhat easier than other afflictions of the esophagus. The value of differentiation of benign from malignant tumors is obvious. There is a responsibility to diagnose and, if possible, remove a malignant tumor as early as possible. The recognition of benign lesions may avoid or alter the surgical approach.

BENIGN TUMORS OF THE ESOPHAGUS

Benign tumors of the esophagus are uncommon. When present, they are usually submucosal. The most frequent benign tumor is a leiomyoma; however, practically every type of benign tumor occurring in the intestinal tract has been found in this region, such as fibromas, lipomas, neuromas, angiomas, intramural cysts and others. Benign mucosal tumors, such as adenomatous polyps, are rare. Since nearly all benign tumors of the esophagus are submucosal, they present similar radiological findings and can be considered together.

Submucosal tumors may vary considerably in size. The smallest myoma recognized on roentgen study measured one centimeter in diameter and the largest involved the lower two thirds of the esophagus, extending below the diaphragm. Ulceration of the overlying mucosa, in contrast to similar lesions in the stomach and small intestine, is uncommon probably due to the absence of acid and peptic digestion. These tumors may encroach upon the esophageal lumen or grow peripherally and appear as an extra-esophageal mass. They may be pedunculated and lie freely within the esophageal lumen or partially encircle the wall producing an annular constriction. Their distribution is usually in the lower two thirds of the esophagus. Since the musculature of the upper third of the esophagus is striated, smooth muscle tumors in this region are uncommon.

Benign tumors are frequently asymptomatic. When symptoms present, dysphagia is the most common complaint.

Roentgen Findings

In profile, a benign submucosal tumor, when it encroaches on the esophageal lumen, produces a smooth semilunar defect in the barium column with intact mucosa and distinct borders. An abrupt angle is seen where the edge of the tumor meets the uninvolved wall of the esophagus (Fig. 1A). En face, there is a sharply circumscribed filling defect within the barium filled esophagus. The barium

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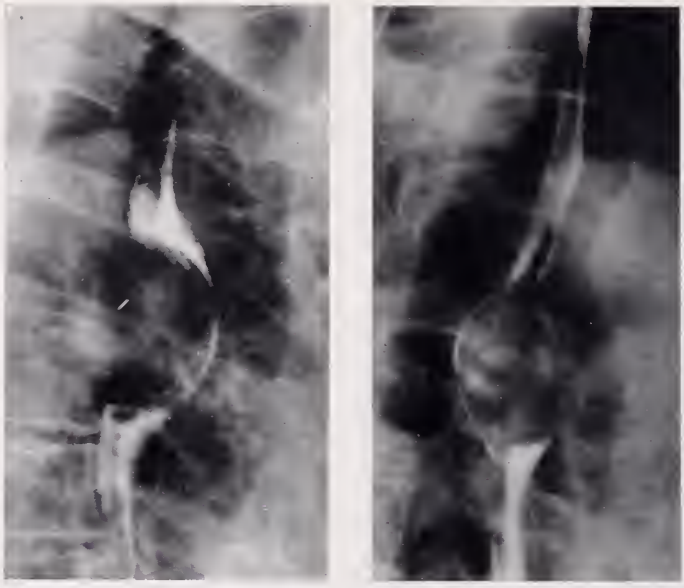

A B

FIG. 1A. Fibromyoma (in profile). There is a smooth semilunar defect within the esophageal lumen with intact mucosa and distinct borders.

Fig. 1B. Fibromyoma (en face). Same case as 1A. A sharply circumscribed defect in the middle third of the esophagus is again noted.

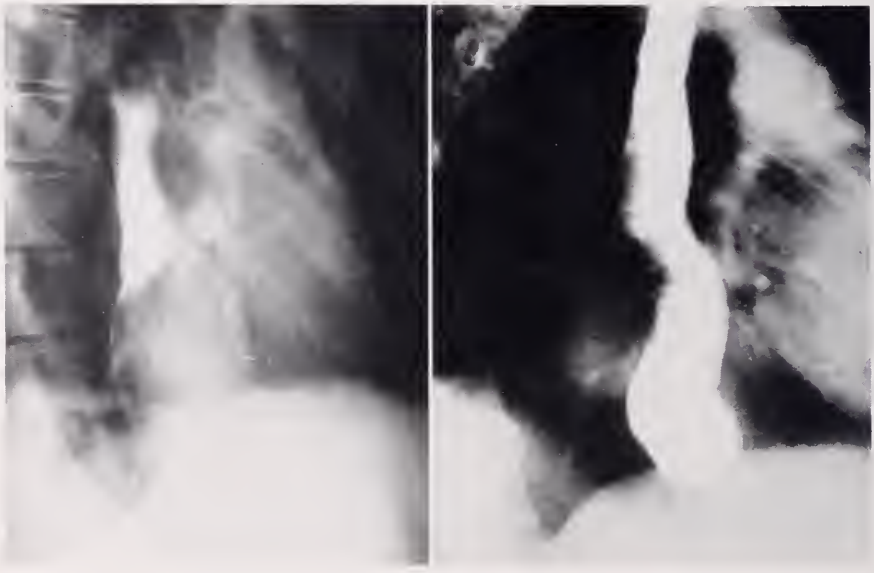

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FIG. 2A. Myoma. A soft tissue mass is seen in the lower end of the esophagus with sharply defined borders. There is both an intrinsic and extrinsic component which are similar in size.

FIG. 2B. Dermoid cyst. There is a fairly well defined extrinsic soft tissue mass displacing the lower end of the esophagus.

column may be deflected or forked as it passes over the mass (Fig. 1B). Due to stretching over the tumor, the normal longitudinal mucosal folds may disapear over the convexity of the defect and reappear at the upper and lower margins. Mucosal folds may appear to pass over the tumor, while in fact, they are due to superimposition from the opposite uninvolved wall. An extraluminal soft tissue mass is often noted immediately adjacent to the defect and corresponds in size to the intraluminal component. This mass can displace the esophagus (Figs. 2A, 2B). After the barium has passed the tumor, an arc like shadow which is due to retention of a thin layer of barium collecting in a groove between the lower margin of the mass and the adjacent normal esophageal wall is occasionally observed at the lower border of the defect. In one case, the lesion completely encircled the lower end of the esophagus, producing a smooth fusiform narrowing, simulating cardiospasm.

The characteristic features of these lesions may be obscured by overdistention of the esophagus, or by the use of too little barium. When the tumor is large, some delay in the barium passage and slight proximal dilatation may be noted. In larger tumors, there may be considerable stretching of the esophageal wall and encroachment upon the lumen with only a slit-like opening remaining. In these cases, the thin layer of barium within the lumen may have a smudged appearance and differentiation from mucosal destruction secondary to carcinoma may be difficult.

Irregularity of the tumor, excessive lobulation, and ulceration are suggestive but not pathognomonic of malignant change (Figs. 3A, 3B).

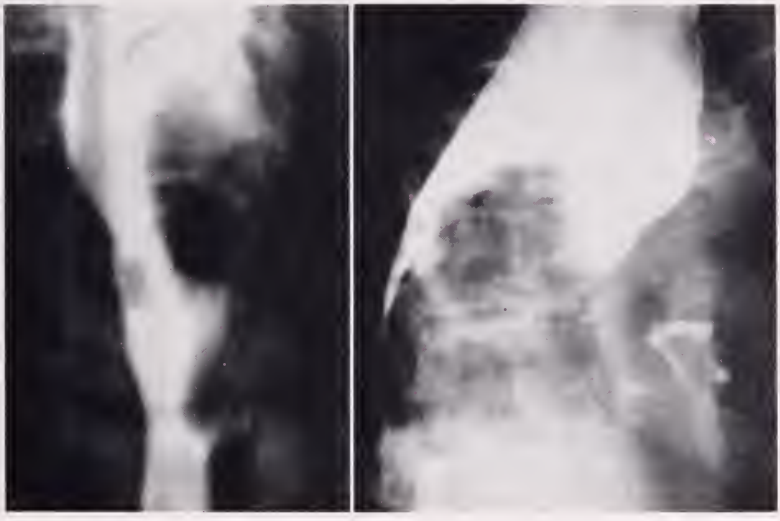

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FIG. 3A. Myoma. Lobulation of a benign tumor in the upper third of the esophagus.
FIG. 3B. Lipoma. There is a large filling defect involving the lower third of the esophagus with a large paraesophageal soft tissue mass. Ulceration within the mass is noted. The roentgen diagnosis was myosarcoma.

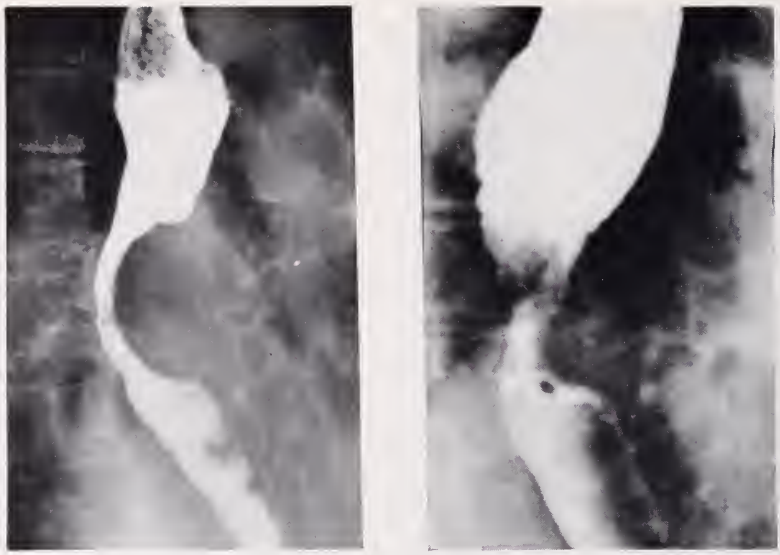

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FIG. 4A. Carcinoma. Carcinoma simulating a benign tumor in the right anterior oblique projection.

FIG. 4B. Same case as 4A. In the left anterior oblique projection, mucosal destruction is evident.

Differential Diagnosis

The differentiation of mucosal from submucosal tumors is important as practically all mucosal tumors of the esophagus are carcinomas. Benign tumors offer little difficulty in diagnosis. The common and characteristic signs of esophageal cancer, namely, mucosal destruction, rigidity of the wall, eccentricity of the lumen and luminal stenosis are not present. There is an occasional polypoid carcinoma that produces a sharply defined defect which may be difficult to distinguish from a benign submucosal tumor. Roentgenograms in various positions may illustrate the presence of some of the signs of carcinoma, in particular, mucosal destruction and irregularity of the mass (Figs. 4A, 4B).

The presence of a paraesophageal soft tissue mass favors the diagnosis of a benign tumor. Although soft tissue masses may be identified with carcinoma, when this occurs, there is usually no doubt of the diagnosis. Malignant change in a benign tumor can produce mucosal destruction, irregularity of the lumen and mural rigidity and roentgen differentiation from a carcinoma, particularly in small lesions, may be impossible. There is generally, however, a large soft tissue mass which distinguishes this lesion.

Extrinsic lesions, such as aneurysms and aberrant thyroid, produce a gently sloping, smooth walled defect, in contrast to the abrupt, sharply angled margins of submucosal lesions, which is easily recognizable. On rare occasions, an elongated tortuous aorta can cause impressions upon the esophagus which are difficult to differentiate from submucosal tumors. When an extrinsic mass becomes adherent to the wall of the esophagus, as in tuberculous lymphadenitis, it may assume an appearance identical to that of a submucosal lesion.

CARCINOMA OF THE ESOPHAGUS

Malignant tumors of the esophagus are more common than benign tumors. They occur more frequently in males than in females and mostly in patients over fifty years of age. It is most unusual to discover an esophageal carcinoma by chance. In the presence of symptoms, the lesion may be difficult to identify and frequently multiple examinations are necessary for its discovery. Every examination of the esophagus for a suspected carcinoma should include a study of the fundus of the stomach, as many lesions of the lower third of the esophagus originate in the stomach.

Carcinomas may arise any place in the esophagus. They are most commonly located at the points of natural constriction such as the cervical region, the level of the aortic arch, and the lower end of the esophagus. They can grow to involve most of the esophagus.

The usual primary carcinoma of the esophagus is squamous cell in type. Adenocarcinoma of the lower end of the esophagus is frequent and this is, in most instances, due to extension from carcinoma of the gastric fundus or carcinoma arising in an hiatus hernia. Primary adenocarcinoma of the esophagus is rare. When it occurs, it arises from the submucosal esophageal glands or heterotopic gastric glands and in its incipiency, presents the roentgen picture of a submucosal tumor (Fig. 5A). There is an increased incidence of esophageal carcinoma developing at the site of a corrosive stricture (Fig. 5B), leukoplakia, or in association with Plummer-Vinson's syndrome. Malignant degeneration of be-

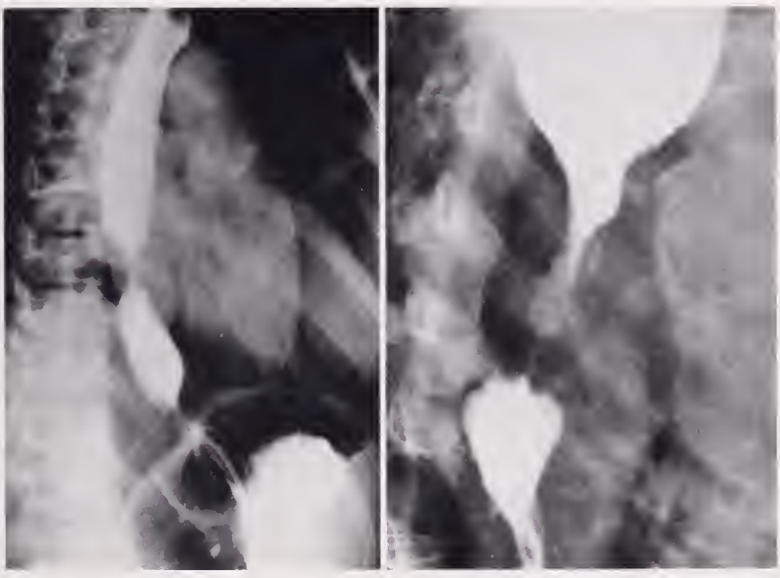

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FIG. 5A. Primary adenocarcinoma of the esophagus. At the junction of the middle and lower thirds of the esophagus, there is a well defined smooth defect with gently sloping margins. The overlying mucosa is intact. There is no associated paraesophageal mass nor evidence of obstruction. The appearance is that of a submucosal tumor.

FIG. 5B. Carcinoma of the middle third of the esophagus developing at the site of lye stricture.

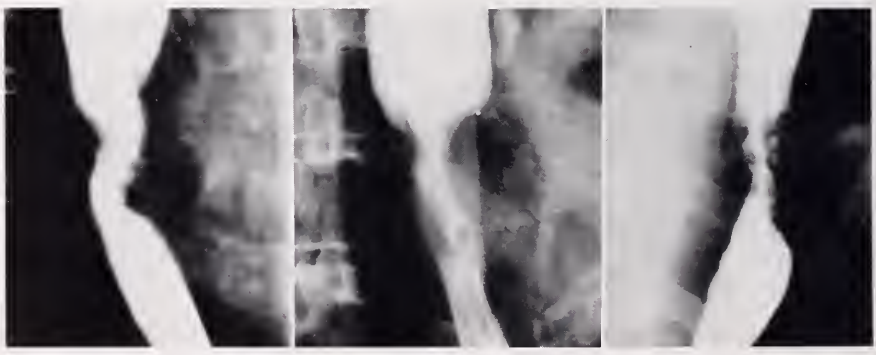
nign tumors is rare. Other malignant tumors are also unusual, but malignant melanoma, Hodgkin's Disease, and lymphosarcoma have been observed.

Roentgen Findings

Grossly, primary carcinomas of the esophagus are usually scirrhous infiltrating or proliferative exophytic tumors. In the first type, there is usually a delay in the passage of the barium through a stenosed rigid segment, the lumen of which may be eccentric or angulated. Above the lesion, the esophageal wall may be flattened and incompletely distensible. This change is due to carcinomatous extension of the tumor and is an important sign in the roentgen differentiation from benign lesions, such as cardiospasm or peptic esophagitis where the esophageal wall above the stenotic segment is distensible. Mucosal ulceration is usually evident; however, in smaller lesions, it may be difficult to identify. The earliest change observed is slight rigidity of the esophageal wall extending over a small segment. The esophagus above the area of stenosis may present varying degrees of dilatation. Dilatation of the magnitude seen in cardiospasm can be seen and does not exclude the presence of carcinoma. Elongation and tortuosity of the esophagus, however, is uncommon with carcinoma. Complete obstruction can occur but is unusual. Tracheal and bronchial fistulas may develop and difficulty in determining the origin of the tumor is occasionally encountered (Figs. 6A, 6B, 6C).

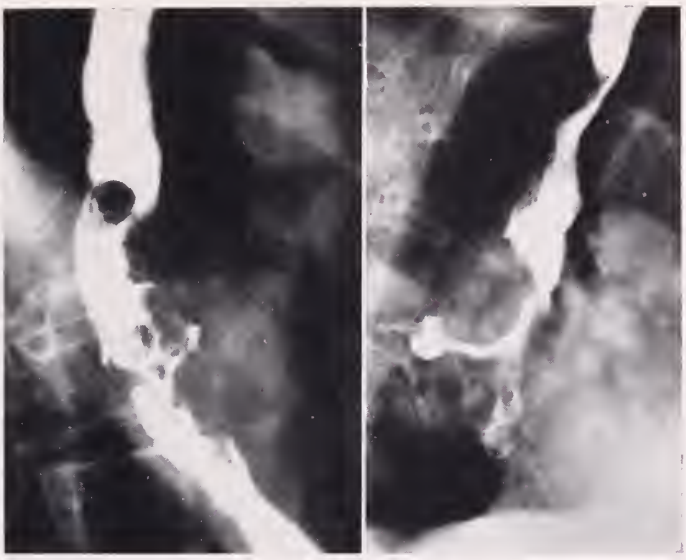
In the exophytic type of tumor, multiple irregular masses, which are frequently ulcerated, are present in the esophageal lumen causing filling defects within the barium column and alterations in its course. There is usually some evidence of involvement of the adjacent mural structures, such as stiffening of the wall (Figs. 7A, 7B).

Occasionally it is possible to show not only the internal contours of the esophagus but extraluminal soft tissue shadows as well (Fig. 6B). In the normal esophagus, the wall and periesophageal tissues may produce a thin uniform shadow along the barium filled lumen. In carcinoma, this shadow may be widened and the irregular outline of the tumor seen. This can be especially well visualized



A B C

FIGS. 6A, 6B, 6C. Squamous cell carcinoma of the middle third of the esophagus with mural rigidity, luminal narrowing and irregularity, and mucosal destruction.



A B

FIG. 7A. Squamous cell carcinoma. There are multiple irregular intraluminal filling defects with mucosal ulceration.

FIG. 7B. Squamous cell carcinoma with sinus tract formation.

A B

FIG. 8A. Squamous cell carcinoma of the upper third of the esophagus.

FIG. 8B. Benign stricture of the upper third of the esophagus. The mucosa is intact and the lumen enters the stenosed segment in a fusiform manner.

when the lesion is adjacent to an air containing structure such as trachea or bronchus.

Special Roentgen Features Relative to the Site of Carcinoma of the Esophagus

Upper Third. Carcinoma is least frequent in the upper third of the esophagus and may be difficult to identify (Fig. 8A). The presence of webs incident to Plummer-Vinson's syndrome requires careful study as carcinomatous change occurs in this lesion. A positive vallecula sign or the retention of barium in this region may indicate the presence of an esophageal abnormality. A lateral view of the soft tissues of the neck may show soft tissue swelling and alterations in position of adjacent structures. A wedge shaped soft tissue swelling parallel to the cervical esophagus in the pre-vertebral area is of special significance as this is frequently associated with carcinoma. Extrinsic pressure upon the esophagus caused by tumors of the thyroid, dermoids, aneurysms, etc. should not be confused with intrinsic lesions.

Middle Third. Carcinomas of the middle third of the esophagus present consistently the most characteristic appearance (Figs. 6A, 6B, 6C, 7A, 7B). On rare occasions a bronchial carcinoma may involve the esophagus to such an extent that there is some difficulty in determining the origin of the neoplasm.

A B

FIG. 9A. Extensive squamous cell carcinoma of the esophagus.
FIG. 9B. Adenocarcinoma of the esophagus arising in an hiatus hernia extending to the upper third of the esophagus.

Lower Third. Squamous cell carcinoma of the esophagus may involve the lower third of this organ and present the roentgen findings noted in the middle of the esophagus. Occasionally these tumors are extensive, extending almost to the cervical esophagus (Fig. 9A). More frequently, however, carcinomas of the lower third of the esophagus arise from an hiatus hernia (Figs. 10A, 10B, 11A) or are due to extensions from carcinomas of the fundus of the stomach. This extension is frequently obvious and associated with a fundal mass (Figs. 12A, 12B). On occasion, however, carcinoma of the fundus of the stomach may grow insidiously until it invades the lower end of the esophagus. The first spread may be submucosal and the effect one of obstruction. The stenotic area may appear quite smooth and the findings can be indistinguishable from cardiospasm. Before the growth ulcerates or a mass becomes apparent, it is of some help to study the peristaltic activity of the esophagus. In cases of carcinoma, this is usually intact, whereas in cardiospasm, it is disordered with numerous secondary and tertiary contractions. Air is rarely noted in the gastric fundus in cardiospasm; however, it is usually present in carcinoma. The air in the fundus of the stomach is especially helpful in outlining mucosal irregularities or the growth in the fundus. Depression, elongation, of the esophago-gastric junction is in favor of carcinoma. Slight flattening of one wall of the esophagus and eccentricity of the lumen are especially helpful.

A B

FIG. 10A. Adenocarcinoma of the lower third of the esophagus arising in an hiatus hernia.
FIG. 10B. Adenocarcinoma of the lower third of the esophagus arising in an hiatus hernia.

FIG. 11. Adenocarcinoma of the lower end of the esophagus arising from an hiatus hernia. The wall above the lesion is flattened and irregular and enters the stenotic segment eccentrically. Compare with Figs. 15A and 15B.

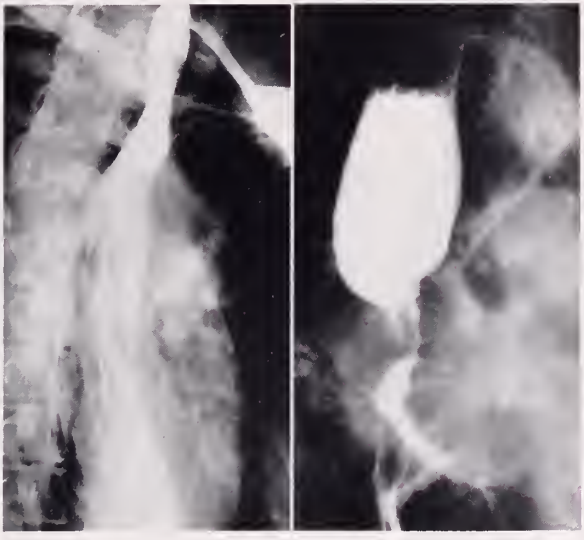
THE POST-OPERATIVE ESOPHAGUS

Operations upon the esophagus are increasing in frequency and it is important to differentiate the normal variations of such procedures from recurrent disease. The most common operation for esophageal carcinoma is subtotal esophagectomy and esophagogastrostomy with displacement of the stomach into the chest (Fig. 13A). The determination of the presence of recurrent cancer presents a difficult situation to the radiologist. For this reason, it is important to have a post-operative roentgen study as a baseline for subsequent examinations. The appearance of the anastomosis may vary from patient to patient, depending on the type of anastomosis employed and its location. Distortion of the mucosal pattern and intraluminal soft tissue masses secondary to suturing and inversion of the mucosa should not be confused with recurrent cancer. Again the most reliable sign of cancer is lack of distensibility, mucosal rigidity and mucosal ul-

A B

FIG. 12A. Adenocarcinoma of the fundus of the stomach extending into the lower end of the esophagus producing an appearance simulating cardiospasm. In this case, the fundal mass is conspicuous.

FIG. 12B. Adenocarcinoma of the stomach producing almost complete obstruction at the lower end of the esophagus.

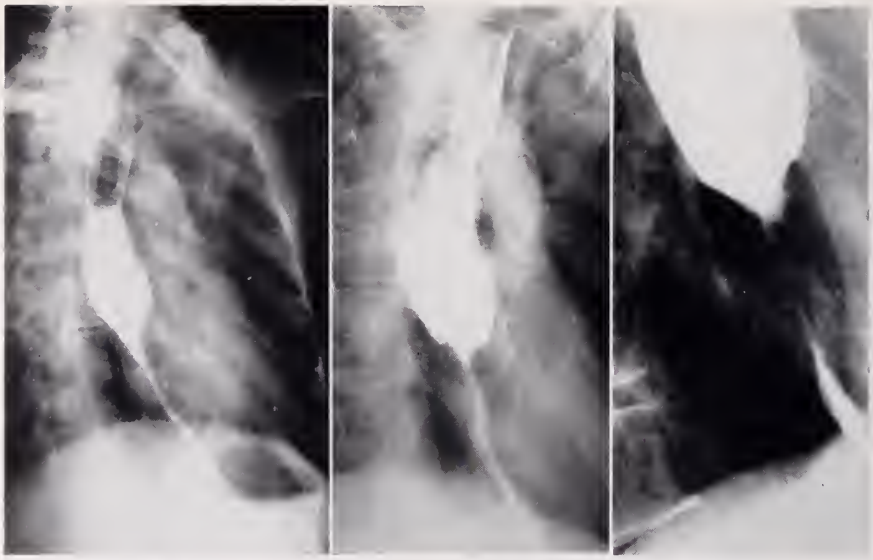


A B

FIG. 13A. Status post esophagogastrostomy.

FIG. 13B. Recurrent carcinoma at the stoma following esophagogastrostomy.

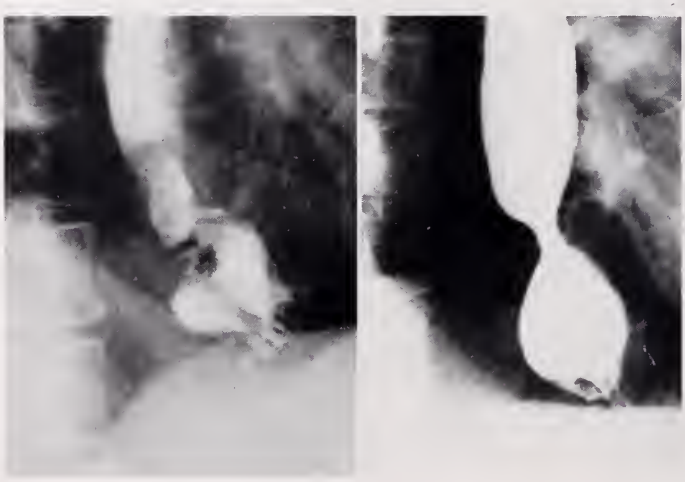
ceration (Fig. 13B). Changes in the appearance of the anastomosis from the initial post-operative study are significant in determining the presence of recurrent disease. Recurrent carcinoma outside of the esophagus is frequent and may be seen as isolated soft tissue masses or it may produce alterations in the contour of the lumen and course of the esophagus.



A B C

FIG. 14A. Peptic esophagitis with marked narrowing of the lower third of the esophagus. The lumen above is slightly dilated and enters the narrowed segment in a smooth, conical, fusiform manner.

FIG. 14B & C. Squamous cell carcinoma of the lower third of the esophagus with characteristic flattening and irregularity of the wall above the narrowed segment.



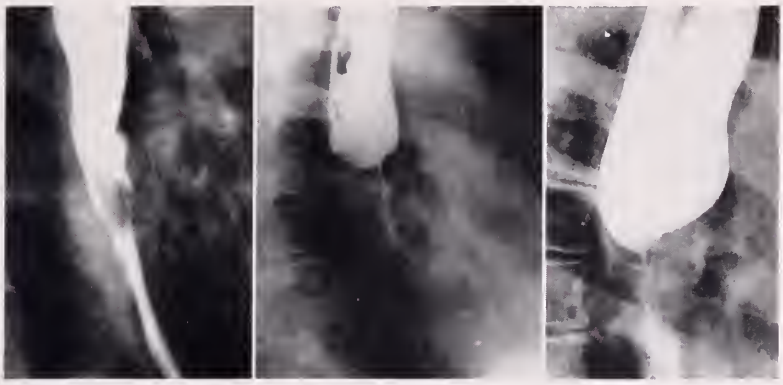
A B

FIG. 15A. Peptic ulceration of the esophagus. There is a large flat ulceration at the lower end of the esophagus above a small hiatus hernia. Biopsy of the upper end of the ulcer revealed esophageal mucosa and of the lower end, gastric mucosa.

FIG. 15B. Same case. One year later. There is now a stricture at the site of the previous ulcer. The esophagus above is slightly dilated and enters the stricture in a smooth, conical fashion.

DIFFERENTIAL DIAGNOSIS

Peptic esophagitis. There is a long segment of narrowing extending either to the cardia or to the apex of an hernial sac. The contour of the esophageal lumen is slightly irregular due to mucosal ulceration. The esophagus above is moderately

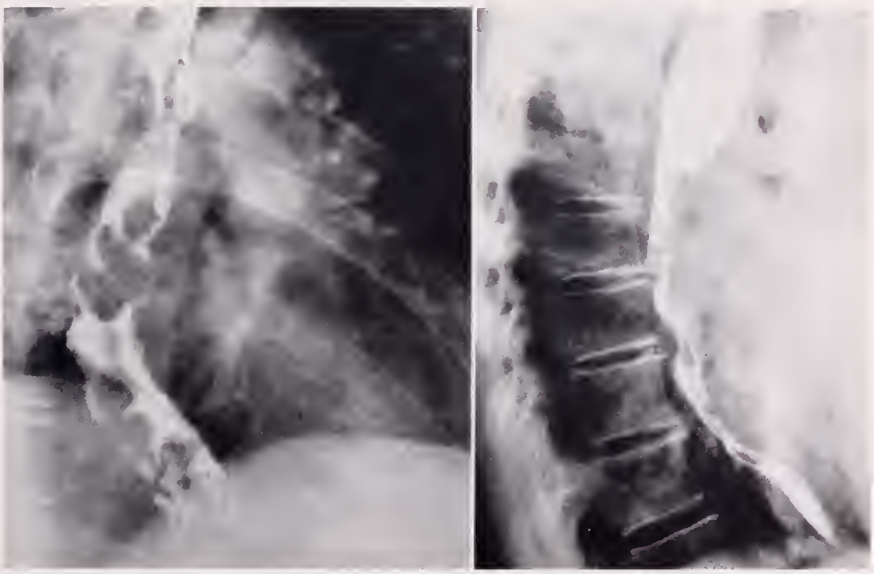


A B C

FIG. 16A. Prune pit caught within a lye stricture of the esophagus. A smooth filling defect is present within the lumen of the smoothly tapered lower third of the esophagus. On multiple projections, the wall of the esophagus was always intact suggesting that the defect was actually a foreign body within the esophageal lumen.

FIG. 16B. Corrosive stricture of the middle third of the esophagus simulating carcinoma.

FIG. 16C. Squamous cell carcinoma of the middle third of the esophagus with marked obstruction.



A B

FIG. 17A. Esophageal varices.

FIG. 17B. Lymphadenopathy due to metastatic hypernephroma. Note the upper and lower extremities of the compressed segment of esophagus suggesting varying degrees of involvement of the esophageal wall.

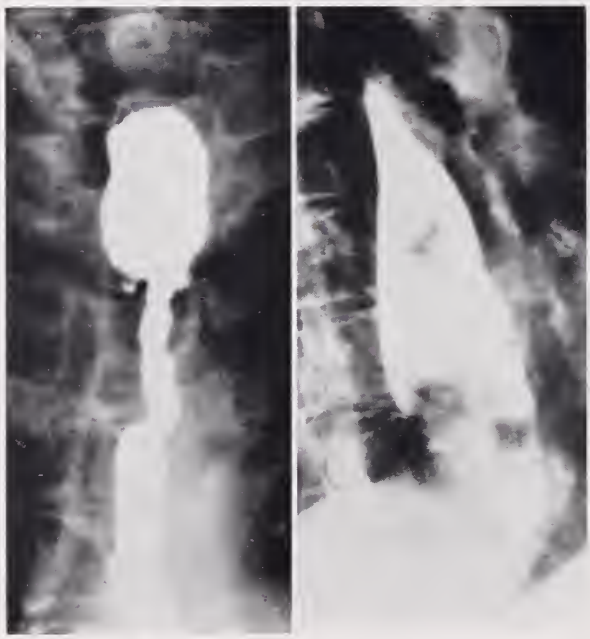
dilated and enters the narrowed segment in a fusiform, smooth, conical fashion. The presence of a duodenal ulcer or the history of intubation or prolonged vomiting are frequently associated with this condition (Fig. 14A).

Peptic ulceration of the esophagus. In this instance, an hiatus hernia is usually present above which there is a short stenotic segment of varying degrees of distensibility. A discrete ulcer may or may not be present. Regurgitation is easily demonstrated. The esophagus above may be dilated and enters the narrowed segment in a fusiform manner. Esophagoscopy is essential for confirmation of the diagnosis (Figs. 15A, 15B).

Stricture due to corrosive substances. These usually present a smooth segment of stenosis of varying length in the lower middle third of the esophagus. After healing a web may be seen. Luminal contours are smooth. There is no evidence of mucosal destruction. The wall of the esophagus proximal to the stenosis is distensible. The lumen is not eccentric (Fig. 16A).

Benign strictures of the esophagus of unknown etiology. These may occur anywhere in the esophagus and present roentgen characteristics similar to those described above (Fig. 8B).

Varices of the esophagus. These produce multiple intraluminal defects of varying sizes. The mucosa is intact and the esophageal wall is pliable and distensible. There is no obstruction. The margins of the esophagus may be smooth or scalloped. They are usually limited to the lower third of the esophagus (Fig. 17A).



A B

FIG. 18A. Cavernous hemangioma of the upper third of the esophagus. Roentgen diagnosis: carcinoma.

FIG. 18B. Melanosarcoma. Roentgen diagnosis: carcinoma. Lymphosarcoma was also suggested because of dilatation of the lumen in association with intraluminal masses.

Foreign body. Foreign bodies in the esophagus are only a diagnostic problem when they occur in association with a stricture in the lower esophagus and produce a radiolucent defect which may be interpreted as tumor. The fact that the defect can be completely encompassed by barium and no attachment to the esophageal wall can be demonstrated may identify its extraneous origin. (Fig. 16A).

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THE ROENTGEN DIAGNOSIS OF MINIMAL HIATAL HERNIATION

Motor Phenomena in the Terminal Esophageal Segment ("Vestibule")

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The esophagogastric region and the esophageal diaphragmatic hiatus which encircles it have been subjects of intense interest to numerous investigators (1–7). The purpose of this report is to describe and illustrate certain roentgen phenomena in this region associated with widening of the hiatus and weakening of its attachments to the esophagogastric region, i.e. hiatal herniation of the so-called pulsion or sliding type. With elevation of the terminal portion of the esophagus above the hiatus, it also becomes possible to study the special physiological properties of this region.

The roentgen method of investigation, including fluoroscopy, serial and spot radiography, permits visualization of dynamic phenomena under relatively physiological conditions. In the presence of a hiatal abnormality, a variety of appearances may be seen which are difficult to interpret because of the lack of fixed landmarks. The most important factors which determine and vary the appearance are the position of the patient, the nature of the barium mixture, the way the patient drinks or swallows, and the state of contraction of the diaphragm. A complete examination of this area is a time-consuming procedure. Most of the observations to be recorded have been made with the fluid barium mixture used routinely for gastrointestinal examinations, in the erect and recumbent positions. The supine or prone Trendelenburg position, with the stomach filled and the esophagus emptied of barium, has been utilized regularly to determine whether reflux or regurgitation of barium above the hiatus would occur. Another test for the presence of reflux—more severe, if well performed—is the maneuver described by Johnstone (8) in which the standing patient bends over as if to touch his toes while observations are made in the lateral projection of the region above the diaphragm. The Trendelenburg and Johnstone positions may be combined with deep inspiration and the Valsalva maneuver.

The roentgen diagnosis of minimal hiatal herniation would be quite simple if (a) the hiatal ring could be visualized, and (b) if the Z line or ora serrata, i.e. the esophagogastric mucosal junction, or the cardia, i.e. an abrupt transition between tubular esophagus and sacculated stomach, could be identified. Unfortunately, none of these basic landmarks can be recognized with certainty. There is no contrasting air or fat within the hiatus necessary to permit visualization of its borders. The application of opaque clips to the esophagogastric mucosal junction through the esophagoscope has demonstrated the uncertainty of roentgen identification of this junction (8). Under normal circumstances (Figs. 1A, 1B), thick longitudinal folds in the hiatus are esophageal and often can be followed without discontinuity (Fig. 2) into linear folds along the lesser curvature of the stomach. There is evidence that the mucosal junction may spontaneously

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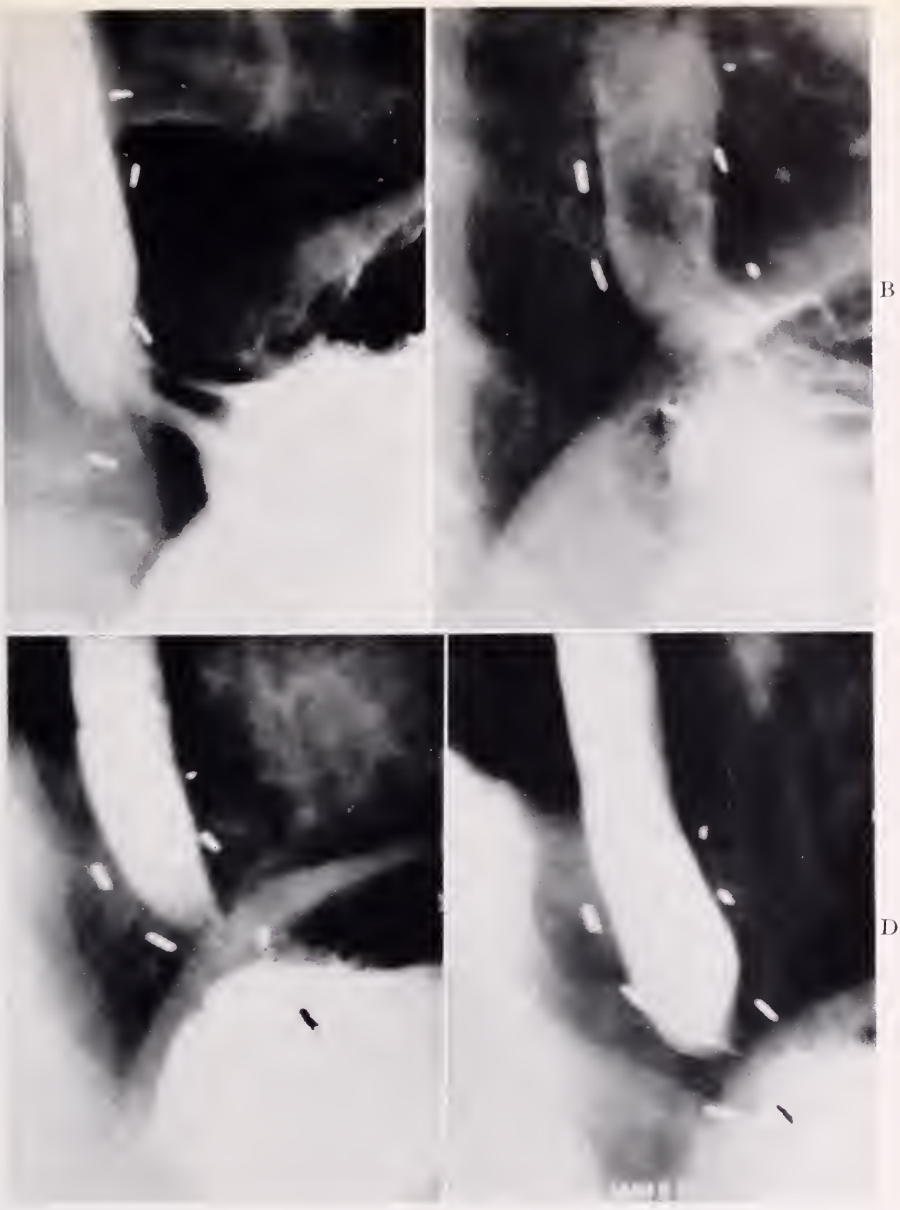


FIG. 1. This patient, 26 years old, presented himself after a transthoracic vagotomy with three opaque clips on each side of the esophagus down to the hiatus.

FIG. 1A. Erect, P. A. The marked obliquity of the hiatus is indicated by the relative levels of the distal clips—the left is about 1.5 cm. higher than the right. The left contour of the distended suprahiatal esophagus shows the impression of the adjacent portion of the diaphragm. The hiatal channel begins at this level and is angulated towards the left to correspond with the obliquity of the hiatus. At a later date, an opaque clip placed at esophagoscopy on the esophagogastric mucosal junction was located at the *distal* margin of the thick linear folds seen in the hiatal channel.

FIG. 1B. Prone view, left side elevated; shortly after esophagoscopy. Opaque clip placed on the proximal margin of gastric rugae was clearly within the fundus of the stomach.

FIG. 1C. Erect, right oblique; successive spot views taken with fixed level of spot device shows that all of the clips descended on inspiration about 2 centimeters. The distance between individual clips increased slightly if at all. Similar phenomena were noted in the prone position, the excursion of the clips being somewhat greater. There is no evidence of slippage or sliding through the hiatal ring. Incidentally, first film shows momentary delay above the hiatus which is often evident normally independent of inspiration and suggests "tonic" contraction in the distal esophagus a short distance above the hiatus.

FIG. 2. Normal esophagogastric region: patient is prone with left side elevated, drinking fluid barium continuously and as rapidly as possible. This is a "right anterior oblique projection" with the over-the-table tube and a "left posterior oblique" projection with the fluoroscopic tube. The suprahiatal portion of the esophagus is most distensible and shows a distinct transition to a narrower "hiatal channel" of rather uniform calibre containing two or three linear folds. The superior margin of the "channel" corresponds to the level at which the esophagus ceases to be subject to intrathoracic pressures, i.e. to the superior margin of the hiatus. The cardiac orifice or "cardia" cannot be identified with exactness.

change its relationship to the cardia (4, 9). The cardia, when normally located, is occasionally quite evident, especially with mucosal studies (10). However, the normal junction of the esophagus with the stomach is somewhat funnel-shaped and the amount of stomach contributing to the funnel may depend on the degree of distention of the fundus. In the presence of minor herniation of the sliding type, the cardia is unrecognizable and an apparent "cardia" may be deceptive (7). In the absence of direct demonstration of the basic landmarks, roentgen evidence of hiatal abnormality must be indirect.

The terms "level" or "plane" of the hiatus are not easy to define anatomically. The normal hiatus is said to be funnel-shaped (11) with its margins rolled or inverted downwards, producing a short canal rather than a simple ring. In the presence of herniation, the margins may be everted and difficult to define and may not lie in a single plane. Moreover, the hiatal opening is normally markedly oblique (Fig. 1A), highest on its left and anterior aspects. The "level" of the hiatus is therefore not an unequivocal term and depends on the point of view of the observer. It is therefore often necessary to speak of the "region" rather than the "level" of the hiatus.

The determination of the location of the region of the hiatus by roentgen methods depends on visualization of adjacent structures and demonstration of the "pinchcock" action of the diaphragm. This pinchcock action is a striking

phenomenon roentgenologically. The esophagogastric region is visualized by having the patient drink continuously and rapidly. When the patient takes a deep breath, the barium column in the region of the hiatus suddenly narrows and becomes obliterated if inspiration is sufficiently deep (Fig. 3). The barium trapped in the esophagus collects above the hiatus in a somewhat pear-shaped

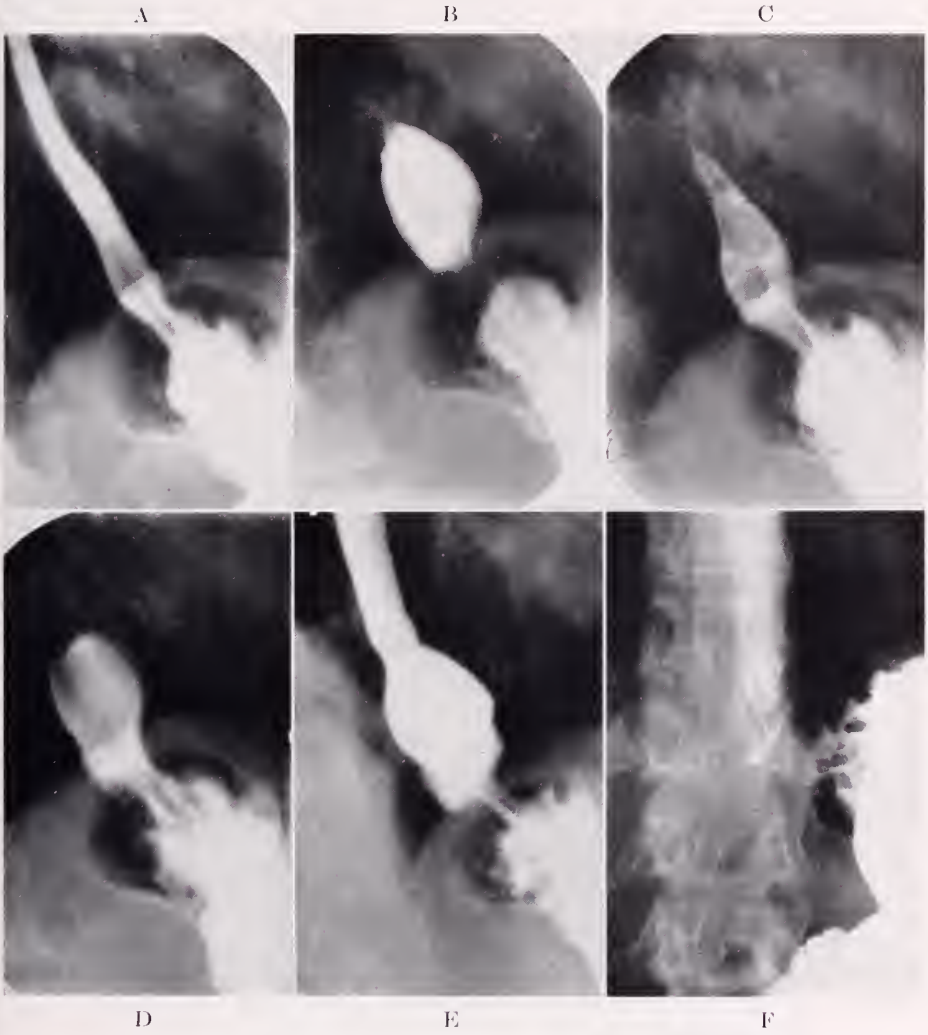


FIG. 3. Patient, 50 years old, with minimal complaints.

FIG. 3A, 3B, 3C, 3D are successive prone spot views—A, continuous swallowing; B, inspiration; C and D, during expiration. The varying width and relatively constant length of the hiatal channel can be seen as well as the fact that the pinchcock action occurs throughout the same area. In D, the width of the hiatal channel appears slightly wider than the "perfect" normal.

FIG. 3E. Also prone but patient was drinking more rapidly; small sac (?) above hiatus.

FIG. 3F. Residual barium in small sac above hiatus. The appearance of these folds is not helpful in identifying their location. In fact, the proximal portion of this sac may be esophagus and the distal part stomach. (see Fig. 18).

configuration, the "phrenic ampulla". The size of the phrenic ampulla and the location of its neck depend on the amount of residual barium in the esophagus. The presence of the phrenic ampulla signifies only that the suprahiatal portion of the esophagus is normally distensible. The constriction that appears below the ampulla during inspiration usually measures about two centimeters in length and is considerably greater than the thickness of the diaphragmatic musculature. Moreover, with a normal hiatus, a segment of the same length remains relatively narrowed with the diaphragm relaxed. The "region" of the hiatus anatomically appears to correspond to a "range" of action of the hiatus functionally. The term "hiatal channel" is suggested for this region or range of action of the hiatus as demonstrated by the area of narrowing in the barium column. Used in this fashion, it is a term of reference applicable to the hiatus and is independent of the particular viscus, i.e. esophagus or stomach, which may occupy the area. Even in the presence of sizeable hernias, an area of narrowing in the region of the hiatus persists (Figs. 4, 9).

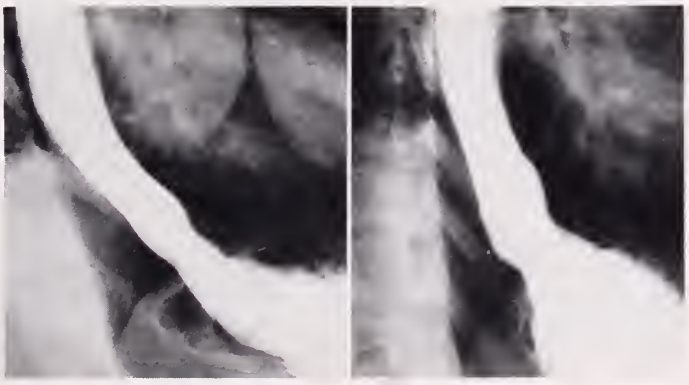
Under normal conditions, the viscus in the hiatal channel is the terminal portion of the esophagus, in both the erect and recumbent positions (Figs. 1A, 1B). There does not appear to be any significant slippage or sliding of the esopha-

FIG. 4. In this patient, at laparatomy primarily for duodenal ulcer, a hiatus hernia with a peritoneal sac admitting 3 or 4 fingers was found and "repaired". Two opaque clips were placed on the anterior border of the hiatus and a third clip distally on the peritoneal reflection at the "junction of esophagus and stomach". The roentgen findings, except for clips, were the same pre- and post-operatively. With the diaphragm relaxed, the hiatus was markedly widened. On inspiration, the hiatal channel is seen to begin distal to the proximal two clips and to include the distal clip. Incidentally, narrowing at the neck of this sac was persistent and free regurgitation was present pre- and post-operatively. At esophagoscopy, a mild esophagitis was noted.

gus through the hiatus on deep inspiration (Fig. 1C). It is possible that, with loosening of the hiatal fascial and peritoneal attachments, a small amount of sliding does occur when intraabdominal pressure is increased. A small suprahiatal sac which seems to appear only in the Johnstone position (Fig. 17B) may be explained on this basis.

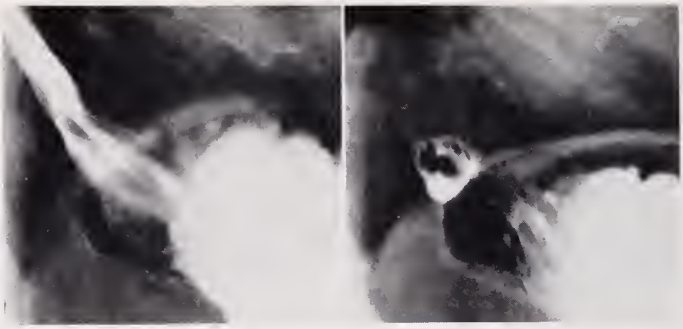
While the pinchcock action of the diaphragm is easy to demonstrate, it is of little use for diagnostic purposes. In instances of minimal herniation, the pinchcock appears to be normally effective. Occasionally, in such instances, if excellent filling can be obtained, i.e. if the patient drinks rapidly, the pinchcock may demonstrate a small sac above the hiatus (Fig. 3E). Occasionally, it appears that the hiatal channel or pinchcock action is unusually long and elevated but these changes are difficult to judge because of the wide range in normal cases. For diagnostic purposes, observations of the maximum diameter of the barium column in the hiatal channel are much more valuable. An effort must be made to obtain complete filling of this area by directing the patient to drink rapidly and continuously (Figs. 5A, 5B). In patients who cannot accomplish this, spot films in expiratory phases (Fig. 3D) may be required. Since the width of the hiatus must be greater than the maximum diameter of the barium column, an abnormally wide barium column in this region is indicative of an abnormally wide hiatus. If the width of the barium column in the hiatal channel is similar to the width of the barium column above the hiatus, the hiatus is abnormally wide. Of course, a hernial sac above the hiatus may be much more distensible than the limited widening of the hiatus. With a little experience, however, it is not difficult to recognize widening of the hiatus (Figs. 6A, 10B, 11A, 16A), particularly since small differences are of little significance. The usual criteria may not apply to the special physiological phenomena which occur during vomiting or belching. Under these circumstances, active paradoxical relaxation of the crural portion of the diaphragm may conceivably occur to distort the normal relationships.

The demonstration that the hiatus is abnormally wide does not per se indicate the extent of herniation which may be present. It may be impossible in some of



A B

FIG. 5A, 5B. Two cases showing different degrees of widening of the hiatal channel. Patients are prone, left side elevated drinking continuously and rapidly.

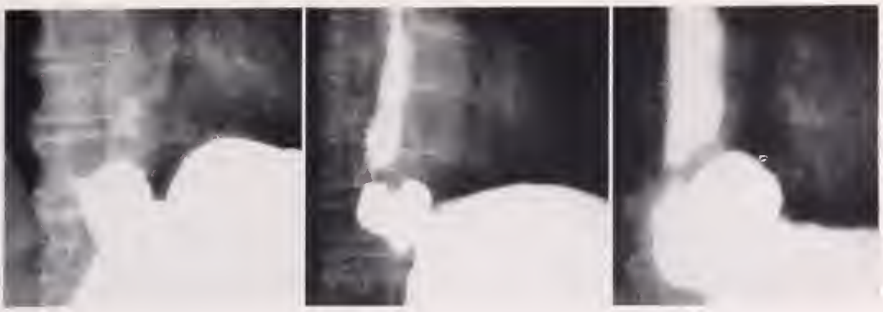


A B

FIG. 6A. Patient with wide hiatus and triangular sac with diaphragm relaxed.
FIG. 6B. Residual barium shows a bell-shaped sac with tortuous, scalloped folds above the hiatus. Folds such as these can be identified as gastric.

FIG. 7. Patient with crossing folds, i.e. gastric rugae, in a widened hiatal channel. A gastric sac above the hiatus might not be present in such a case unless intraabdominal pressure is increased. The elevation of the esophagus entirely above the hiatus is, however, indicative of herniation.

these cases to demonstrate a sac with a "neck" above the hiatus even though, by other evidence, e.g. esophagoscopic or surgical, it is known that herniation of significant degree, five to six centimeters, is present. In some instances, visualization of the mucosal pattern (Figs. 6, 7) may be sufficiently convincing to indicate the extent of herniation. In other cases, the filling of a sac by reflux (Fig 8A) may serve the same purpose. In others, the motor phenomena (Figs. 10, 11) characteristic of the terminal esophagus are helpful.



A B C

FIG. 8. Three examples of reflux in Trendelenburg position.

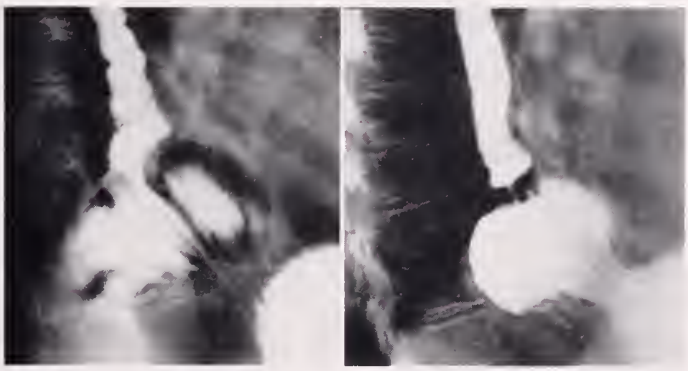
FIG. 8A. Wide short hiatal channel with reflux into small sac and no reflux into esophagus. Projection on right corner of superior margin indicates location of terminal esophagus.

FIG. 8B. Limited reflux into esophagus through persistent short narrowed segment in terminal esophagus.

FIG. 8C. Free reflux into esophagus but constriction in terminal esophagus persists.

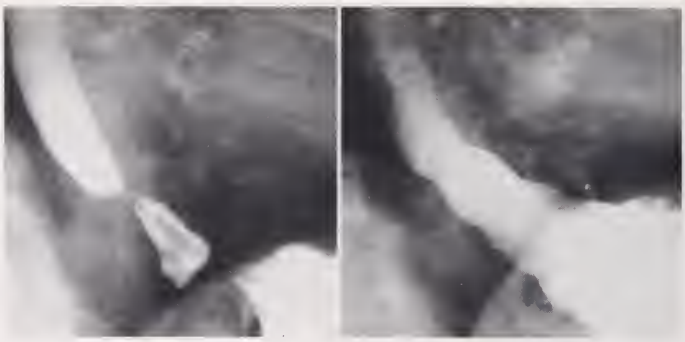
Findings such as these indicate sphincteric action in the terminal esophagus which plays a rôle in prevention of reflux. It is not possible, however, to determine whether the entire terminal esophageal segment is contracted or only its distal part ("constrictor cardiae"?).

An an introduction to the motor phenomena in the distal esophagus, it is instructive to study the appearance seen during reflux in the Trendelenburg and Johnstone positions. Reflux occurring in these positions must be considered abnormal and indicative of hiatal herniation. However, in some instances of both small and large hernias, barium fails to enter the esophagus from the hernial sac or enters it to a limited degree through a short narrowed channel located in the most distal, i.e. terminal, portion of the esophagus (Fig. 8). Even in the presence of free reflux into the esophagus, a constricted segment of the same character may persist. During normal swallowing in these patients, transient localized contractions, 0.5 to 2.5 centimeters in length, in the same region may be seen (Figs. 9–11). In a sense, the term contraction may not be accurate since the



A B

FIGS. 9A, 9B. Patient with large hiatus hernia; successive polygraph views. Transient localized contraction in terminal esophagus. In other films, the contracted segment showed a variable width but a similar length. Hiatal channel persists, though widened and elongated. No regurgitation into the esophagus occurred in the Trendelenburg position.

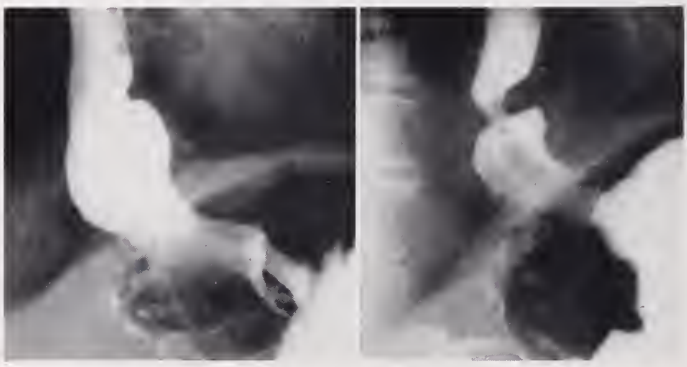


A B

FIGS. 10A, 10B. Successive polygraph views of patient with wide hiatus.

FIG. 10A. Short localized transient contraction in distal esophagus; conical configuration of barium column proximal to narrowing is characteristic.

FIG. 10B. Contraction has disappeared; slight shallow bilateral indentations at level of previous contraction. Hiatus is unusually wide but the size of the hernia cannot be easily evaluated.



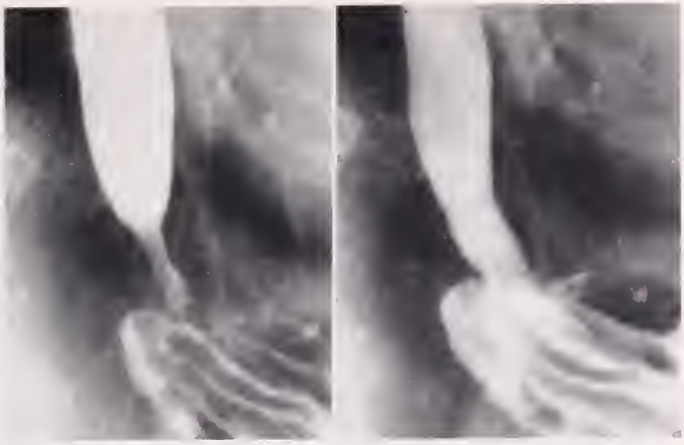
A B

FIGS. 11A, 11B. Successive polygraph views.

FIG. 11A. Wide hiatus, somewhat saccular dilatation above the hiatus.

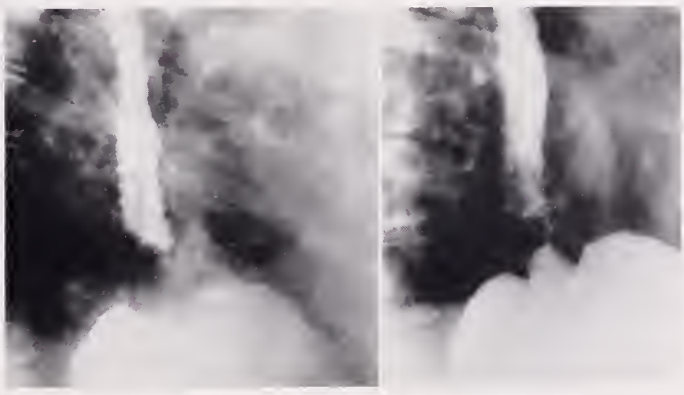
FIG. 11B. Localized contraction in terminal esophagus indicates that saccular dilatation is a hernial sac. Next film of polygraph series was identical to Fig. 11A.

phenomenon often appears to be a physiological delay in relaxation of a normally contracted segment. A slight hardly noticeable delay to the passage of barium may occur normally just above the level of the hiatus (Fig. 1C). With herniation, the delay occurs at a higher level (Fig. 18D) and the esophagus distal to this point may remain partially contracted for a short time. In a given patient, the length of this segment with independent ability to contract, or to fail to relax, appears to be fairly constant (Fig. 12). At times, however, the esophagus proximal to this region seems to share in the contraction. Moreover, when distended from below by reflux, the distal portion of the terminal esophageal segment may relax prior to its proximal part (Fig. 13). There is no doubt about the dynamic nature of this type of constriction since it is transient, not constant in calibre, extends over a significant length, narrows the lumen and the barium column proximal to it has a short funnel configuration. A slight concentric indentation may persist at the proximal margin of the terminal segment (Fig. 4, (10, 12)).



A B

FIGS. 12A, 12B. Example of long terminal esophageal segment.
FIG, 12A. Contracted segment.
FIG. 12B. Relaxed terminal segment; faint indentations at proximal margin persist.



A B

FIGS. 13A, 13B. Patient with large hiatus hernia.
FIG. 13A. Long contracted terminal segment seen during swallowing of barium.
FIG. 13B. Oblique Trendelenburg position; deep inspiration was required to produce reflux into the esophagus. Distal portion of terminal segment relaxed prior to the proximal portion.

The phenomena in the distal esophagus described so far have been relatively simple. A terminal esophageal segment about two centimeters in length, which remains tubular when distended and which may contract as a whole or only in its proximal portion is demonstrable in cases of hiatal herniation. This segment serves to a limited degree to prevent regurgitation into the esophagus and may cause transient delay during normal swallowing. If, during swallowing, a contraction persists in this segment, an additional complication such as esophagitis (Fig. 4) or scleroderma (Fig. 14) must be suspected. There is, however, another type of concentric, circular indentation, sulcus or fold, in the distal esophagus which, in a marked form, has been referred to as a "contractile ring" (12) or as a "lower esophageal ring" (13). A circular fold of this type, in its most char-

acteristic form, appears as a short, sharply demarcated shelf which is seen consistently whenever the esophagus is distended. In profile, the indentations caused by the circular fold are sharp and rectangular and have been referred to as "notches" (5). The lumen of the esophagus is rarely narrowed by these folds. In two reported cases (12, 13) operated upon because of dysphagia, the rings were found in the distal esophagus and small hernias were also present. Figures 15 and 16 illustrate two cases in which the available information confirms the esophageal location of such circular sulci. In these cases, hiatus hernias were also present. Circular sulci or notches which are not as sharp or rectangular as those described above, occur rather commonly and presumably represent the same phenomenon. The nature of these sulci is unknown. It has been stated

FIG. 14. Case of scleroderma with narrowing of terminal esophageal segment. This narrowing was constant in two examinations and changed only slightly in calibre.

that they may be normal structures. While this may be so, their presence above the hiatus, in the author's experience, has been indicative of hiatal herniation of minimal degree (Fig. 17).

A persistent circular sulcus or notch may be present in addition to a transient localized contraction occurring a short distance proximal to the sulcus, giving the appearance of a double sac (Fig. 15C). In many cases with notches, the terminal esophageal segment appears unusually long. Contraction may occur throughout the entire segment including the level of the sulcus, thereby obliterating it (Fig. 16B). More commonly, however, the distal portion of the terminal segment appears unusually distensible (Fig. 15A) and residual barium may remain in the distal esophagus and the associated hernia for some time. A "double sac" appearance may also be seen as a functional phenomenon without a per-

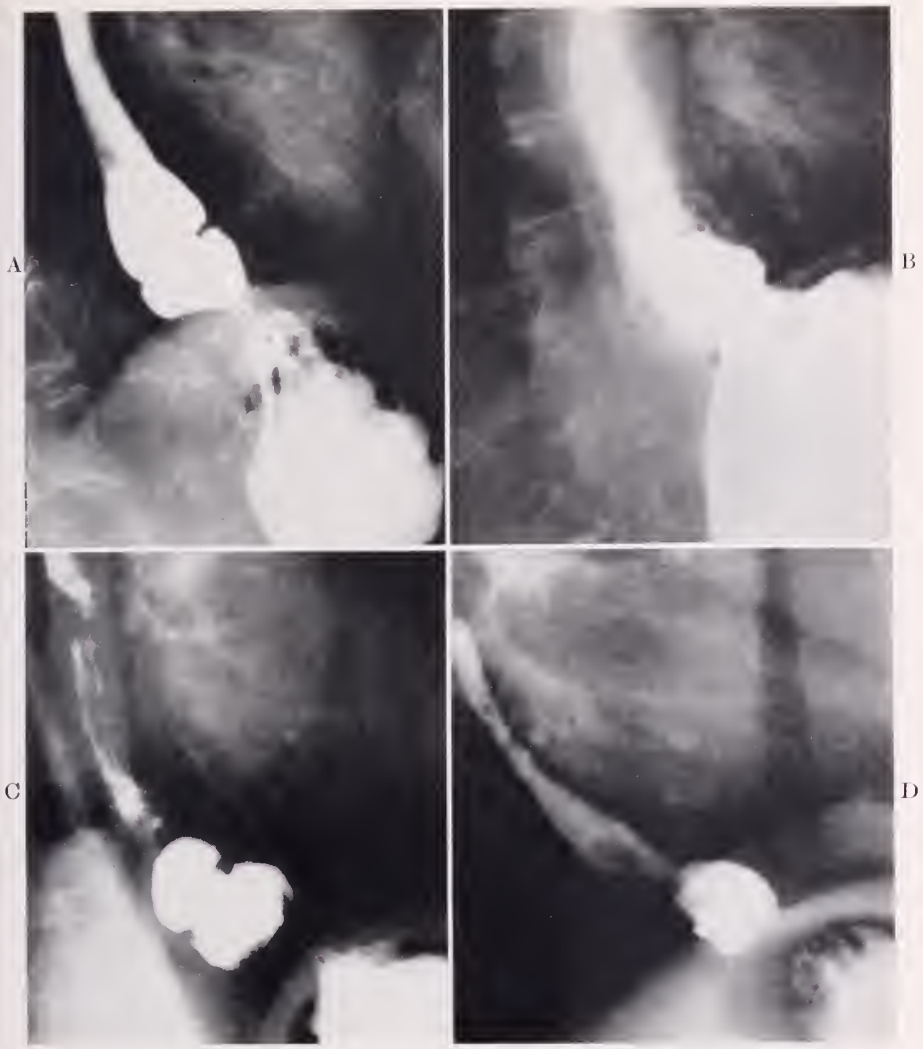


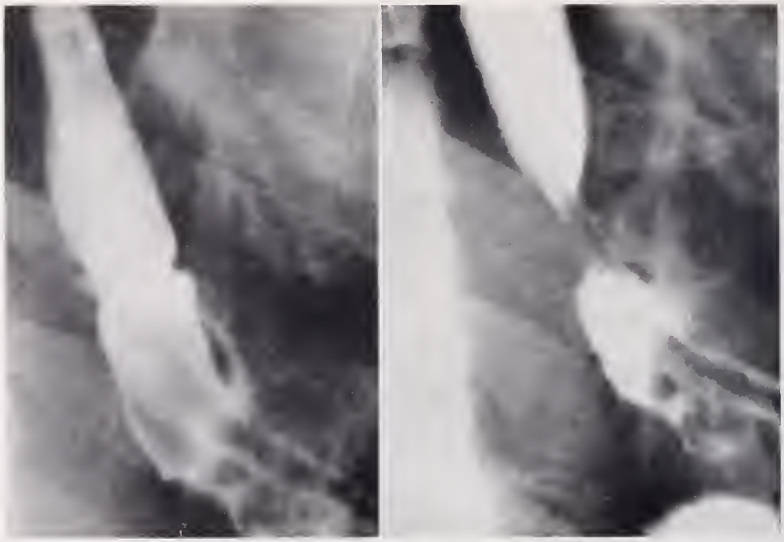
FIG. 15. Patient with a circular sulcus or fold in the distal esophagus.

FIG. 15A. During first examination, the circular sulcus ("notches") was constantly seen in the same location and no "neck" or constriction occurred proximal to it.

FIG. 15B. Free regurgitation occurred in the Trendelenburg (and Johnstone) positions.

FIG. 15C. Re-examination two hours after esophagoscopy shows a double-sac configuration due to persistent localized contraction about 0.5 cm. in length in the distal esophagus. Remainder of esophagus was also irritable. The length and width of the sac between the localized contraction and the notches varied remarkably, in contrast to the distal portion. The anterior notch appears broader and not as deep as on the first examination. On esophagoscopy, the esophagogastric margin was found at 35.5 cm. from the incisor teeth. Assuming a minimum normal distance of 38 cm. for this small patient, a hiatus hernia of 2.5 cm. was present.

FIG. 15D. At a subsequent esophagoscopy, an opaque clip was placed on the esophagogastric margin. Notches were not seen during this examination but the relationship of the clip to the sac indicates that its proximal portion is esophageal and its distal part gastric.



A B

Fig. 16. Patient with circular sulcus in distal esophagus, hiatus hernia and free reflux.

Fig. 16A. Sulcus broadens posteriorly into flat indentation with projection in its center.

Fig. 16B. Terminal esophageal contraction includes the level of the sulcus.

Esophagoscopy in this patient showed the esophagogastric margin at 34 cm. from the incisor teeth. A short distance proximal to the esophagogastric margin on the right posterior wall, there was a fibrous scar with mucosal thickening. This appears to correspond to the projection seen in Fig. 16A and therefore to the location of the circular sulcus as well.

A B

Fig. 17A. Notch is seen posteriorly a short distance above the hiatus; notch anteriorly is obscured.

Fig. 17B. In Johnstone position, regurgitation occurred and a small sac above the hiatus was seen.

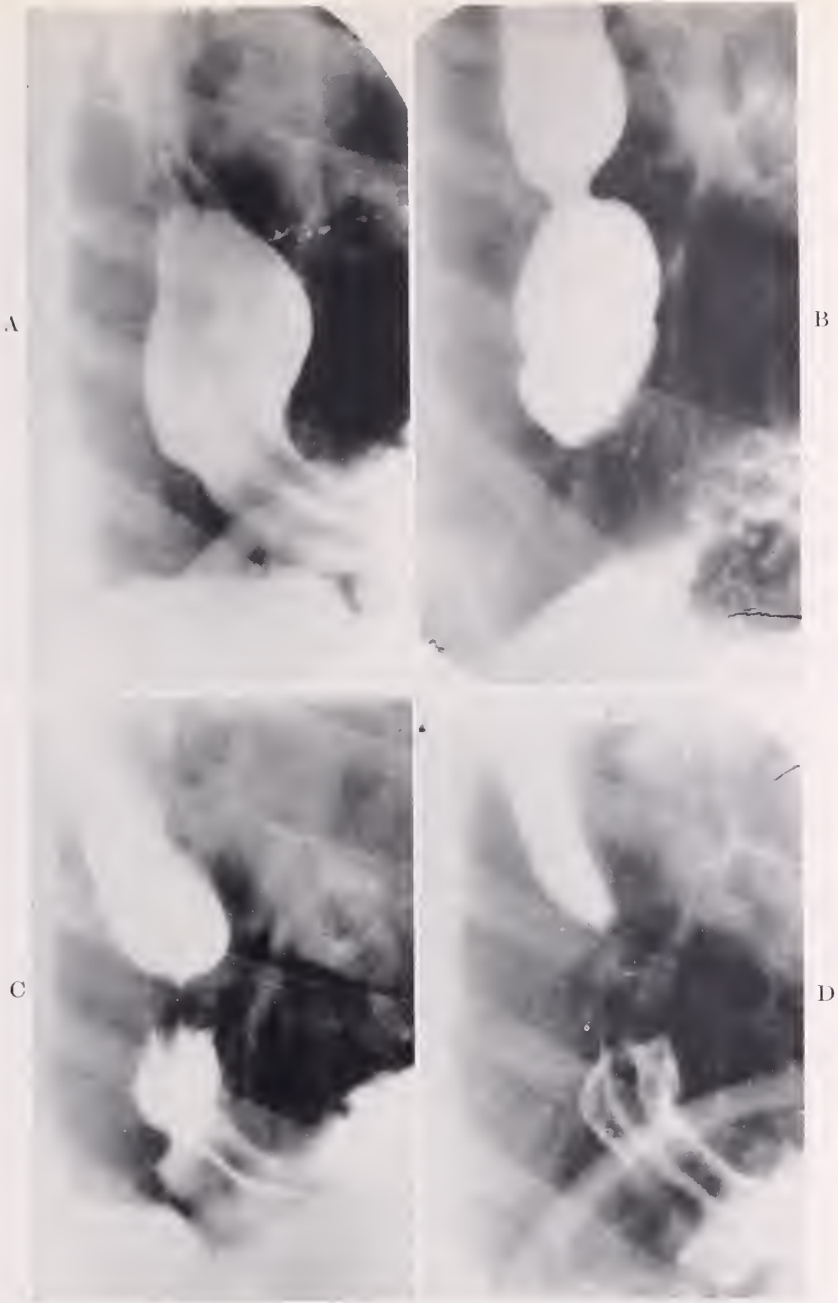


Fig. 18. Multiple spot views, in prone position, of patient with small hiatus hernia.

Fig. 18A. Wide hiatus with elongated saccular dilatation above.

Fig. 18B. Localized contraction in distal esophagus with shallow ring around sac giving a double sac appearance; pinchcock action is completely effective.

Fig. 18C. Distal portion of sac is partially emptied; proximal portion of the sac is shorter and the localized contraction proximal to it longer than in Fig. 18B but the sum of the two parts appears about the same 18D.

Fig. 18D. Residual barium in distal portion of previously seen double sac; long contracted segment replaces proximal portion of sac as well as the previously seen localized contraction.

A B

FIG. 19A. Inconstant circular sulcus in distal esophagus.

FIG. 19B. Same examination; localized contraction which appears to be at the site of the sulcus seen in Fig. 19A. The appearance of the contraction suggests that it is in the proximal portion of the terminal esophageal segment. The suggestion of a double sac confirms this impression.

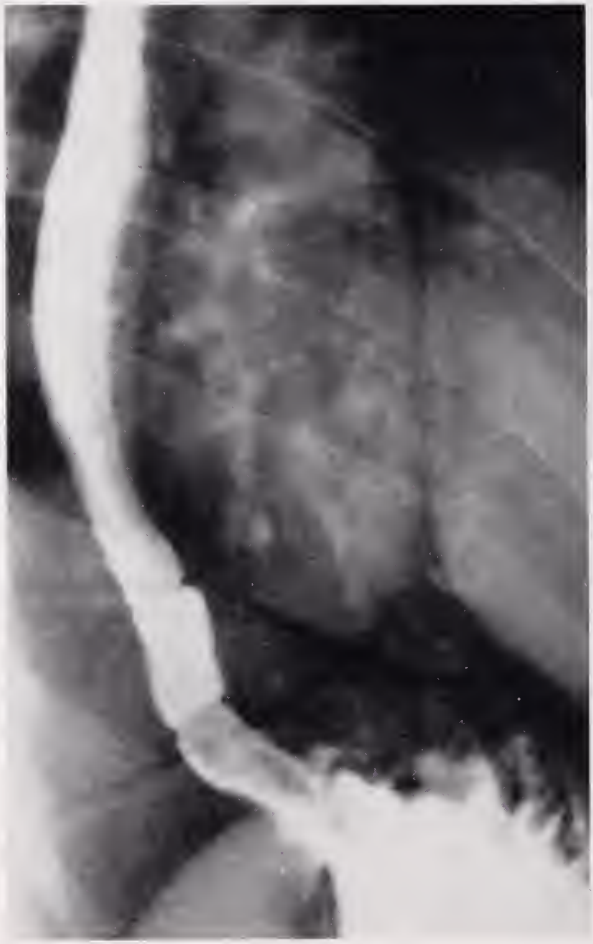
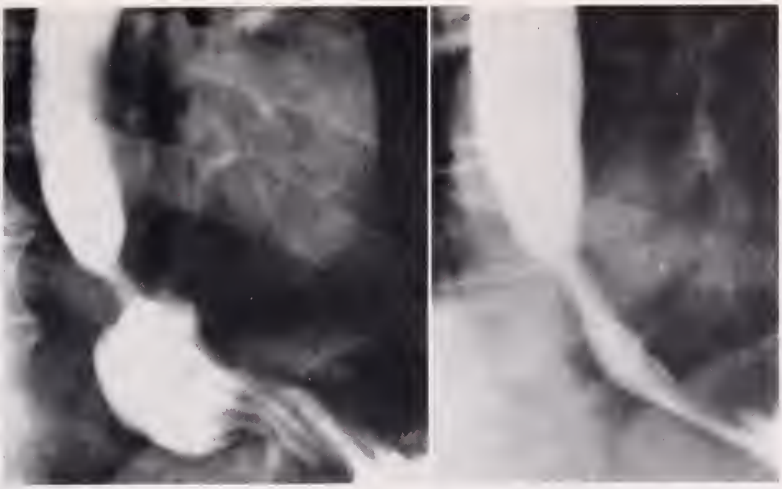


FIG. 20. Case with two circular sulci and widened hiatus.



A B

FIG. 21. Patient with hiatus hernia, duodenal ulcer and probably minimal esophagitis.

FIG. 21A. Prone position shows a widened hiatus and contraction of terminal esophagea segment.

FIG. 21B. In the erect position, the terminal esophageal segment can be identified intervening between the wider esophagus above and the elongated hernial sac below. In other cases, only a slight circular indentation at the proximal margin of the terminal segment may be seen in the erect position and raise the suspicion of herniation.

A B

FIG. 22A. Idiopathic cardiospasm of many years duration; diagnosis confirmed at necropsy. A small hiatus hernia is also present. Short obstructive localized contraction in the proximal portion of the terminal esophageal segment followed by a plate-like distended area and a circular sulcus. There is a remarkable resemblance of this film to the anatomical dissection of a case of cardiospasm illustrated by Lerche (4). In this specimen, the vestibule is described as "reduced to a shallow groove because it is contracted in its long axis" and the "constrictor cardiae" lies under cover of the mucosa of the vestibule immediately proximal to the Z line.

FIG. 22B. An asymptomatic patient with a vestibular configuration similar to Fig. 22A—a localized contraction of the type usually seen in the proximal portion of the terminal esophageal segment, a circular sulcus a short distance distal to this and a hiatus hernia. These two cases in conjunction with the specimen described by Lerche suggest that a circular sulcus in the distal portion of the terminal esophageal segment is related to the presence of the "constrictor cardiae" above the esophagogastric mucosal junction. A sulcus in the proximal portion (Fig. 19) may be related to the inferior esophageal sphincter.

sistent circular sulcus (Fig. 18). One gains the impression that, in some individuals, the terminal esophageal segment is unusually long and unusually distensible and that, when this obtains, a circular fold may appear in its distal portion immediately proximal to the esophagogastric margin. However, a circular sulcus less marked and less constant, may persist at the proximal margin

FIG. 23 A, B, C, D. Successive polygraph views of a patient with dysphagia for many years due to cardiospasm. On the conventional films, the esophagus was markedly dilated throughout its entire length. At the lower end of the esophagus, a small sac of variable shape and size is produced by a localized contraction of variable length proximally and a narrowed segment in the hiatal channel distally. This sac presumably corresponds to the vestibule. The narrowed segment in the hiatal channel was about 2 cm. in length, was completely obliterated in inspiration, increased to only about 5 mm. in width and remained the same length with the diaphragm relaxed. On the basis that the suprahiatal sac is the terminal esophageal segment, the persistently narrowed hiatal channel suggests that spastic changes also involve the "constrictor cardiae" and a portion of the stomach.

of the terminal esophageal segment (Fig. 19) and one case has been observed with two circular sulci (Fig. 20). Notches are not seen with large sacculated hernias but a circular collar at the cardia (Fig. 13B) is often present which may be of similar nature.

The findings described above are based essentially on observations made with the patient recumbent. In the erect position (Fig. 21), similar phenomena presumably occur but are difficult to identify because the barium passes through the esophagus with great rapidity. Moreover, a small hernial sac in this position is usually elongated and distends less than the esophagus above. A "false" cardia is thus often present in such instances. However, certain observations may occasionally be made which suggest the presence of minor herniation. A faint indentation in the barium column above the hiatus may be noted and there may be slight delay at this level. This level corresponds to the proximal margin of the terminal esophageal segment and this segment as a whole may distend less than the esophagus proximally.

Additional information about motor phenomena in the terminal esophagus may be obtained from cases that show unusual irritability or spastic changes. In idiopathic cardiospasm, the esophagus is usually elongated as well as dilated and the esophageal hiatus is unusually low in position. Figure 22A illustrates a case of idiopathic cardiospasm and a hernia with several points of interest. The narrowed obstructive segment in this case appeared to be considerably shorter than in the usual case of cardiospasm with a relatively long narrowed segment in the hiatal channel. This additional length in the usual case may signify that contraction of the proximal portion of the stomach also plays a rôle in cardiospasm. The same possibility is suggested by the findings in another case of cardiospasm (Fig. 23) in whom, however, the evidence for herniation is not conclusive. The question whether widening of the hiatus, associated with atony of the terminal esophageal segment and regurgitation, may occur on a functional basis and be transient is raised by the syndrome of "cardio-esophageal relaxation" or "chalasia" in infants. In this condition, it is said that regurgitation may disappear in three or four weeks. It remains to be proved, however, that anatomical abnormalities, specifically herniation or a short esophagus of congenital nature, are absent in these instances.

DISCUSSION

Applying strict criteria for the normal width of the hiatus and the specification that the normal location of the terminal esophagus is in the hiatus results in the recognition of a large number of cases of minimal herniation. One may prefer to consider minimal herniation as part of the normal ageing process and therefore within physiological limits. Simple displacement of the terminal esophagus above the hiatus with a cuff of stomach lying in the hiatal channel may reasonably be called a prehernial stage rather than an actual hernia. Anatomically, however, no sharp line of demarcation is possible. It has been suggested that the diagnosis of hiatal herniation should not be made unless regurgitation can be demonstrated (5). Unfortunately, however, regurgitation may be present during one examina-

tion and not on a subsequent examination. To a certain degree, the demonstration of regurgitation also depends on the persistence of the examiner and the number of maneuvers he utilizes, as well as on the coöperation of the patient in performing these maneuvers. Moreover, an occasional patient is seen with no demonstrable sac above the hiatus who nevertheless shows free regurgitation. Functionally, therefore, there is also no sharp line of demarcation. To avoid inconsistencies, it seems advisable to consider all deviations from the perfectly normal status as herniation. Other names such as "epiphrenic bell" or "hiatal insufficiency" or "cranial dystopia of the cardiac antrum" suggest that a special syndrome is present. However, unless the clinician realizes that minimal hiatal herniation is rarely the cause of significant symptoms, it may be wise to avoid the term hiatus hernia in cases without easily demonstrable sacs and to speak of "widening of the hiatus" with or without regurgitation. Small hernial sacs in general are of very limited clinical significance. Such a patient may complain of heartburn or occasional substernal discomfort or sticking of food presumably due to temporary spasm in the terminal esophagus. Severe bleeding is rare. These patients may develop a severe esophagitis if a duodenal ulcer is present, as a result of vomiting or intubation, or subsequent to a laparotomy under general anesthesia. A small number are also presumably susceptible to localized ulceration in the terminal esophagus but these may be individuals who have, in addition, heterotopic gastric epithelium in the distal esophagus.

Because of the independent physiological properties of the distal two to three centimeters of esophagus, the name "terminal esophageal segment" has been used for this region in the descriptions given above. It is likely that this segment is equivalent to the "vestibule" as described by Lerche (4). The proximal portion of this segment which also appears at times to contract or remain contracted independently of the distal part would then correspond to the "inferior esophageal sphincter" of this author. It has been difficult, however, to obtain convincing evidence that circular contraction of the distal portion of this segment occurs independently of contraction of the segment as a whole. It would appear that the action of the "constrictor cardiae" is such an integral part of the functioning of the terminal segment that isolated contraction of the muscle bundles comprising this structure (4) is not evident except perhaps in some cases of cardiospasm (Figs. 22, 23). The esophagoscopic observations of Som (14) indicating the presence of a physiological contraction, the "rosette", about two centimeters proximal to the beginning of gastric rugae and an intervening channel lined by squamous epithelium are also consistent with the description of the inferior esophageal sphincter and the terminal esophageal segment, or vestibule of Lerche. While it may be reasonable to assume that the vestibule in its normal location, i.e. within the hiatal channel, functions in the same fashion as it does in the presence of herniation, this conclusion cannot be established from the evidence presented.

SUMMARY

1. The roentgen diagnosis of minimal hiatal herniation must often be based on indirect evidence; specifically (a) the demonstration of an abnormally wide barium

column in the region of the hiatus; (b) the presence of regurgitation; and (c) the appearance of localized contractions or circular sulci or notches above the hiatus.

2. In the presence of herniation, it can be demonstrated that the terminal two to 3 centimeters of the esophagus has physiological properties distinct from the remainder of the esophagus. Circular contraction of the proximal portion of this terminal esophageal segment or of the entire segment may act to delay the passage of barium during normal swallowing and may serve to prevent or hinder regurgitation into the esophagus. This segment presumably represents the "vestibule" of Lerche. Its proximal portion may be equated with the "inferior esophageal sphincter" of Lerche and with the rosette described by Som.

3. Persistent or frequently recurring contractions of the vestibule are indicative of abnormal spasm or of a complicating process such as esophagitis or scleroderma.

Acknowledgement

The author wishes to acknowledge his indebtedness to Dr. Max L. Som for the esophagoscopic observations in these cases and to Dr. Richard H. Marshak and Dr. Sigmund A. Brahms for their assistance in these investigations.

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RESULTS OF SURGICAL TREATMENT OF CARCINOMA OF THE ESOPHAGUS AND GASTRIC CARDIA

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During the past two decades, there has been widespread interest in the surgical treatment of neoplasms of the esophagus and gastric cardia. The literature now contains many communications relating to the results obtained by various surgeons working in this field. While some of these reports (1–4) reflect an attitude of pessimism and discouragement, others (5–13) suggest that the long-term survival rate is sufficiently encouraging to make it worth while to operate on patients suffering from neoplasms of the esophagus or cardia.

It would seem that a fair and accurate appraisal of the results of surgical therapy in this disease cannot be made if conclusions are based upon cases indiscriminately grouped together for analysis. In order to present a true statistical picture of the efficacy of radical extirpation of malignant lesions of the esophagus and cardia, it is important to differentiate sharply between the grossly inoperable cases and those subjected to obviously palliative resections, and the patients with lesions which may be considered operable and resectable with a reasonable prospect for cure. The operability and late survival rates are bound to be low and the operative mortality unduly high in cases treated mainly in the late stages of the disease.

Another factor has contributed to the confusion in determining the results of resection of cancer of the esophagus and cardia. This concerns a lack of uniformity in the anatomical and pathological classification of these tumors. In the series of cases to be presented in this paper, the epidermoid cancers of the esophagus and the adenocarcinomas which originate in the gastric cardia, about half of which secondarily invade the contiguous lower esophagus, have been grouped separately for purposes of analysis. In addition, the esophageal cancers have been studied according to their location in the organ, namely, the middle and upper thirds and the lower third, since different anatomical and technical problems pertain at these respective levels which have a direct bearing upon operability, morbidity and mortality (11).

From the pathological point of view, the cases have been further classified as follows (13): those in which the tumor growth was limited to the wall of the cardia or esophagus; those with peripheral extension of the tumor requiring excision of adjacent structures; those with local lymph node spread; those with distant lymph node involvement, and those with various combinations of these pathological features. A situation was classified as operable only when it was feasible to radically remove the primary lesion and all gross evidence of regional lymphatic metastatic involvement. Otherwise, resection of the tumor was considered to be a palliative procedure.

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In this connection, it must be remembered that, while a cancer of the esophagus may be readily resectable locally, there may be extensive distant lymph node involvement below the diaphragm, particularly in the paracardial, coeliac and peripancreatic chains. The usual direction of lymphatic spread is toward the regional mediastinal nodes and proximally to the lower cervical nodes, particularly on the left side (Virchow's node). However, retrograde metastasis may occur when local lymph channels become blocked.

The characteristic tendency of squamous cell carcinoma of the esophagus to extend proximally via the submucosal lymphatics is also noteworthy, and has a direct bearing upon the incidence of local recurrence at the anastomotic suture line (13). It is therefore of paramount importance, in attempting to perform radical resections, to transect the esophagus as high as it is technically feasible. With this is mind, it is now felt that, with the possible exception of tumors located very low in the esophagus, resection and anastomosis above the level of the aortic arch should be the operation of choice in most cases of epidermoid carcinoma of this organ. In the series to be reported, the operative mortality with supra-aortic anastomosis has been no higher than with the infra-aortic procedure (32 per cent and 34 per cent respectively).

Involvement of the liver by metastasis from an epidermoid carcinoma of the esophagus was once considered to occur but rarely, if at all (13). However, we have had four such cases in our series, the primary lesions being situated in the lower esophagus. Recently, extensive hepatic metastases were observed in a patient who appeared to have an operable tumor of the esophagus located just above the level of the aortic arch.

From the clinical point of view, certain other features of esophageal and cardial cancer are worthy of emphasis.

If patients with this disease are to be afforded an opportunity for cure, it is essential that the diagnosis be made and treatment instituted early in their clinical course before local involvement of irremovable structures and distant lymph node or visceral metastasis have taken place. Dysphagia is not actually an early symptom, since the mechanism of its clinical manifestation is dependent upon sufficient growth of tumor to encroach upon the lumen of the esophagus or cardia, thus producing progressive interference with the function of deglutition.

The roentgenologist rarely picks up an esophageal neoplasm as an incidental finding in the course of routine gastrointestinal examinations. Rather, the experience has been that such lesions are found when specifically looked for on the basis of clinical symptoms which direct attention to this viscus. It is therefore incumbent upon the physician to consider the possibility of esophageal neoplasm, or tumor in the so-called "silent area" of the gastric cardia, when eliciting vague or indefinite symptomatology referred to the substernal, dorsal or epigastric regions. Such symptoms may early manifest themselves as a burning sensation or slight discomfort on swallowing hot liquids or foods, or any other abnormal subjective sensation in association with the act of swallowing.

In this series, there was apparently no relationship between the length of time that had elapsed between the apparent onset of symptoms and the application

for treatment, and the status of operability and resectability at operation. Some cases were found to be hopelessly inoperable after only three weeks of symptoms of sufficient degree to cause the patient to seek medical attention. On the other hand, resection was easily accomplished in some patients whose symptoms had apparently been present for more than a year.

With the aid of the modern methods of preoperative preparation, anesthesia and postoperative care, extensive surgical procedures can be successfully carried out upon patients of advanced age. Many of our patients were in the older age groups, and we have not considered their age a contraindication to surgery.

Despite the well known tendency of malignant lesions of the middle third of the esophagus to involve adjacent vital structures within the confines of the mediastinum, an aggressive surgical attitude has nevertheless been rewarded by finding a considerable number of patients in whom the tumor was operable. We are of the opinion, therefore, that except in cases which are obviously hopeless by virtue of clinical evidence of cervical lymph node involvement, left recurrent nerve palsy or bronchial or pulmonary invasion, all patients should be given the benefit of exploration. Various palliative procedures such as the use of a plastic tube (14, 15), by-passing operations (2) or postoperative deep intensive radiotherapy (16, 17) may be properly considered if the situation is then found to be inoperable, in order to temporarily restore a channel for deglutition.

Although roentgenographic diagnosis of esophageal lesions has reached a high degree of accuracy, there are still encountered occasional instances in which the differential diagnosis between certain benign obstructive conditions and cancer presents great difficulty. This is particularly true in some cases of obstruction of the distal esophagus, the result of peptic esophagitis or conical cardiospasm. It is therefore essential to secure endoscopic and histological proof of the nature of the lesion before considering surgical intervention in these cases.

RESULTS OF SURGICAL TREATMENT

The group of cases of cancer of the esophagus and gastric cardia which forms the basis of this report consists of 401 patients who were operated upon between 1936 and December 31, 1952. In addition, there were 56 patients who did not come to surgery for various reasons, so that our experience during this period covered a total of 457 cases.

An initial statistical analysis of this series has been reported previously (5). The present communication is intended to present the long term results in this group based on continued follow-up from December 1952 to February 1955. A considerable number of patients have been operated upon since 1952, but because of the short follow-up period, these have not yet been subjected to statistical analysis and therefore are not included in the present report.

The epidermoid cancers of the esophagus and the cardial adenocarcinomas are to be considered separately.

Cancer of the esophagus

There were 214 patients in this group. By the criteria noted above, 92 were operable (42.9 per cent operability rate). In the group of 122 inoperable cases, there were 14 deaths, an operative mortality of 11.7 per cent.

TABLE I

Carcinoma of esophagus

Operative mortality

Operation	Number	Deaths	Mortality Percentage
Torek operation	16	10	60%
Infra-aortic anastomosis	32	11	34%
Supra-aortic anastomosis	43	14	32%
Combined series-total	91	35	38%

In the operable group, the operation was completed in 91 cases; in one case with a resectable tumor, it was necessary to terminate the operation before its completion because of the patient's poor condition. There were 35 deaths in this group or an operative mortality of 38 per cent (Table I). The Torek operation was performed in the first 16 patients of this series. This procedure consisted of resection of the involved segment of esophagus, the establishment of a cervical esophagostomy, the latter connected at a subsequent date by a prosthesis to a previously prepared gastrostomy (6). There were ten operative deaths in this group, or 60 per cent. This high mortality may be ascribed to the fact that this procedure was performed in the early days of our experience with this problem, and before the advent of the newer antibiotics, improved anesthesia and advanced concepts of postoperative problems in abdominal and thoracic surgery.

The Torek procedure was then abandoned in favor of transthoracic resection of the lower esophagus and gastric cardia, with anastomotic re-establishment of esophago-gastric continuity (18), classified under the designation of "infra-aortic resection". This procedure was employed in 32 patients, with 11 deaths or an operative mortality of 34 per cent. "Supra-aortic resection", including two cases with cervical anastomosis, was performed in 43 cases. In this group there were 14 operative deaths, a mortality of 32 per cent. The causes of death included pneumonia, coronary occlusion, right heart failure, cerebral accidents and pulmonary embolism.

Survivals. **Torek Operation.** There were 16 patients in this group, six of whom survived the operation. Three of these cases presented no obvious extension beyond the esophageal wall and no nodal involvement; one of them is alive and well 18½ years after operation. The other operative survivors died of recurrence between eight and 20 months postoperatively. In this group of six operative survivors, the long term survival rate may be computed as 16.6 per cent (Table II).

Infra-aortic anastomosis. Table III depicts the survival rate in this group. There were seven patients with no local extension of the tumor (as evidenced by gross appearance and ease of resection), of whom three survived more than five years. One of these died after seven years of cardiac disease; the other two are alive and well nine and 13 years respectively. The former patient had a leiomyosarcoma. One patient in whom a large segment of the right mediastinal pleura had to be resected along with the tumor to which it was attached by neoplastic extension is now living 16 years after operation. None of the five patients with

TABLE II

Survivals: Torek operation

	Number	Late Survival
No extension or nodes	3	1–18½ years
Extension beyond wall	2	0
Extension beyond wall and local nodes	1	0

5 year and over survival—16.6%

TABLE III

Survivals: infra-aortic anastomosis

Lower third tumors

	Number	Survivals
No extension or nodes (includes 1 case—leiomyosarcoma)	7	3 1 alive and well 9 years 1 alive and well 13 years 1 died after 7 years (cardiac death)
Extension beyond wall	1	1 alive and well 16 years
Local node involvement	5	0
Extension beyond wall and node involvement	4	1 died after 10½ years of pneumonia. Autopsy: No recurrence.
Distant node involvement	2	0
Local and distant nodes	2	0

Note: Of 12 patients operated upon before January 1948, 5 survived more than 5 years —41.6%. One patient died after 7 years of unrelated disease; 1 died after 10½ years also of unrelated disease. At autopsy there was no evidence of recurrent carcinoma. If these two are excluded, the survival figure is now 25%.

local lymph node involvement have survived. One of the four patients listed under the heading "extension beyond wall and node involvement" lived for 10½ years. The cause of death was pneumonia; there was no sign of recurrence of cancer at the autopsy.

The survival rate for this group of patients who were successfully operated upon for lower third tumors is now 25 per cent, excluding the two patients who died seven years and 10½ years after operation, of unrelated disease.

Supra-aortic anastomosis. Four patients survived this procedure who were operated upon prior to January 1948. All died of mediastinal recurrence within 11 months, seven months, three years and 3½ years respectively. Of the patients operated upon since January 1948, there are now two patients living six years and seven others are alive over four years (Table IV).

If we combine the 24 cases of cancer of the esophagus who were operated upon over five years ago and survived operation, there are eight who are now living more than five years, a long-term survival rate of 33 and one-third per cent. This represents the overall relative survival rate.

TABLE IV

Survivals: supra-aortic anastomosis

Middle and upper third tumors

	Number	Survials
No extension or node involvement	12	8 3–4½ years 2–6 years 1–2½ years 1–4 years and 9 months 1–3 years
Extension beyond wall	2	0
Extension beyond wall and local node involvement	2	1 1–4½ years
Local node involvement	8	4 2–4 years 1–18 months with recurrence. 1–2 years and 9 months
Distant node involvement	2	0
Local and distant node involvement	3	0

Note: Only 4 patients were operated upon prior to January 1948. None of these were alive after 5 years; the longest survival being 3½ years. However, there are now 2 patients living 6 years, and 7 others are alive over 4 years.

Combining 24 cases of squamous cell carcinomas who were operated upon over 5 years ago and survived operation, 8 lived more than 5 years, or 33⅓%.

Adenocarcinoma of the cardia

There were 187 patients in this group, of whom 89 were operable (45.4 per cent) including one case of lymphosarcoma. Fifteen palliative resections were performed in the group of 98 cases classified as inoperable. The incidence of metastatic liver involvement was almost 20 per cent. The operative mortality in the inoperable group was 5 per cent.

Local lymph node involvement was present in more than two-thirds of the group of 89 operable cases, and half presented extension to the lower esophagus.

The operative mortality in the entire operable group was 24.7 per cent (22 deaths). Of 33 patients operated upon through the left trans-thoracic approach, 16 died (48.4 per cent). In striking contradistinction, 56 resections were done utilizing the combined abdominothoracic incision, with only six deaths, or a mortality of 10.7 per cent. We believe the use of this approach has been a major factor in reducing the mortality in this group of cases.

It is noteworthy that half of the operative deaths in this operable group were due apparently to acute coronary occlusions. Although we are well aware of the increased surgical risk in patients with a history of preceding coronary artery disease, we feel nevertheless that this risk must be accepted in view of the malignant nature of the primary disease.

Survivals. Of the 89 patients in whom resection was performed for cancer of the cardia, 67 survived the operation (Table V). Thirty-two of these were operated

TABLE V

Adenocarcinoma of the cardia survivals

	Number	Survivals
No local extension or node involvement	19	11
		1 died after 14 years. Autopsy showed carcinoma at distal end of stomach, of microscopically different appearance than the initial lesion.
		1–11 years (to 1953)
		1–9 years
		1–6 years
		2–5 years
		2–3 years
		2–2½ years
		1–2 years (to 1953)
Extension beyond wall	2	0
Extension beyond wall and lymph nodes	4	1–11 years (to 1953)
Lymph node involvement	42	7
		1–11 years (to 1953)
		1—Died at 4 years, 9 months.
		2–4½ years
		1–5½ years
		1–3 years (to 1953)
		1–2½ years

Note: This chart graphically demonstrates the influence of node involvement on the survival rate. Occasionally, however, one will encounter a long-term survival in the presence of extensive lymph node spread.

Of 32 patients operated upon prior to January 1948, 9 lived over 5 years, a late survival rate of 28.12%. Another died after 6 years of a coronary occlusion.

upon prior to January 1948. One of these died after 14 years. At autopsy, there was found at the distal end of the stomach, a carcinoma of microscopically different appearance than the initial lesion at the cardia. While this may represent a new neoplasm rather than a recurrence, we have classified it as the latter. Of the 32 patients operated upon prior to January 1948, nine lived over five years, a late survival rate of 28.12 per cent. Another died after six years of a coronary occlusion.

Table V graphically demonstrates the influence of lymph node involvement on the long term survival rate. Occasionally, however, one will encounter a long survival despite extensive lymphatic spread. The surgeon must, therefore, make every effort to perform as wide a dissection as possible when confronted with local lymphatic spread, even though prevention of recurrence is a difficult goal to attain.

SUMMARY

1. The surgical experience with a series of 401 patients operated upon for cancer of the esophagus and cardia is presented.

2. Anatomical, pathological and clinical features are discussed.

3. Criteria of operability are discussed, and inoperable cases or those treated for palliation sharply distinguished from those which may be considered operable with reasonable chance for cure.

4. Operability, mortality and survival rates are presented, in relation to a suggested pathological classification as well as to the anatomical situation of the tumor, and the type of surgical procedure performed.

5. The results of surgical treatment of cancer of the esophagus and gastric cardia justify continuation of an aggressive surgical attitude toward this disease.

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THE SURGICAL MANAGEMENT OF HIATUS HERNIA

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Newer concepts concerning the physiologic mechanisms associated with herniation through the esophageal hiatus of the diaphragm (commonly called hiatus hernia) have led to a markedly increased interest in recent years. Considerable experience is accumulating and much has been written, but the problem still resolves itself, from the standpoint of practical management, into several basic questions: (a) When should hiatus hernia be surgically treated? (b) What definitive operative procedures are available? (c) What is the prognosis of patients with hiatus hernia?

There are no unchallenged answers to these questions but it may be profitable to summarize briefly some basic facts, correlating the present status of opinion with our own experience. Of 200 patients with hiatus hernia at the Mount Sinai Hospital over a four year period, 42 (34 women and 8 men) had 53 operative procedures performed. The ages varied from 36 to 76 years.

CLASSIFICATION

Hernia through the esophageal hiatus is the commonest diaphragmatic hernia. There are two principal anatomical types: paraesophageal and "sliding" (for this we prefer the term first used by F. A. Jones (1), "esophagogastric hernia" because it describes the essential feature: herniation of the junction). The two forms differ in pathogenesis, symptoms and prognosis. The crucial difference is the position of the esophagogastric junction. A third rare type of thoracic stomach is due to a congenital defect.

Paraesophageal Hernia

This hernia occurs with the esophagogastric junction in its normal location below the diaphragm. The peritoneal sac is in the mediastinum in front of the esophagus and is either empty or contains a portion of the anterior surface of the stomach. It is comparable to a Richter's hernia of the inguinal region in which a part of the wall of a viscus is pinched off in the sac. The neck of the sac is usually wide, adhesions are unusual, and it is uncommon to find in the sac any viscus other than the stomach except occasionally for the colon. No matter what the contents of the hernia, the esophagus is of normal length and enters the stomach at an acute angle. Regurgitation of gastric fluid into the esophagus does not occur. The paraesophageal type accounts for about 25 per cent of hiatus herniae.

Esophagogastric Hernia (sliding; pulsion).

Here the esophagus appears short because the esophagogastric junction is displaced upward above the diaphragm. The stomach moves into the posterior

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mediastinum, taking with it a pouch of peritoneum. The anterior wall of the stomach lies behind this peritoneal sac and the gastric serosa forms the posterior wall of the sac, just as a sliding inguinal hernia has the cecum or sigmoid as part of the sac wall. There is produced a stretching of the ligaments at the cardia and of the phrenico-esophageal attachments. The acute angle between esophagus and stomach is gone and the esophagus enters the stomach as if at the summit of a dome. The stomach appears to hang from the esophagus which retracts because of its elasticity and appears to be shorter than normal. However, it can easily be pulled back into normal length and position by slight traction at operation. Regurgitation occurs in approximately 50 per cent of cases (2). The esophagogastric hernia accounts for approximately 70 per cent of hiatus herniae. Combinations of the two types have been reported in approximately 5 per cent of cases.

The mechanism of production of both types of herniae is still not clear, although there are many theories, as yet unproved, to explain their occurrence.

Congenitally Short Esophagus.

This is not a true hernia, but represents a failure during embryologic development of the full descent of the stomach as the diaphragm develops. The esophagus is short and cannot be lengthened. The stomach lies in the mediastium or pleural cavity. The ligaments from the diaphragm attach to the adjacent stomach rather than to the esophagus. This abnormality is uncommon. Until recent years it was often confused with acquired esophagogastric hernia (3, 4).

Demonstration of the presence of a hiatus hernia and definitive differentiation of esophagogastric from paraesophageal herniation are possible only by means of Roentgen examination with a barium meal. It is to be emphasized that special methods of increasing intra-abdominal pressure may be necessary in order to visualize the hernia and to look for reflux into the esophagus (5). Furthermore, esophagoscopy is necessary whenever there is any doubt concerning the integrity of the mucosa in the esophagus or cardia.

Sometimes at the operating table one has difficulty in discerning the position of the cardia in relation to the diaphragm, because the hiatus is not in one plane but rather an oblique canal. Thus the surgeon may find it difficult to tell with certainty whether he is dealing with a paraesophageal or esophagogastric hernia or a combination of both types.

PATHOLOGIC COURSE

Esophagogastric Hernia

Mechanism of Reflux. There are three principal functional mechanisms acting at the cardia to prevent reflux: (a) the support and pinch-cock action at the diaphragmatic hiatus (6); (b) the esophagogastric angle (7); (c) a muscular contractile mechanism at the cardia (8, 9). The relative importance of each is still in dispute. It is highly probable that all three factors contribute to esophagogastric continence. A fourth sphincteric mechanism, the inferior esophageal constrictor is apparently more concerned with impeding downward flow than with preventing reflux (9, 10).

When the cardia has ascended above the hiatus, as in esophagogastric herniation, the pinchcock action of the hiatus is lost. More importantly, the esophagus enters the stomach at the summit of the thoracic pouch, thus straightening the normal acute angle between esophagus and greater curvature which is apparently necessary in order to permit the sling of muscle fibers in the gastric wall encircling the cardia to pull down the esophagogastric junction and obliterate the lumen. With the loss of the three mechanisms maintaining continence, regurgitation of gastric contents into the lower esophagus may then take place.

Effects of Reflux. The regurgitation which occurs in esophagogastric hiatus hernia may cause esophagitis with erosions or may lead to ulcer (5, 11, 12, 13) at the esophagogastric margin (marginal ulcer). The esophagitis may progress to involve all coats of the wall and eventually the mediastinal tissues as well. Healing with fibrosis follows and the end result can be stricture and fixation of the esophagus ("frozen" esophagus). In the 176 cases of esophagogastric hernia reported by Allison (7), 63 had chronic esophageal ulcers with stenosis.

According to Wolf, Som, and Marshak (5), the reflux occurring in hiatus hernia is more apt to produce a localized ulceration at the esophagogastric junction with a short segment of esophagitis than a long diffuse area of inflammation. When ulcerative esophagitis over a long segment is found in the presence of hiatus hernia, an additional factor is to be expected [e.g. duodenal ulcer or history of prolonged intubation (14)].

Incarceration. The portion of the gastric pouch above the diaphragm may become pinched off by the contraction of the pillars of the hiatus, thus causing delay in emptying and sometimes erosions of the gastric mucosa. Occasionally, this trapping of contents may be so marked that a high gastric obstruction results. If the hiatus margins encircling the gastric pouch interfere with blood supply (an extremely rare complication) strangulation can lead to necrosis and perforation (6).

Paraesophageal Hiatus Hernia

Ulceration. Erosions or peptic ulceration are common and hemorrhage is a not infrequent complication (15). The bleeding may consist of a slow ooze, or may be manifested by a serious hemorrhage (16). Perforation of such ulcers is rare. The erosions or ulcerations are usually superficial.

Incarceration. Compression by the hiatal pillars is more common here than in esophagogastric herniae. Obstruction of the supradiaphragmatic pouch is less liable to lead to complete gastric obstruction because the continuity of the gastric lumen remains intact, unless the distended, trapped pouch causes mechanical obstruction by pressure on the esophagus and cardia. Strangulation with necrosis and perforation by the same mechanism as in esophagogastric hernia is uncommon (17).

Of course, the advancing course may never occur and a hiatus hernia may remain without progression. For example, at the Mayo Clinic (18, 19), 25 per cent of patients seen with hiatus hernia had minimal or no symptoms, 50 per cent moderate to severe symptoms, and only 25 per cent had complications (4).

SYMPTOMS

Heartburn. The sensation of heartburn is due primarily to distention of the lower end of the esophagus (20), by either solid or fluid material of acid or alkaline reaction. For example, Jones (21) was able to reproduce this symptom consistently by inflating balloons in the lower esophageal segment. Also, patients with regurgitation of anacid gastric juice often have heartburn. Furthermore, patients without gastrointestinal disease may also have heartburn. Flood, Wells, and Baker (22) found that half of such random patients showed regurgitation on x-ray studies. Both types of hiatus herniae may produce this symptom.

Thus in esophagogastric hernia, in which regurgitation occurs, heartburn is common. A second cause of heartburn in esophagogastric hernia may be the presence of esophagitis which is a late effect of the reflux. Over 66 per cent of our patients operated on for esophagogastric hernia had this symptom. Paraesophageal herniation, which characteristically has no reflux, may nevertheless be associated with heartburn produced by a third mechanism. Physiological dysphagia leading to accumulation of ingested food in the lower esophagus may result from reflex dysrhythmia in the esophagus. This disturbed esophageal transport is often associated with the presence of hiatus hernia. Whether the suggestion of Lorber and Shay (23) is correct that dysrhythmia may actually be a cause of hiatus hernia is not of concern to us here, but the retention of swallowed material above the cardia as a concomitant of any hiatus hernia does offer a logical explanation of the heartburn sometimes seen in paraesophageal hernia (20 per cent in our operated group).

Pressure Symptoms. Upper abdominal discomfort, fullness, belching, and nausea usually result mainly from distention of the pouch of stomach above the diaphragm. These symptoms are therefore more apt to occur after a heavy meal or on lying down, for the filled upper gastric pouch is then unable to empty rapidly. If gastric contents are actually trapped above the diaphragm because of pinching off by the diaphragmatic hiatus, the constant sensation of the need to empty the stomach may lead to marked belching, nausea and occasionally vomiting.

The distended thoracic gastric pouch may also have effects on contiguous organs. Large herniae for example may produce dyspnea. Palpitation and tachycardia, especially after a heavy meal, may cause the cardiovascular system to be erroneously suspected. In fact, many of these patients have been treated for many years for coronary artery disease until the real state of affairs was disclosed on x-ray examination.

Pain. The pain caused by hiatus hernia may be epigastric or may radiate to the chest, shoulder, neck, jaws and back. It may resemble peptic ulcer in periodicity and character. When located substernally, there may be confusion with heart disease. The pain is often worse after lying down or at night after retiring.

One of the causal mechanisms of pain is overfilling and distention of the gastric pouch above the diaphragm. Erosions in the gastric mucosa or true peptic ulceration leading to the complete clinical syndrome associated with gastric ulcer are more common in paraesophageal hernia, whereas the pain produced by esopha-

gitis or ulceration at the esophagogastric margin occurs in the esophagogastric type of hernia. Pain was present in all but two patients.

Dysphagia. Difficulty in swallowing, with the passage of food becoming delayed at the lower esophagus, may be caused by organic stricture (a late result of the esophagitis associated with esophagogastric hernia) or by a physiologically retarded esophageal transport. This delay may be due to either muscular constriction or disorganized muscular function, and resembles cardiospasm in symptomatology but apparently differs in mechanism (23). Dysphagia can also be produced occasionally, particularly in the paraesophageal type of hernia, by direct compression of the esophagus by the herniated gastric pouch. Dysphagia was a symptom in 14 per cent of our cases.

Bleeding. Bleeding is not as common in esophagogastric hernia as in the paraesophageal type. In our operated cases 60 per cent of those with paraesophageal hernia had bleeding whereas this preoperative symptom was found in only 13.3 per cent with esophagogastric herniae. The association of bleeding with paraesophageal hernia is not always well recognized. For example, the loss of blood may be so slow and insidious that the patient develops unexplained secondary anemia. Guaiac positive stools may then point to the gastro-intestinal tract as the site of origin, but often even after roentgen examination, the presence of a paraesophageal hiatus hernia may not be accepted as the source of bleeding until all other possible causes are eliminated. Brisk hemorrhage can also occur, either from superficial gastric erosions or from peptic ulceration, and cause melena or hematemesis. However, the ulceration in the gastric pouch of a paraesophageal hiatus hernia may not be demonstrable on roentgen examination (24).

Although the symptoms may be virtually the same in both paraesophageal and esophagogastric herniae, heartburn and dysphagia are more common with the latter and pressure symptoms and bleeding in the former.

INDICATIONS FOR SURGERY

Non-Symptomatic Hiatus Hernia

Esophagogastric. The fear of esophagitis and its sequelae, which are resistant to all forms of therapy, has prompted some investigators to advocate surgical repair of all esophagogastric herniae whenever discovered. This decision is given further weight by the frequent finding of esophageal reflux in 50 per cent of herniae and by the reported high incidence of the development of esophagitis in the presence of regurgitation (70 per cent in one series).

Other opinions favor operation in accidentally discovered herniae only when regurgitation is demonstrable by roentgen examination, for it is the failure of esophagogastric continence which leads to esophagitis.

In our view, however, the undesirable train of events (esophagogastric hernia, regurgitation, and esophagitis) may not be as frequent as the reports indicate. It is difficult to assess the true incidence of inadvertently discovered hiatus hernia (25) (figures vary from 1 per cent to 8.9 per cent). Furthermore it is also known that many people who have no hiatus hernia may have reflux without the development of symptoms or esophagitis (22). At the present time we believe

TABLE I

Hiatus hernia, principal preoperative symptoms
4 year study

Type of Hernia	No. of Cases	Bleeding	Heartburn	Dysphagia	Pain
Paraesophageal	20	12	4	4	18
Esophagogastric (sliding; pulsion)	15	2	6	1	15
Combined forms	4		1	1	4
Unspecified	3		1		3
Total	42	14	12	6	40

that the current state of knowledge does not warrant the prophylactic operative repair of hiatus hernia, with or without regurgitation, which produces no symptoms.

Paraesophageal. It is generally agreed that patients with paraesophageal hernia which produces no symptoms are best left alone.

Symptomatic Hiatus Hernia

Esophagogastric. We believe that all cases with symptoms which show reflux on Roentgen study should be repaired, for here the future danger is clear and the progressive development of esophagitis likely.

When symptoms are severe enough to cause disability or interference with activities, surgery may be necessary even in the absence of demonstrable reflux. But mild or minimal symptoms without reflux, especially when the hernia is small, do not warrant operation, particularly since hiatus hernia as the cause of the symptoms may not always be clear.

Paraesophageal. Persistent or recurrent bleeding requires operative repair. Paraesophageal hernia associated with chronic anemia, guaiac positive stools, and no other discernible causes of bleeding, constitutes an indication for surgery. One gross hemorrhage should also lead to operation, as other hemorrhages are likely. The principal difficulty in deciding on surgery because of bleeding is in determining that the hernia is the cause. Thus other possible sources in the gastrointestinal tract must be excluded first. Complications, such as strangulation or perforation, are of course also prime indications for surgery.

In the absence of complications, the severity of symptoms is the criterion for operation. Patients with mild discomfort or infrequent episodes of even severe pain may go for many years without the necessity for surgery, since the ultimate outlook does not include, as with esophagogastric hernia, the future possibility of esophagitis.

At the Mount Sinai hospital in the most recent four year period, 42 patients with hiatus hernia were operated upon. Twenty had paraesophageal hernia, 15 esophagogastric, four combined, and three unspecified forms. These operated cases constituted 21 per cent of all cases of hiatus hernia admitted to the hospital during the same period. Bleeding was an indication for surgery in 70 per cent of the patients operated upon. Heartburn was a prominent symptom in 24 per cent

and dysphagia in 14 per cent. The most constant preoperative finding however was pain, which was present in one form or another in virtually every patient who came to operation.

METHODS OF OPERATIVE CORRECTION

Phrenicectomy

In earlier decades, phrenicectomy as a palliative procedure was used more often than in recent years. The rationale of this operation was concerned with the relaxing effect of the nerve section on the hiatus, permitting the stomach to slip down with ease. Some of the results were extremely good, yielding excellent improvement in approximately 45 per cent of patients and some amelioration of symptoms in an additional 40 per cent.

In our series, of the 13 palliative phrenicectomies, seven were completely relieved, whereas six required subsequent definitive repair. The failure to effect better results was probably due to several factors: (a) The symptoms were often not due to constriction by the hernial opening in the diaphragm but rather to the thoracic position of the stomach and the esophagastric derangement; (b) The hernial pouch often cannot slide down spontaneously even with slackening of the hiatal opening; (c) Widening of the hiatus may actually lead to increase in the bulge into the thoracic mediastinum and further exaggerate any reflux which is already present.

Phrenicectomy has also been used as a preliminary procedure, before a more definitive operative repair, to allow easier approximation of the pillars of the hiatus (as advised by Harrington) or to permit easier reduction of larger herniae. However, it is believed by others that the resulting atrophy of the diaphragmatic muscle makes the repair less secure, postoperative ventilation less efficient, and the phrenicectomized diaphragm permanently paralyzed in a definite number of instances. Phrenicectomy as a complementary step was employed six times in the 40 definitive operative repairs in our series.

Definitive Repair

The principal features of the operative repair consist of reduction of the hernia to a position below the diaphragm, narrowing of the hiatus, and fixation of the esophagogastric junction below the diaphragm.

Approach.

Transabdominal. The abdominal approach was more popular in earlier years when thoracotomy was not considered simple or safe. It is still preferred by some (3, 18) who feel that pleural complications are thus avoided and postoperative ventilation made more efficient. Harrington (19) also claims that the hiatal repair is simpler when approached infradiaphragmatically. It is also true that other abdominal lesions can be more easily discovered and managed by the transabdominal route.

However, the hernial sac and stomach cannot be managed as well, especially if they are fixed or adherent to surrounding structures. Ligamentous repair is

TABLE II

Hiatus hernia, operative procedures
4 year study

Type of Procedure	Number Performed	Secondary Repair Required
Palliative phrenicectomy	13	6
Definitive Repair:		
Trans-abdominal	12	3 (Transthoracic)
Transthoracic	25	0
Total definitive repairs	37	3

also more difficult. Moreover, the posterior position of the hiatal canal is not easily reached by this approach. Transabdominal approach was used in 12 of our 40 definitive repairs. It is to be noted that the three patients requiring secondary repair for recurrence in our series all had their original operations by the abdominal route.

Transthoracic. This approach has become quite safe in recent decades and pleural complications can be avoided by making sure that the lung is fully expanded and brought to the chest wall during closure of the thoracic wound. The sac and stomach are easy to free and the ligaments may be repaired more easily. In being able to see above and below the diaphragm at the same time, one can repair the hiatus with facility and accuracy (4, 7). Transthoracic repair was used in 25 of the 40 patients subjected to definitive operation.

Management of the Sac.

The decision to open the sac often depends on the size of the hernia. The larger bulges usually are best managed by opening and trimming the sac before reducing the hernia. Some surgeons however prefer to perform the repair with the sac unopened.

Narrowing the Hiatus.

Although all surgeons narrow the diaphragmatic hiatus, the methods employed vary. To Allison (7) the crucial step is displacing the esophagus forward and approximating the hiatal pillars behind, thus repairing the very portion of the opening which has been split by the upward slide of the hernia. On the other hand, Harrington (19) prefers to narrow the opening by converting it to a transverse slit, which leaves the esophagus essentially in its former posterior bed in the hiatal canal. The principles promulgated by Allison are intriguing and logical, but the spectacularly good results also reported with Harrington's methods should not be overlooked.

Management of the Ligaments.

To some, notably Allison (7), the operative fixation to the undersurface of the diaphragm of the stretched phrenico-esophageal ligaments is of prime im-

portance in preventing recurrence of an esophagogastric hernia Others do not consider the ligaments an important part of the repair. But if we can judge from the descriptions of the operation (e.g. by Harrington), the sutures passed into the remnant of the sac or in the peri-esophageal tissues probably catch the ligaments anyway and fix them to the diaphragm.

It is our opinion that the best chance of successful repair is obtained by using Allison's technique (7):

1. Transthoracic approach.
2. Opening the diaphragm transversely through an incision a few inches from the hiatal opening to permit the operator to see and work above and below the diaphragm.
3. Opening the sac for easier reduction and better placement of the cardia in its proper location.
4. Narrowing the hiatus by approximating the pillars behind the esophagus, which is displaced forward.
5. Fixation of the phrenico-esophageal ligaments to the diaphragm (this step apparently is of importance only in esophagogastric hernia).

MANAGEMENT OF ESOPHAGITIS WITH STENOSIS

Once fixation of the esophagus has occurred (as found in advanced esophagogastric hernia with longstanding esophagitis), surgical correction offers little hope at the present time. It may be impossible to free the esophagus from the mediastinum. Even when brought down, the esophagogastric angle may no longer be restored to normal function because of fibrosis and rigidity. Thus competency at the cardia may have been permanently lost and regurgitation with all its pathologic sequelae may be an inevitable, continuing, progressive process.

Several operative methods for treating this complication have been proposed, all with the primary concept that it is the acidity of the regurgitated gastric contents which leads to the esophagitis and stenosis:

Esophagojejunostomy. The esophagus is transected above the stricture and anastomosed to the jejunum in order to by-pass the stomach (26). This is a formidable procedure and may be associated with problems as bad as the original disease. The difficulty, we believe, lies in the fact that the subsequent regurgitation of jejunal contents into the esophagus may in itself lead to the same set of circumstances. It is not known whether jejunal contents are tolerated better than gastric juice.

Partial Esophagogastrectomy and Esophagogastric Anastomosis. The operation of radical proximal gastrectomy, excision of the diseased segment of esophagus, reestablishment of continuity by anastomosing the distal segment of stomach to the normal remains of the esophagus with an added complementary bilateral vagotomy, has given the best results so far at The Mount Sinai Hospital. Although the same regurgitation of gastric contents into the esophagus occurs, there has been noted a marked reduction in gastric acidity.

Subtotal Gastrectomy. This operation (27) is considered suitable only when the inflammation in the esophagus has not progressed to the point of advanced stenosis and yet is severe enough to cause fixation of the esophagus, thus prevent-

ing the repair of the hernia by bringing down the esophagus below the diaphgram. The same objectives exist as with the other two procedures.

Evaluation of these three operations in obtaining amelioration of symptoms must await the elapse of time.

To relieve the dysphagia resulting from stricture, dilation with bougies under direct vision through the esophagoscope has offered promise. But here too, although the stricture has often been successfully widened with striking improvement in symptoms, the regurgitation continues and the future course is therefore in doubt.

RESULTS OF SURGERY

The mortality rate in repair of hiatus hernia is very low in most recent series. For example, Sweet (28) had no post-operative deaths in 111 cases. Allison (7) reports one death in 33 patients (3 per cent) operated on for esophagogastric hernia with esophagitis and ulceration but no stenosis. Harrington (19) reports six deaths in 450 repairs (1.3 per cent). We had one death in 40 hernial repairs (2 per cent).

The end results are universally excellent in cases of paraesophageal hernia, with the hernia cured anatomically and physiologically as well as clinically. In esophagogastric hernias results are also good, although not with the same regularity as in the case of paraesophageal hernia, if the repair is done before the advent of a "frozen" esophagus.

Sweet reports that 87 per cent of 111 cases (97 esophagogastric, 7 paraesophageal, 2 composite and 5 congenital short esophagus) obtained full relief of symptoms and 10 per cent had partial relief. Only 3 per cent showed recurrence of the hernia or persistence of symptoms. Of Allison's 33 patients operated on for esophagogastric hernia with esophagitis, 30 became free of symptoms and revealed no regurgitation. One patient had a recurrence of the hernia and another developed a recurrence of esophagitis. Among 450 operated cases, Harrington found 13 recurrences. Seven of these required a second operation. Three patients in our series required reoperation after the original repair (8 per cent).

SUMMARY

1. The important anatomic difference between esophagogastric and paraesophageal hernia is in the position of the cardia in relation to the diaphragm.

2. The term esophagogastric hernia, is preferred to that of sliding or pulsion hiatus hernia because it describes the essential feature, i.e. upward herniation of the esophagogastric junction.

3. Reflux of gastric contents into the esophagus complicates the prognosis in esophagogastric hernia.

4. The principal preoperative symptoms of hiatus herniae of both types are: pain, bleeding, heartburn, abdominal or thoracic pressure sensations, and dysphagia.

5. Asymptomatic, accidentally discovered hiatus hernia of either type is not considered an indication for operation.

6. Esophagogastric hernia with mild symptoms and no reflux also does not

require surgery. Surgical repair is indicated in symptomatic esophagogastric hernia when reflux is seen on Roentgen examination.

7. In paraesophageal hernia, the severity of symptoms determines the necessity for operation.

8. Phrenicectomy occasionally is useful as a palliative procedure.

9. The transthoracic approach is preferred for definitive operative repair. The technique of Allison which replaces the cardia in its normal position and fixes the ligaments offers the best chance of cure.

10. At the Mount Sinai Hospital, in a four year period, 42 patients with hiatus hernia were operated upon: 20 paraesophageal, 15 esophagogastric, 4 combined, and 3 unclassified.

11. Operative mortality in hiatus hernia is low. In 40 definitive operations there was one mortality.

12. The chance of permanent cure of hiatus hernia is excellent if operation is performed before complications occur.

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PSYCHOPHYSIOLOGY AND PSYCHIATRIC MANAGEMENT OF THYROTOXICOSIS: A TWO YEAR FOLLOW-UP STUDY

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In view of the multiplicity of the dynamic aspects of Graves' disease, a long range follow-up study would appear to be especially rewarding. The literature abounds with reports on the role of traumatic experiences, prolonged emotional stress, and conflict situations as immediate precipitating, and possibly etiologic, factors in hyperthyroidism. The classic clinical picture of acute emotional disturbance accompanying Graves' disease has been described in its varied aspects. Psychotic episodes, either concurrent with the thyrotoxic state or subsequent to thyroidectomy, have occasionally been followed-up for more extended periods. Few investigators report observations exceeding a three month period (1, 3), while systematic follow-up studies of entire series of hyperthyroid patients have not been undertaken. This seems all the more surprising in view of the emphasis in recent publications on specific personality make-up and on specific mode of reaction to stressful life situations in these patients. The question of how a patient—once euthyroid—would react to renewed threats to his ego in future life situations is of considerable interest since recurrences of Graves' disease are relatively infrequent after thyroidectomy (10–15 per cent) and are rare indeed following treatment with radioactive iodine (1–2 per cent).

The advent of radioactive iodine as a diagnostic and therapeutic agent has increased diagnostic accuracy and simplified therapeutic procedure, while at the same time increasing its effectiveness. These advances have provided near to ideal conditions for an intensive psychiatric study, by reducing diagnostic uncertainty and eliminating such a complicating factor as fear of surgical intervention.

PATIENTS AND PROCEDURES

Eighty-four patients were studied, all but two of whom underwent radioactive iodine treatment for Graves' disease. Two private patients, who had been treated with thiouracil and tapazol, respectively, were included in this study because of the special opportunity for prolonged observation they both provided.

Each patient was seen in psychiatric interviews prior to isotope treatment, after a series of tests had confirmed the clinical diagnosis of thyrotoxicosis. Whenever possible, each patient was given a minimum of two interviews at this point

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TABLE 1

Number of patients studied and followed-up

Patients seen during the two year study		84
Patients seen during the first year		48
First year patients suitable for follow-up	30	
Patients followed-up by psychiatrist	26	
Patients given psychological tests	27	
Patients retested by psychologist	17	
Patients followed-up by social worker	13*	
Patients seen during the second year		36

* Some patients were followed-up both by the psychiatrist and the social worker.

and was then seen again at weekly intervals for three or more sessions, to be followed by monthly interviews. Since many of the consecutive unscreened patients proved extremely reluctant to report back at regular intervals, a rather uneven distribution of the number of interviews resulted: some were seen only twice, others five times, while nine patients entered a therapeutic situation by returning for individual sessions ranging from 10 to 76 interviews.

Of 48 patients seen during the first year of this two year study, 30 were found suitable for follow-up. Of the remaining 18, six were not included because the presence of myasthenia gravis, diabetes or angina pectoris made them unsuitable; three could not return; and nine refused to cooperate. It is interesting to note that these nine patients, who were acutely disturbed emotionally, some quite severely, nonetheless kept their appointments for periodic physical checkups at the Thyroid Clinic.

Twenty-seven patients of this series of 30 were given a battery of psychological tests prior to treatment with radioactive iodine. This battery of tests consisted of (a) a short multiple choice vocabulary test, (b) the Bender-Gestalt Test, (c) Buck's House-Tree-Person drawing test, (d) the Rorschach, (e) a list of sixty word associations, and (f) ten cards of the Thematic Appereception Test, which required one and one-half to two hours testing time. Psychological reports with diagnostic summaries were written on the basis of qualitative and quantitative evaluation of the test responses. Salient features of the psychological adjustments and maladjustments of these patients were abstracted from the reports.

Seventeen of the 27 patients who were initially tested could be persuaded to return for retesting, which was completed at intervals which ranged from three to twenty months. The average time between the psychological test and retest was about ten months. The ten patients who could not be retested, as well as the three who could not submit to psychological tests at all because of language limitations, were seen in follow-up interviews by the psychiatrist and the psychiatric social worker of this investigating team.

In the series of 30 intensively worked-up subjects, 26 are female and four are male patients. Among the women the ages range from 24 to 66, with a mean age of 39 years. The age distribution for the male patients is from 38 to 51 years, with a mean age of 45 years. These age and sex distributions correspond closely

to those obtained for the total two year series of 84 patients, with 70 female and 14 male patients and an age range from 24 to 72 years, with a mean age of 44 for both sexes. The mean age for men is 48 years and for women, 41 years.

Eleven of the group of 26 female patients in the follow-up study are post-war European immigrants. Fifteen are native born, four of whom are Southern-born Negroes. Three of the four male patients are recent European immigrants; one is native born. Nineteen of the female patients were married; three single, when first seen; three widowed; and one separated. Three of the men are married; one is single.

The diagnostic entities in the total group of 84 patients showed a considerable number of cases of severe emotional disturbance. There were eight schizophrenics (9 per cent), nine borderline cases (10 per cent), and twenty-two patients with moderate to severe character disorders (25 per cent). Of these 84 unselected consecutive patients, 81 (96 per cent) gave clear evidence of emotional disturbance antedating the onset of Graves' disease. Some could not be classified as distinct psychiatric disorders. The most frequent features found were anxiety, phobias, obsessive-compulsive manifestations and depression. In three cases there was no evidence of severe pathology, but rather of acutely precipitated anxiety with a measure of depression in otherwise fairly well-adjusted individuals.

In the follow-up group of 30 patients there were four schizophrenics (13 per cent), five borderline cases (17 per cent), eight patients with character disorders (27 per cent), and 13 patients with manifestations of anxiety, phobias, obsessive-compulsive mechanisms, and depression (43 per cent).

TABLE II

Classification of total group of eighty-four patients

	Number	Per Cent
Schizophrenics	8	9
Borderline cases	9	11
Character disorders	22	26
Other emotional disturbances	45	54
Total	84	100

TABLE III

Classification of follow-up group of thirty patients

	Number	Per Cent
Schizophrenics	4	13
Borderline cases	5	17
Character disorders	8	27
Other emotional disturbances	13	43
Total	30	100

TRAUMATIC EXPERIENCE, CONFLICT AND PROLONGED STRESS

In 71 of the cases, 85 per cent of the group, there was evidence of traumatic events chronologically related to the onset of the thyrotoxicosis. These events were, however, within the realm of usual life experiences. The striking feature was precisely the absence of traumata of overwhelming magnitude. In the remaining cases, no distinct precipitating factor could be elicited other than prolonged emotional stress.

In accordance with observations of Bleuler (4), Lidz (5), and Lidz and Whitehorn (6, 7), we found that the traumatic events predominating in our material are more within the range of life's vicissitudes experienced by all, such as the loss of a love object. The classic 'Schreck-Basedow', often described in the older literature, was not encountered in our patients. Reference is made to a sudden crushing experience which overwhelms a person who has been well adjusted and whose life has been well organized until the moment of a tragedy such as being forced to watch the brutal slaying of wife and children, followed by the onset of Graves' disease within four to five days. These patients have been known to make rapid recoveries with treatment.

The following case provides an example of the onset of Graves' disease immediately preceded by a personal loss.

Case 1

A 58 year old woman noticed the first symptoms of Graves' disease two weeks after the death of her husband, who had been ill for several months with a heart ailment. His doctor had advised hospital care. But the patient found the thought of separation intolerable and insisted on keeping her husband home, caring for him day and night.

During this period her son of 24 years, who had been in service, came home with his wife and baby. His departure to his own home took place shortly before the husband's death. Since she felt on "closest possible terms" with her son and detested the daughter-in-law who had taken her son away, his leaving was, therefore, an added threat to her emotional security. Not only was she faced with the loss of her husband after 39 years of a good marriage, but she also was deserted by her son. When the patient related that her husband, shortly before his death, had complained that the daughter-in-law's presence was killing him, the patient's remark sounded apocryphal, expressing her very own feelings.

She also had a daughter of 29 years who, with husband and child, lived in the same building, was devoted to the patient, and saw her every day, but the patient felt lonely because she missed her son. She always considered herself generous with her children, giving presents as well as advice, controlling her daughter completely. Her son's emancipation mobilized tremendous hostility, and she vowed never to visit him in his home, not even to see the grandchild, despite the fact that her son tried his best to continue a good relationship by visiting her and bringing his child along. She refused financial help from her children and her sister after being widowed and insisted on working hard, though suffering from Graves' disease. She said that she would rather wash dishes; and so she did. During the height of the summer she worked in the kitchen of a resort hotel, badly bothered by sensitivity to heat, palpitations, and tremor. She became severely depressed and when seen three months later was unimproved. After she had been euthyroid for more than six months, she was still mildly depressed and her hostile attitude toward her son and grandchild had changed very little.

This patient's loss of her husband was coincident with the seeming desertion by her son. Her need to control her environment, her deep resentment and her

unforgiving attitude toward those "loved ones" who rebel against her domination, and her need to secure affection in this manner, presents a picture which conforms to the description of the hyperthyroid patient reported by Lidz and Whitehorn (6, 7). The main defenses against inordinate emotional insecurity and repressed dependency needs in their patients were aggressive oversolicitousness, constant manipulation of people around them and rigid demands for compliance and fidelity. This pattern, however, is not at all common in our group.

In some instances we find a minor traumatic experience such as a car accident, in which only slight damage was done to the people or property involved.

Case 2

A 30 year old married woman was diagnosed thyrotoxic four days after a car accident in which she was shaken up but neither she nor her two small daughters were injured. Immediately following the collision, the patient became so agitated that she was hospitalized for observation. As soon as she was told that she was physically ill and required treatment, she began to calm down and became manageable.

When first seen in the Thyroid Clinic two weeks later, this patient was depressed and anxious. She accused herself of responsibility for the accident which might have killed her children, but in the next moment she blamed the driver of the second car for what had happened. She was unable to account for the severity of her guilt feelings which, even to her, seemed disproportionate to the actual experience.

She entered a psychotherapeutic situation and for the next seven months came for weekly sessions. It appeared that she deeply resented her sexual role, envied the male "his power and freedom", and hated her husband for his "extroverted, happy-go-lucky ways" and his self-assurance and acceptance of life. Taking care of the children and the house meant to her submission and inferiority to her husband and exclusion from the attainment of higher intellectual goals. Insecure about her intellectual capabilities and disappointed in herself for "brooding but never doing anything about it", she had come to the conclusion some time prior to the accident that her only salvation was a divorce, the abandonment of her children to her husband, and eventual remarriage to a rich man who could surround her with servants so that she would find sufficient time and energy to devote herself to those "higher goals". This extremely immature woman was incapable of love, sexually maladjusted, intellectually shallow, and very exhibitionistic. Her severe guilt was caused by her destructive fantasies directed against mate and children whom she wanted to abandon. When she almost succeeded in destroying her children while driving the car, the guilt caused a state of panic which threatened to overwhelm her. Her stormy reaction to the "accident" stemmed from death wishes which were hidden beneath her emphatic criticism of people who "made a great fuss at funerals" and her insistence that the dead should be buried quietly, "once and forever", and without the need for repeated visits to their graves.

This woman belongs to a large group of patients who were seen to fail in their attempts at intellectual compensation for deep-seated feelings of inferiority and inadequacy concerning their respective sexual roles. They are unable to back up their fantasied strivings with active investment of energy in concrete achievement of goals. They are often keenly aware of this inability and are constantly on the verge of channelling what quantities of energy they have at their disposal into ambitious artistic and intellectual projects, but, for the most part, they exhaust this energy in verbally aggressive activity in their contacts with others. The volume and tone of their verbalizations is perhaps what has led other investigators into characterizing them as striving and eager to overburden themselves with responsibilities. These verbalizations are essentially empty and cannot be

considered as manifestations of working defenses. These defenses are unsuccessful in the sense that they represent spurious gratification of intense oral needs rather than successful channelling of effort into purposeful activity. The reliance on such ineffectual defenses results in feelings of 'let-down', lowered self-esteem, and a dysphoric mood, often leading to fully developed depression. These defenses are a thin cover for basic oral dependency which is denied.

We see in this patient highly elaborated fantasies centering around *abandonment* of her entire family. Self-realization for her can be achieved only through egocentric and intellectual strivings untrammeled by any maternal and domestic responsibilities. This is in direct contrast to formulations presented by Ham, Alexander and Carmichael (3) which portray the thyrotoxic woman as one who customarily secures affection by having a large family, even adopting children, and taking on unwarranted responsibilities, thus overcompensating for unfulfilled infantile dependency needs.

While the precipitating trauma in this case was relatively minor, its impact derived from the fact that the patient's ego could not handle such a critical break-through of long repressed destructive impulses.

Yet another type of 'traumatic experience' must be mentioned. A reported traumatic event may prove on further exploration to be entirely a product of the patient's fantasy, as in the case of a female patient who stated that she could trace the onset of her illness to an attempted rape.

Case 3

A 43 year old married woman who had a nine year old son had a first episode of Graves' disease at the age of 34 during her pregnancy. She underwent a subtotal thyroidectomy at the time. A year before she was seen in the clinic she again became hyperthyroid but seemed to respond well to medication. Ten months later there was a flare-up which eventually brought her to the clinic for radioactive iodine treatment. She is certain that the most recent illness had its onset a few days after a man tried to attack her at night in a dark street. Subsequent sessions brought out that the only evidence for this purported rape attempt was the fear caused by the footsteps of a man whom she assumed to be following her in the dark.

This woman was extremely guarded in her responses, alert, suspicious, and used laconic evasions and bitingly ironical remarks. She had been disappointed in her mother, who was cold and distant and had deprived her of affection. She was disappointed in life because her sexual role as a woman was unacceptable to her. She has resented her only child from the time of her pregnancy and she is very rigid in disciplining the boy. Her instinctual demands were repressed and her aggressive impulses controlled through compulsive rituals. But her hysterical and compulsive defenses are not always successful in warding off anxiety.

The findings of the psychological report are as follows:

This woman has a good grasp of the verbal aspects of the English language, indicating an above average or superior mental endowment. Nonetheless, the range of her interests is narrow and the efficiency of her intellectual functioning is poor. She does, however, have certain cultural pretensions, and is hence rather defensive about the limitations of her educational background which included only high school. While her innate abilities are reflected in a fine potential for speed and dispatch in manual tasks, diffuse anxiety and resultant poor planning interfere with performance and lower its quality. It would appear that her haste is in large part dictated by a need to get things over with in a hurry and be

done with them, this feeling growing out of her personal conviction of her own inadequacy. She is apprehensive about the impression she will make and is so self-critical and insecure that she races to finish up tasks in order to minimize the self-betrayal and condemnation that would ensue from a belabored but still, to her mind, inevitably deficient performance.

Her verbal productions thinly mask intense aggressivity, the covert target of which is the world in general, for her dissatisfaction with life is pervasive. The most obvious specific focus of her hostility is the male. She autistically belittles, immobilizes, feminizes and castrates men—all the while envying their phallic prerogatives. Feminine attributes are discounted in favor of masculine strivings. There is more a hopeless preoccupation with such strivings than any sort of impulse to achievement; for the patient's strong desire for concrete attainments remains unrealized through a failure to utilize her inborn resources. An awareness of this consistent falling short of her dreams conduces to a flatness and hollowness in her responsivity and a depression of mood. She is secretive and suspiciously alert about sizing up all the elements in a situation, but she does not respond in an adult socialized manner. Since she becomes excited and disturbed very easily, she is very much concerned with holding the reins on her feelings. In the process, any genuine emotional impulses get seriously bottled up or submerged and her synthetic controls only serve to isolate and alienate her from the very experiential realms that she longs for. Her anxiety is profound; her interpersonal relationships cold and strained. She probably suffered unusual deprivations in childhood and never enjoyed more than a hollow hopefulness during temporary periods of amelioration. Severe disciplining and intimate acquaintance with pangs of shame must also have been a part of her childhood. She does not accept her own child as an integral part of her life scheme and handles him in accordance with the demands of duty, exercising a very restrictive surveillance and supervision under the self-blinding pretext of promoting his welfare and protecting him from the rigors of the world. Her relationship with her husband is disturbed by her castrative impulses, her envy of the male's dominant position, her feelings of vulnerability and fear of letting go. She wants desperately to be able to rely wholly upon some dependable person, to find security through utter dependency, but her husband obviously does not fill this role for her. Another impulse is to throw up her responsibilities and flee. Since it is primarily her own weakness and distractability that she hopes to escape, she has contemplated suicide, but harbors strong moral objections to it as a solution.

Her response to all these forces is to try to routinize her life, to cover up her worries and involvements with a facade of normality and placidity through keeping her focus superficially on concrete things and avoiding thoughts and activities that threaten to arouse and disequilibrate her. Cleanliness compulsions play a part here. Her criticality and oppositionalism cause her to collide with other people; and acceptance of them and identification with them is impossible for her. Her alternations of depressed mood and extreme excitability are too disturbing to allow her any real peace.

In summary, she appears to be a severe neurotic depressive with both hysterical and compulsive features. No thinking or perceptual distortions of psychotic degree are apparent, but her defenses are notably brittle.

Real or fantasied traumatic experiences touch upon more fundamental anxieties which arise from unconscious conflicts and remain unresolved. It would seem that because of the link with early life experiences which constitute basic threats to the ego, a minor traumatic event, or even an anticipated or imagined traumatic happening, can cause as serious a reaction as one of greater objective intensity.

Patients who claimed prolonged stress due to occupational and financial worries as a causative factor and who glossed over upsetting circumstances in their recent life history provided particularly convincing examples of the mobilization

of excessive anxiety due to the breaking of defenses under the impact of a deeply disturbing experience which they did not recognize as such.

Case 4

A 51 year old man came for treatment a few months after the return home of his younger daughter whose recent marriage had been short-lived as a result of her husband's impotence. The patient had ideas of reference, had a difficult time getting along with people in his job, and displayed many paranoid projections.

He is the third of four children. His parents died about 20 years ago. His relation to his family was never close. His father was a withdrawn, anxious man who retreated from his responsibilities and avoided any competitive situation. The mother bore the burden of the household and had a hard time making ends meet. The patient had to work at an early age to contribute to the home. He recalls his childhood as unhappy and overshadowed by poverty and deprivation. He described an early ambition to become hardened to life's demands and to develop into a man quite different from his weak, ineffectual father.

But for as long as he can remember, he has been anxious and depressed, as well as irritable and afraid of what people were thinking of him. He worried about his health and finances and worked hard, always preoccupied with the thought that he had to be a good provider for his wife and three children. He is meticulous, has many compulsive habits, and gives evidence of obsessional thinking. During the past two or three years he has been increasingly afraid of loss of control of his aggressive impulses toward his co-workers. He worries mainly about retaliation.

In the months just preceding his illness, he experienced loss of libido, but doubts about his sexual adequacy were of long standing. This patient, who was in psychotherapy for slightly more than two years, brought out a great deal of material which confirmed the initial impression that the return to his house of his younger daughter after she had left her husband because of the latter's impotence, had been the precipitating factor in an acute emotional disturbance. Many of the signs pointed to a homosexual panic leading to fantasies of being ridiculed by his co-workers and fired by his superior. Eventually, he was afraid even to go to work because he felt that he could not face the other men. He expressed bitterness against his daughter for having married this boy whom he had disliked from the first because he seemed weak and "not much of a man". After successful treatment with radioactive iodine, his symptoms shifted to a severe hypochondriasis with cancerophobia predominating. He felt that malignant illness in the rectum and in the stomach was destroying him, and he was very much concerned about an imagined change in his body configuration which made him look "girlish".

The summary of the psychological report states:

This man's perceptions are distorted by a need to tone down emotional stimuli lest he be swirled into a vortex of uncontrollable impulsivity, although at present little self-assertiveness is likely. He is insecure, tremulously anxious, and almost wholly incapable of successfully masking his low self-esteem. Even in his partially suppressed compensatory fantasy or in his painful reaction formations to feelings of decrepitude and inner emptiness and coldness, his sights are set low. Not to be a great strong man, but just to be at least an average man, would be a boon to him. This is an intellectually well endowed person who is immobilized by rigid, ineffectual defenses and by an abject lack of self-esteem. He would like to extend himself, give rein to his need for self-expression, but invariably he withdraws, tense, dysphoric, and liable to resort to regressive devices. He presents primarily a picture of a decompensating obsessive-compulsive with some paranoid trends.

This patient presents a conflict between his need to assert himself as a virile male, stronger than his father, and his fears of retaliation for this masculine

assertiveness which can end only in destruction. The fear of retribution leads to fantasies of relinquishing his maleness altogether. He is without insight into the emotional nature of his problems and denies any but physical ailments. He is one of a large number of patients who casts the blame for his illness on prolonged economic stress. His inability to stand up under even minor traumatic life experiences, such as the return of his daughter to the parental home, seems to him to be an admission of fundamental weakness which is utterly intolerable to him.

In an intensive study of this and other patients in the series of cases followed-up for some time, it became apparent that there was no specificity in the structure of personality, in the nature of traumatic experience, nor in the conflict situation of the hyperthyroid patient. There is no uniform pattern or profile of character traits in evidence. The findings reported by Ham, Alexander and Carmichael (3) in this connection were not borne out by our observations.

The conflict situations uncovered were as varied in our group of patients as those seen in neurotic and psychotic patients in general. In some instances they were reminiscent of constellations sometimes described for patients with peptic ulcer, hypertension, or asthma. Stokvis (8) came to a similar conclusion in his structure-analysis of 100 patients treated for various psychosomatic disorders.

ANXIETY, AGGRESSION AND DEPRESSION

The prominent features commonly found in the hyperthyroid patients in this series were a severely disturbed affectivity together with marked sexual maladjustment. Excessive anxiety, destructive aggression, and depression were usually present and dominated the clinical picture.

The thyrotoxic state has been described as "crystallized fright", and the patient suffering from Graves' disease has long impressed clinical observers as being, indeed, overwhelmed with anxiety. However, depression and, less frequently, a hypomanic state, are present, and at times, the clinical features resemble those of an agitated depression.

Superficially, one might be inclined to ascribe the depressive reaction to the severely disabling effect of the thyrotoxic condition. In particular, tremor reduces the use of the hands and often strikes the patient as the most revealing sign of his slipping controls, further lowering his already damaged self-confidence and self-esteem. Thus, tremor, as well as tachycardia, might be considered traumatic in this sense. A depressive reaction in the wake of panic caused by such physical disability could then be thought of as part of the process of restitution following a severe physical trauma as described by Shands (9).

Such a sequence of reactions is not borne out by close study of the onset and fluctuations of the depression during and after the thyrotoxic state. In most cases the depression precedes the fully developed toxic state, only to become more severe and accompanied by restlessness—at times to the point of agitation—at the height of the thyrotoxicosis. As a rule, within four to six weeks after the administration of radioactive iodine, a distinctly euphoric reaction sets in. This reaction may last from two to four weeks. Quite commonly there is a short period of hypothyroidism which sets in six to twelve weeks after administration of

radioactive iodine. At this point the underlying depression reappears. Often, a mild psychomotor retardation has replaced the agitation and increased mentation which characterized the depressive picture prior to treatment. But the affective tone continues to be predominantly depressive. The hypothyroid condition coincides with this period of sluggish depression and may be mild or severe. Once thyroid function has reached the levelling-off point, the euthyroid state, the signs of psychomotor retardation disappear as the depression clears up.

Thus it would seem that there exists an intimate correlation between thyroid imbalance on the one hand and affective tone, irritability to the point of self-destructive impulses, and depression on the other. The intriguing aspect of this concomitance is the apparent importance of some state of imbalance, either hypo- or hyperthyroid. The exclusive linking of the hyperthyroid state with emotional disturbance must be expanded. There are manifestations of disturbed affect accompanying the hypothyroid state as well. The evident lack of attention given to psychophysiologic correlations in mild to moderately severe *hypo*thyroid conditions has recently been commented on by Bleuler (4).

A good example of the coincidence of affective disorder and hypothyroidism is provided by the earlier history of the patient already described in Case 2, who experienced such a severe emotional reaction to a minor automobile accident.

Case 5

This 30 year old patient had been diagnosed as hypothyroid by her family physician five years prior to the onset of Graves' disease. Her BMR was minus 24. She was treated with three grains of thyroid extract during the first two years, later continued with one grain for another year. Apart from the characteristic physical symptoms, she had complained of mental sluggishness, listlessness, loss of libido, irritability with members of her family, a desire to withdraw from friends, and rapid and frequent mood swings. Thyroid medication helped little. Her depressive moods recurred. She remained overweight and, therefore, stopped the thyroid medication in favor of 'reducing pills' (dexedrine combined with thyroid extract) which she continued to take until her accident and the onset of thyrotoxicosis.

In some instances the period of hypothyroidism after radioactive iodine treatment is prolonged. The following case illustrates the changes in affect during the period of hypothyroidism as well as the important role of aggression and sexual maladjustment which are so prominent in thyroid disturbances.

Case 6

A 44 year old married woman, a recent European immigrant, came for treatment of a recurring thyrotoxicosis three years after thyroidectomy. The first illness was ascribed to her fear of being "trapped" in Europe where she had led the hard and hazardous life of a displaced person for a number of years. She fell ill while in the process of preparing for entrance into the United States. The onset of her recent illness followed shortly the discovery that her elder daughter was to have an illegitimate child.

This intelligent, cultured woman, who was seen at irregular intervals over the course of two years for 32 psychotherapeutic sessions, showed marked rivalry with an older sister whom she had tried to outshine by superior intellectual achievements since childhood. She was close to her mother, whose arrival from Europe she was eagerly awaiting. The description she gave of her mother's personality revealed a high degree of identification. Like her mother, the patient was superficially cheerful and poised, but she tended toward brooding

and self-deprecatory attitudes, and was frigid and phobic sexually. Any dependence on her mother, however, was emphatically denied and the degree of ambivalence toward the mother manifested itself in her frequent facetious remarks which were meant to show the patient as far superior intellectually and more sophisticated than the mother. Death wishes toward the older daughter and against her husband appeared in dreams and fantasies about "emerging from a tragedy such as losing my husband, stronger than ever". Though able while toxic to maintain her poise and to "laugh off" her depression, this patient showed more severe mood swings and, later, a moderately severe depression while hypothyroid.

She reacted slowly to thyroid medication, with her physical symptoms of hypothyroidism clearing up long before her affective lability was alleviated.

Superficially, she had made an excellent adjustment to an extremely difficult life situation. Without financial resources or relatives to help, she worked with her husband as a domestic on a country estate. She denied any resentment of such work or of her employers, whose kindness and thoughtfulness she never ceased to praise. But the repressed hostility against them, as well as her self-destructive drives, were expressed in phobias, one of which centered around the destruction of her employer's house by fire.

The psychological tests revealed the following:

This patient is secretive and evasive, going even further than to deny her illness. She does, in fact, attempt to keep from awareness any knowledge of herself or those near to her that would prove psychologically painful. Being somewhat obsessive, she takes care always to weigh and balance opposing considerations. She has difficulty in settling on the pleasant, gratifying aspects of a matter and seems to be under a compulsion to dredge up all sorts of contrary particulars once she has expressed a positive attitude about a thing. It would appear that her very capacity for pleasurable indulgence is a formidable threat to her; and thus moderation, measured pleasure, becomes a good in itself. Enjoyment of beautiful things, consumption of alcohol and smoking are handled along these lines, but sexual expression is far more stringently controlled, in fact, outrightly condemned, blocked out. Her own extremely aggressive, phallic impulses are denied or diverted into materialistic channels.

Having thus dealt with her own impulses, she proceeds to squelch and degrade the male whose dominance she cannot tolerate. Wifehood is a demeaning rather than a fulfilling estate; motherhood is not much more satisfying although both are socially expected and hence necessary. It is very likely that this woman has experienced murderous rages against her husband and children and that she has been afflicted with great fear of losing control in this regard and that she has even suffered self-inflicted minor martyrdoms on their behalf, in keeping with the rigors of her personal talion-like morality. She harbors a guilt ridden and resentment laden attachment to her mother which probably stems from old familial frictions over her achieving independence and demanding freedom of choice in vital decisions. A mild dysphoria is shown, but its specific oral derivation is not clear. Rather, there is an unfocused, diffuse sensation of foreboding of generalized loss. At a superficial level, this is handled by means of the sour grapes mechanism according to which others who have not suffered loss are not happy anyway and therefore the lost objects are of doubtful value.

The above case provides a good example of the dynamic interrelation of aggression and anxiety in depression seen during periods of thyroid imbalance. The exact nature of the psychophysiologic correlations between thyroid imbalance and affective lability remains to be explored more fully. Mandelbrote and Wittkower (1) were impressed with the constancy of depressive reactions in Graves' disease and refer to the thyrotoxic state as a possible "depressive equivalent". This formulation, however, does not seem very felicitous since it implies an al-

termation of thyroid imbalance and depression, whereas they actually occur concurrently.

Although the link between endocrine disturbances and the depressive reactions is not as yet clearly established, the widespread evidence of conflict over oral needs and deprivations in these thyroid patients is impressive.

Case 7

A 51 year old single man who had immigrated to the United States two years prior to being seen at the clinic, was an only child who never knew his father and was brought up by his mother and maternal grandmother. He recalled their attitudes as especially protective. During the war he became separated from his mother. Upon hearing of her death, he developed gastrointestinal symptoms, which were alternately diagnosed as duodenal ulcer and nervous stomach. Ever since his arrival in this country he has been disappointed because of his feelings that the people he has met are cold and unfriendly. Though engaged to be married he displayed extreme resentment toward his fiancee, describing her as unreliable and selfish because she did not "keep her promise" to set him up in business. Nevertheless he was unwilling to terminate the relationship. His mother-centered frustrations have left him with a profound fixation on sources of oral gratification as indicated by his extraordinary percept of "breaded fried chicken" to Card VII of the Rorschach, and by his drawing of an apartment house which had a bakery shop with a display of bread-stuffs in its window when he was asked to draw a picture of a house.

Case 8

A 24 year old married woman maintained a close relationship with her mother throughout her six years of marriage. She has not seen her father since the age of four as the result of divorce. Six months after a brief hospitalization of her mother, the patient noticed first symptoms of Graves' disease. She has always been a "worrier" and obsessionally preoccupied with finances, and been high-strung and short tempered with her only child and her younger sister.

The psychological test findings reveal that her primary attachment appears to be to her mother, whom she regards consciously as a close ally and protectress, and yet whom she projects as a dominant and phallic figure. Though the precise circumstances are in doubt, there is weighty evidence that this woman has experienced very traumatic oral deprivations which have conditioned her to resort to uninhibited aggression in this one area, whereas aggressiveness in other directions is in large measure controlled. So pervasive is the effect of the oral trauma that a generalized fear of loss of love and loss of loved ones shows itself.

Case 9

A 31 year old married woman gives a history of being entirely dominated by her mother with whom she has a relationship that she herself describes as "maybe too close" and which is fraught with conflict. Attempts at freeing herself from her mother's domination are frequent but short-lived despite support in this by her doting husband. Her psychological test responses abound in oral associations, most of them reflecting infantile, primitive and aggressive orality.

Changes in affective tone have received less attention than the anxiety experienced by thyrotoxic patients since their physical manifestations appear as vivid expressions of excessive anxiety. But there are patients in whom excessive anxiety is not a prominent feature. They continue throughout their illness almost as if their somatic symptoms were contributing to their ability to function. Once physical treatment has started, these patients relate well to their physician whom

they accept only in a regressed dependent relationship. This trust and acceptance further alleviate anxiety. Here lies also the clue to some of the impressive results with the most superficial kind of psychotherapy. But the physical symptoms, the tremor and the palpitations and perspiration, may continue for quite a while *after* lessening of anxiety has taken place.

Efforts have been made by various investigators to equate anxiety with increased thyroid activity (10–12). Extensive exploration along this line is in progress at the Radiophysics Laboratory of the Mount Sinai Hospital. Only preliminary findings are reported here. Patients from the Psychiatric Clinics of the Mount Sinai Hospital and from private practice were selected for study of levels of thyroid functioning after it had been ascertained that they had never been diagnosed as either hyper- or hypothyroid and that they had not taken thyroid for any reason whatever. Patients with kidney trouble as well as those who had recently undergone x-ray examinations of the gall bladder were excluded. These psychiatric patients were selected specifically for displaying marked free-floating anxiety and aggression as well as multiple phobias. In other words, an attempt was made to find psychiatric patients who were similar in many salient clinical and dynamic aspects to the patients in the hyperthyroid group. Sexual maladjustment, disturbed relationship with the mother, denial of hostility toward parental figures, frustrated dependency needs leading to unsuccessful attempts at autonomy, efforts to gain affection through domination of mate and children were evidenced in many of these psychiatric control cases.

Seven women and four men, ranging in age from 21 to 55 years, in treatment with six different psychiatrists, constitute this small control series which is reported here in a preliminary account of work in progress. Plans have been made to extend this control series and to carry out such physiologic investigations on a larger scale. Summaries were prepared from the clinical notes and routine psychological reports on the eleven psychiatric control cases.

Psychiatric Control Case 1

A 45 year old married woman with multiple phobias and given to impulsive verbal outbursts of a very hostile nature, became acutely depressed following a stormy scene which involved her husband and two daughters. She feels blameless and bitterly resents her younger daughter's and her husband's rebellion against constant domination. Married for 20 years, she has never been satisfied sexually. Completely unproductive and almost paralyzed by her phobias, she nevertheless sees herself as self-sufficient. Her relationship to her 78 year old mother has always been very disturbed, and she never forgave her mother for separating from her father when the patient was five.

Psychiatric Control Case 2

A 44 year old married woman with a severe obsessive-compulsive neurosis, cancer phobia, and overt hostility against her mother had been brought to the United States at the age of five, following the death of her father. Her mother remarried shortly thereafter, but the patient "loathed" her stepfather. The middle of three girls, she felt strong rivalry toward her sisters whose "social achievements" have remained a continual threat to her. Her failure to accept her sexual role has led to frigidity and a hostile attitude toward all men. She has tried to dominate her whole family and has succeeded with her husband. She wants

TABLE IV

I^{131} *per cent blood levels*

	Mean	Standard deviation of the mean*
Euthyroid cases	0.1	0.003
Hyperthyroid cases	0.92	0.074
Psychiatric control cases	0.083	0.016

* Cf. Arkin, H. and Colton, R. R.: An Outline of Statistical Methods, Barnes and Noble, New York, 1939, 4th Ed., p. 120ff.

children but is terrified of childbirth. The thought of having to go to a hospital for the delivery provokes panic and fantasies of being abandoned by her family.

Psychiatric Control Case 3

A 21 year old unmarried nurse, diagnosed as a character neurosis with obsessive-compulsive and depressive features, expressed strong feelings of guilt for not being more self-sacrificing toward her mother. The psychological report states that the patient's basic problem revolves around a conflict between dependency needs and her desire for autonomy. While she feels that she cannot trust others, and, therefore, does not wish to depend on them, her feelings of low self-esteem lead her to believe that since she cannot depend on herself, she must necessarily look for narcissistic supplies from others. The material indicates that she sees the mother figure to be dominating as well as depriving.

All psychiatric control cases were interviewed by the senior author prior to thyroid function tests. In a brief session, some probing into their conflicts was undertaken. In two instances an almost immediate anxiety reaction could be noted. The patients began to show restlessness, free perspiration, and tremulousness. Other than by these signs it was impossible to arrive at a clear picture of whether the interviews had a cathartic or anxiety-increasing effect.

Immediately after interviewing, tracer doses of radioactive iodine were given. Seventy-two to 96 hours after the tracer doses, tests for protein-bound I^{131} were done to check the radioactive thyroxin. Values above 0.26 per cent of the administered dose per liter of plasma are indicative of a hyperactive thyroid gland.

The findings in all eleven of the psychiatric control cases were within normal range. Protein-bound I^{131} levels in the plasma were: 0.03, 0.05, 0.05, 0.05, 0.06, 0.06, 0.07, 0.08, 0.12, 0.15 and 0.20 per cent of the tracer dose per liter of plasma. The mean value for the group is 0.083 per cent with a standard deviation of this mean of ± 0.016 per cent. In order to evaluate whether this result classifies our psychiatric control group as euthyroid or hyperthyroid, we can compare their blood levels with the available data on the blood levels of euthyroid and hyperthyroid subjects, as presented in Table IV.*

* The data on euthyroid and hyperthyroid cases have been calculated by Dr. Josefine Mayer from the rough data for the paper by Newburger, R. A., Silver, S., Yohalem, S. B. and Feitelberg, S.: Uptake and Blood Level of Radioactive Iodine in Hyperthyroidism. New Eng. Jour. Med., 253: 127, 1955.

A simple inspection makes it obvious that our patients belong to these control euthyroid groups. Calculation of significance (critical ratio) of the difference between the psychiatric control cases and the euthyroid group gives a value of 1.0 and between the psychiatric control cases and the hyperthyroid group, a value of 12.0. Thus, there is a highly significant difference between the psychiatric control cases and the hyperthyroids and no significant difference between the control cases and the euthyroids. These findings from the eleven carefully selected psychiatric control patients do not furnish any confirmation of reported thyroid hyperactivity in anxiety states. These control subjects displayed extreme anxiety but when subjected to physiological tests showed no evidence of increased thyroid activity.

THE FOLLOW-UP STUDY

Among the follow-up cases there was a small number of patients whose ambitious goals were backed up by intellectual and creative endowments and who after they became euthyroid seemed to be able to direct their aggression into constructive channels of endeavor. As long as their competitive struggles do not produce excessive anticipatory anxiety arising from expected retaliation and feelings of guilt engendered by destructive fantasies directed against parental substitutes, a period of relative freedom from dysphoric moods and from rapid mood swings sets in and may last for years. This type of patient was encountered but rarely in our group. Only three patients out of the total of 30 (10 per cent) reached this level of emotional balance. These findings seem to hinge upon two main factors: (a) The number of thyrotoxic patients who showed marked strivings was surprisingly small; while the majority were passive, dependent individuals who found it hard to mobilize sufficient energy to attain even modest goals. (b) Some of those patients who expressed strivings toward the attainment of higher goals in life were among the most immature in our group and had utterly unrealistic and rejecting attitudes toward their roles as wives and mothers. Such wholesale rejection of their feminine role and persistent partial identification in some cases with the male parent underlie the unsuccessful attempts at achievement of intellectual productivity or artistic creativity. Such strivings are so charged with conflict that a continued channelling of effort into successful pursuit of planned goals is interfered with.

A good example of a patient with ambitious strivings who, despite her good intellectual and creative resources, was unable to make a lasting adjustment due to unresolved conflicts is presented in the following case:

Case 10

This 33 year old married, childless woman, the youngest of three siblings, lost her father when she was five years old. Her relationship to her mother was characterized by strong ambivalence and feelings of guilt. In school she alternated between periods of enthusiastic application to her studies and of lack of alertness and concentration. In her teens she already started to have spells of depression. Nevertheless, she was able to graduate from high school at the age of 16 and went to college for two years. At 19 she began to work as a secretary and was advanced very rapidly in her job. For the past six years she has held a

responsible administrative position in an important organization. She found her job interesting and felt appreciated by her superiors but was plagued by frequent depressive moods and anxiety states.

Several years ago she married a man two years her junior who was without a job and had a weak and indecisive personality. A few months after the wedding she felt that she had made a mistake, and her initial protectiveness toward her husband changed into irritation and impatience with his problems. By the end of that year she developed Graves' disease. Deeply resentful of being cast in the role of provider for the family, which role she had willingly accepted prior to her marriage, she nevertheless continued to work during her illness.

Three weeks after treatment with radioactive iodine her husband found a job. Almost at once her depression lifted, and a euphoric reaction set in which lasted several months. Then her dissatisfaction with her marriage returned and a markedly dysphoric mood prevailed for the better part of the following year. During all of this time the patient remained euthyroid. At times she became depressed to the point of suicidal ideas but refused to undergo psychotherapy, expressing fear lest she become too dependent on another person.

During the second year following her recovery from the thyrotoxicosis, she gave up her job and temporarily felt contented in her new role as housewife. But feelings of having betrayed her own ideals recurred and she considered returning to work, but did not do so. Multiple phobias and obsessive thinking continued throughout these years.

She accidentally became pregnant, fulfilling a strong unconscious wish of hers, although neither she nor her husband openly expressed any desire for a child. During the early months of her pregnancy, her husband once again lost his job. On this occasion the patient remained utterly unaffected by his unemployment despite the real hardship it entailed, and, in fact, for the first time in two years she gave expression to feelings of genuine contentment. Accompanying this egocentric satisfaction was an utter disregard and contempt for her husband.

Those events which might ordinarily be construed as precipitating traumata had diametrically opposite effects at different times in the life of this woman, depending upon the meaning the events had for her in the context of her varying identifications. Her denial of the realistic problems involved in her husband's unemployment and his anxiety about the pregnancy points to the symbolic fulfillment of unconscious phallic strivings in this woman.

Most of the patients showed far less energetic strivings and attempts at goal directed activity than the patient just described. They were continuously oppressed by their conflicts, but their behavior was consistently passive and dependent and ineffectual. The nine patients who entered prolonged psychotherapeutic relationships with the psychiatrist revealed how acutely the thyrotoxic patient experiences her passive dependency as the core of her conflicts.

The remarkable feature in the group of female patients followed up by the psychiatric social worker is their continued strong denial of depression, their denial of need for help, and their actual rejection of proffered assistance. Again, this frantic avoidance of any implication of dependency may provide a clue to the widely accepted description of the hyperthyroid patient as being ambitious, "striving toward self-sufficiency", and always busy "doing for others". It is their very unwillingness to accept their dependent status that gives rise to their fantasies of achieved independence and assumption of heavy responsibilities. These fantasied obligations are tremendously magnified but they are seldom undertaken in reality. Nor was the claim that the thyrotoxic patient characteristically uti-

lizes the mechanism of gaining affection and protection by oversolicitude and self-sacrifice toward parent, mate, and children borne out by our observations. These patients are passive and dependent underneath the facades they present.

Three of four closely followed male patients developed gastrointestinal complaints, two of them of the peptic ulcer variety. X-ray examinations revealed no physical findings. Simultaneous occurrence of active peptic ulcer and active hyperthyroidism, however, has been described by Garbat (13).

A private patient who had been treated only with complete rest and thiouracil offered an interesting example of alternation of symptoms in different organ systems.

Case 11

A 52 year old married man seemingly made an excellent initial adjustment upon his arrival in the United States from Europe where he had been a successful professional man. Forced to accept a menial job in a factory, he did so without complaining, and was rapidly promoted. He and his wife stayed at the house of close friends who insisted on planning their life and budget in the new country. This was utterly intolerable to him because he felt "trapped" and helpless in this situation. He wanted to tell his friends to mind their own business but did not dare to do so. Three months later a severe Graves' disease was found, and the patient was sent to a rest home and treated with medication. He recovered within four months. A few years later his wife became hopelessly ill with cancer, and for economic reasons he had to nurse her in their home for more than two years. He was revolted by the details of these duties but carried them out faithfully to the end. A few days after the death of his wife he developed a painful myositis in his back which required almost two years of physiotherapy. Recovered, he married an aggressive, impulsive professional woman whose career soon began to interfere with their private life. She was unable to devote enough time to their young daughter, and the patient stayed away from his business in order to take care of their child. Added resentment was mobilized when sexual relations became infrequent. A peptic ulcer syndrome from which the patient had suffered in his twenties flared up, and he was once more in pain. Simultaneously with the gastrointestinal complaint he developed a depression for which he sought psychiatric help. This man who hid his passivity and masochism under the guise of perfect poise and "devotion to duty" found it exceedingly difficult to verbalize aggressive thoughts which he had in abundance.

While this case was given in some detail to illustrate the involvement of different organ systems, the prominence of disturbances in affectivity and diffuse aggression as well as depression is evident here as in the other male patients who were followed up. The sexual identifications of the male hyperthyroid patients were notably feminine, and potency problems were common among them.

Psychological reports based on retests revealed the following: There was no consistent pattern of change discernible in the retest group. Characterological features, as was to be expected, did not show notable changes. Whereas a few of the patients experienced an abatement of intense body preoccupation with the disappearance of hyperthyroidism, several others shifted to hypochondriacal complaints about other organ systems, most commonly the gastrointestinal tract. In some of the patients, a lessening of emotional constriction was perceptible; in others it appeared to have become more pervasive. Anxiety level was lower in some on retest, higher in other patients. In some cases anxiety was apparently at least better channellized. In others it was handled less well in the retest situation.

In several patients there were shifts from paranoid to phobic emphases between the test and the retest. In several others there was accentuation of phobic ideation. And in yet others there was an increase in paranoid thinking. At least one who had seemed to be on the brink of a psychotic reaction when first tested showed better integration later, while, conversely, several who had not presented a pre-psychotic picture while suffering from Graves' disease appeared to have extremely tenuous grips on reality and ego control after the thyroid condition was cured. Nor did dysphoric and depressive manifestations show consistent amelioration with somatic improvement.

Despite the absence of any specific trend of change between test and retest, one generalization can be made; namely, that those patients who showed the best psychological integration and adjustment while suffering from Graves' disease were the ones who were most likely to show improvement after their somatic illness was cured.

The amelioration shown by the eight patients who improved, out of seventeen retested, was mostly in the sphere of socialization. They were more interested in forming relationships and were less inhibited and ambivalent in doing so. They made a somewhat more effective approach to environmental objects because their emotional controls were handled with greater flexibility and their perceptions were less distorted.

THERAPEUTIC MANAGEMENT

The excessive anxiety of thyrotoxic patients, their constant demands for reassurance, and their resistant and often initially overtly hostile attitude toward the psychiatrist indicate clearly the proper psychotherapeutic approach. A casually accepting attitude was maintained throughout the interviews with these patients, and deep interpretations were avoided. Unfavorable therapeutic results with an impatiently probing technique have been reported by Delay et al. (14), Conrad (16) and, more recently, by Dugan (15). Interviews were conducted in such a manner that the probing and searching aspect of the sessions did not overshadow a sympathetic and gentle approach aimed primarily at relieving excess anxiety and establishing a relationship of trust in the psychiatrist. The patients' extreme distress and helplessness at the height of the thyrotoxic state together with their ingrained mistrust of parental figures and parental substitutes cause them to experience acute fear of losing mastery altogether. If these patients, then, are permitted to test the psychiatrist, either by exploding at once in an outburst of outraged pride for being subjected to a psychiatric interview or by displaying aloofness and sullenness without eliciting imminent punishment, their regressed state can be utilized to facilitate the establishment of a psychotherapeutic relationship. Once this has been achieved, long repressed material may come up readily.

A large segment of the group of patients studied responded to such psychotherapeutic endeavors in much the same way as do patients with character neurosis. In these patients resistances are strongly buttressed by the presence of an objective physical illness which provides ready rationalizations for underlying conflicts. No immediate attempt was made to break through these rationaliza-

tions. Rather, a continued and directed exploration of the past history was carried out.

Since separation from their families tends to aggravate their emotional problems, careful consideration should be given to avoid hospitalization. In view of the fact that anxiety and agitation and depression present a serious problem in the management of the thyrotoxic patient, the alkaloid preparation of the rauwolfia root (Serpasil, Reserpine) has been used as an adjunct in the overall handling of several patients included in this series. This drug is effective in the management of hyperthyroid patients and is superior to barbiturates. Moreover, it has the advantage of not interfering in any way with tests of thyroid function.

DISCUSSION

It has been suggested that no specific personality type nor particular psychodynamic constellation can be deemed the etiologic factor in thyrotoxicosis. Excessive anxiety and repressed aggression with attendant depression, which have been pointed out as prominent features in the group under study, are not sufficient in themselves to account for the development of hyperthyroidism. Other factors whose roles are as yet not fully assessed, such as the genetic and the physiopathological, must be considered.

According to the latest report by Bartels (17), a recessive hereditary factor appears to have been established. Carmena (18) in an interesting study of identical twins found an incidence of 64 per cent of hyperthyroidism in both twins. Martin and Fisher (19) report a familial incidence of 22 per cent in a study of 90 patients, and Ham et al. (3) found an incidence of 21 per cent in a study of 24 patients. Mandelbrote and Wittkower (1) report that seven, or 28 per cent, of their 25 patients gave a history of exophthalmic goiter in parents or siblings, as compared to one case out of 25 control patients. Twelve patients in our series of 84, or 14 per cent, revealed a family history of Graves' disease. There was no evidence of Graves' disease in the families of any of our eleven psychiatric control cases.

The disturbed endocrine balance during menstruation, pregnancy, and menopause may account for the greater frequency of Graves' disease among women. Interestingly, there is less difference in frequency between the sexes in patients past the age of fifty. While the interrelations of the thyroid gland and the pituitary are at least partly understood, the exact nature of the effects and counter-effects between the thyroid and the other endocrine glands is not known to any appreciable extent.

While thyrotoxic men in our series present many feminine character traits, the women were not markedly masculine in orientation. In the study of Mandelbrote and Wittkower (1) it is suggested that manifest confusion over sexual roles is very common as indicated by the fact that 15 of their 20 female thyrotoxic patients (75 per cent) drew the male figure first in the figure drawing test, whereas only six (30 per cent) of their control subjects did so. In our series only six of the 21 female thyrotoxic patients (29 per cent) from whom drawings were obtained drew the male figure first.

The complexity of the etiologic aspect is even more evident when an explana-

tion is attempted for the absence of thyrotoxicosis in people during their confinement in concentration camps (20) and its rarity among combat soldiers during the last war (21, 22). Only some time after liberation from concentration camps was Graves' disease seen to develop. The role of the nutritional element in this situation has been held responsible. However, this nutritional variable was not operative among military service personnel either male or female. Gattig (21) emphasizes the remarkably low incidence of hyperthyroidism among many millions of soldiers during the last war, which is in strong contrast to the increased incidence in certain civilian populations during the war (11). How can these facts be reconciled?

Group existence and group identification in the concentration camp and in military units tend to promote regression. Added to this is a redirection, an externalization, of aggressive drives in both groups (23). The camp prisoner found a target for his aggression in the jailor, while the soldier had the national enemy and his military superiors as objects of his resentment and hostility. Three factors combine to ward off and protect against the self-destructive expression of aggression. These are: (a) regression of the ego, (b) libidinal regression, and (c) ready availability of concrete, external targets of agression. In both groups, during the period of readaptation to freedom and demobilization, aggression had to be controlled, and regressive adjustments were no longer compatible with the social and libidinal demands of life. It was at this point that the former camp inmates and the soldiers, now transformed into civilians, were forced to internalize their aggression and to play their respective sexual roles in a mature way. And it was at this precise juncture, also, that Graves' disease became more prevalent among these groups.

It is notable that of the eight Negroes in the total group of 84 patients all were, in effect, displaced persons, having emigrated to the North from their southern homes. The Graves' symptoms in every one of these cases had their onset after the patient's transplantation to the more openly competitive North. Furthermore, 31 of the group of 84 patients were displaced Europeans who, almost exclusively, had not suffered from Graves' disease before they were forced to meet the competitive challenge of their new American environment.

Ham, Alexander and Carmichael (3) have described the hyperthyroid woman as being precociously pseudo-mature because of her early competitive strivings against her mother. In only eight patients in our total series did we find features of this dynamic constellation. These same authors attribute great significance to the position of the patient as oldest child. The number of patients in the present study who were the eldest in their families was slightly lower than the number of patients who were the youngest children and also lower than the number who were middle children. This finding is in agreement with recently reported observations of Mandelbrote and Wittkower (1). Lidz and Whitehorn (6, 7) and Ham and his collaborators (3) have emphasized how important it is to the hyperthyroid woman to secure affection by having more children than the average woman or by adopting children. The average number of children in the series reported by Ham et al. (3) was 6.6. Mandelbrote and Wittkower (1) found an

average of 1.7, and the average for the 60 married women in our series was 1.5 with none having more than four children. In many instances the children were unwanted, and none of the women in our group had formally adopted children. Explicit expression of compelling desire for children was rare. The need of these patients for love and affection is so exaggerated that it inevitably leads to frustration and is not so often compensated for by caring for others as has been reported in the literature. They are so dependent and feel the burden of any relationship so keenly that they avoid rather than seek out added responsibilities.

Early oral deprivations, sometimes with actual abandonment, frustrated dependency needs, and affective lability characterized by a marked readiness to react with hostility to any threat encountered in familial, occupational, or social relationships are prominent in the life histories of these patients. Since their aggressive impulses are not sublimated in constructive endeavors, they produce excessive anxiety, feelings of guilt, and depressive reactions. A wide diversity of mechanisms of defense are called into use by these patients, but these defenses are rendered vulnerable by extreme affective lability.

The widespread presence of emotional disturbance in the patients in this two year study is documented by the case material presented above. The follow-up study throws further emphasis on the role of their deep-seated conflicts and points up the need in many cases for psychotherapy after they have become euthyroid. Without such treatment, unresolved conflicts are likely to lead to new symptoms. Our experiences with those patients who entered a therapeutic relationship showed that once the acute toxic state has passed primarily supportive therapy can be abandoned in favor of systematic working through of basic conflicts.

SUMMARY

Eighty-four thyrotoxic patients, all but two of whom were treated with radioactive iodine, were studied by means of psychiatric interviews. Some were given a battery of psychological tests and had contact with a psychiatric social worker. Thirty of these patients were followed up by various members of the investigative team over a two year period. About half of the patients were severely disturbed emotionally. Among the other half who were less severely disturbed the most common features were anxiety, phobias, obsessive-compulsive mechanisms and depression.

While traumatic events chronologically related to the onset of thyrotoxicosis were present in the majority of cases, these events were not outside the realm of usual life experiences. The importance of traumatic experiences in thyrotoxicosis derives mainly from their touching upon unresolved unconscious conflicts and is not dependent upon the occurrence of an event of objectively overwhelming magnitude. No specificity in the structure of personality, in the nature of traumatic experience, nor in the conflict situation of the hyperthyroid patient was found. The conflict situations uncovered were as varied as those seen in neurotic and psychotic patients in general.

The most outstanding feature found in these hyperthyroid patients was a severely disturbed affectivity manifested in excessive anxiety, destructive aggres-

sion and depression. There appears to be an intimate correlation between thyroid imbalance (hypo- or hyperthyroid) and affective tone, predominantly depressive. The quantity and intensity of conflict over oral needs and deprivations in these patients are impressive.

Evidence from a group of eleven carefully selected psychiatric control patients, the initial group from a large scale study in progress, does not confirm reports of increased thyroid activity in anxiety states. The psychiatric control patients displayed extreme anxiety but gave normal protein-bound I^{131} plasma levels.

No consistent pattern of change in adjustment was uncovered by the intensive follow-up study of 30 patients over a two year period. Patients who showed the least emotional disturbance while thyrotoxic were most likely to show improvement upon becoming euthyroid. In some cases, especially among the male patients, gastrointestinal complaints developed. Case reports illustrate the involvement of different organ systems along with the presence of disturbances in affectivity with diffuse aggression as well as depression long after the clearing up of the thyrotoxic condition.

In interviews with these patients, a sympathetic and accepting approach is essential to establish a therapeutic relationship. With these anxious, depressed, and extremely dependent patients the psychiatrist must make allowance for their ingrained mistrust of parental figures and parental substitutes in his psychotherapeutic approach.

The multiplicity of factors involved in the etiology of Graves' disease was emphasized, and the genetic, physiopathological and psychodynamic approaches to the problem of etiology were touched upon.

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ACUTE INTERMITTENT PORPHYRIA WITH TRANSIENT AUTO-IMMUNIZATION

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A case of acute intermittent porphyria associated with transient erythrocyte auto-antibodies was recently observed. This case warrants documentation because auto-antibodies, with or without hemolytic anemia, have not been reported previously in porphyria hepatica.

Case Report

A 51 year old widowed Negro domestic entered The Mount Sinai Hospital on June 2, 1955 with acute abdominal complaints of three days duration. Past history was not significant except for fatty food intolerance of five years duration. The patient had used barbiturates on three or four occasions and had taken one grain of thyroid daily for several years because of suggestive hypothyroidism.

Four days prior to admission, following a heavy meal, the patient developed epigastric fulness and pressure. A barbiturate tablet (type and size unknown) was taken for relief, but some hours later nausea and persistent vomiting appeared. During the next three days the patient experienced weakness, chills, fever, constipation, and cramping periumbilical pain. Her urine was darker than normal during this time but the stool color remained unchanged. One day prior to admission there was marked right upper quadrant tenderness, fever (104°F.), slight hypertension (150/90), and T wave inversion on the electrocardiogram.

On admission to this hospital the physical examination revealed hepatosplenomegaly 2 cm. below the costal margin, and moderate deep tenderness in the right upper quadrant and epigastrium in addition to the hypertension and fever noted previously.

A double dose of Telepaque failed to produce visualization of the gall bladder, but no radio-opaque calculi were seen. Because of the darkly colored urine and the somewhat atypical abdominal pain, a Watson-Schwartz test (1) for porphobilinogen was performed and found to be strongly positive.

A direct antiglobulin (Coombs) test (2) performed on the morning following admission was weakly positive (one plus). The indirect antiglobulin test was negative, but the patient's serum was found to agglutinate her own and normal enzyme (trypsin) treated red cells (3) to a titer of 1:16. A selected panel of enzyme-treated red cells of differing antigenic constitution failed to reveal evidence of specificity of this auto-antibody.

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Other laboratory data did not show evidence of increased intravascular hemolysis. The initial blood count showed hemoglobin 12.2 grams, leukocytes 14,300, platelets 220,000, reticulocytes 0.6 per cent, and a normal differential of nonsegmented neutrophils 3 per cent, segmented neutrophils 65 per cent, eosinophils 2 per cent, basophils 2 per cent, lymphocytes 21 per cent, monocytes 7 per cent. Subsequent blood counts were normal with no increase in reticulocytes. Red cell morphology and osmotic fragility were normal. Spectroscopic examination of the plasma was negative for abnormal heme pigments and there was no elevation of the serum bilirubin.

Sickling, L.E. cell preparations, acid hemolysis, Donath-Landsteiner, and heat resistance tests were all negative. Hemoglobin electrophoresis, hemoglobin solubility, and alkaliresistant hemoglobin determinations were normal as were tests for liver function.

Cold and warm saline auto-agglutinins were absent. Serum and platelet serotonin levels* were in the high normal range during the hypertensive period accompanying the acute attack, and normal during the normotensive period following the disappearance of symptoms.

There was gradual improvement in the patient's symptoms although fever continued for five days. The spleen could no longer be felt by the fourth day. Urinary porphobilinogen progressively decreased and disappeared on the fourth day. The positive direct antiglobulin test and the trypsin auto-agglutinins also were absent by the fourth hospital day.

DISCUSSION

The simulation of acute and chronic cholecystitis by porphyria hepatica and the precipitation of acute attacks by alcohol or barbiturate ingestion has been noted (4–6).

It should be emphasized that the acute attacks have often resulted in the mistaken diagnosis of a surgical abdomen leading to operative intervention (4–6). In this case, a Watson-Schwartz test for urinary porphobilinogen established the diagnosis of acute intermittent porphyria. Because of the splenomegaly, tests for anti-erythrocyte antibodies were performed and found to be positive. Interestingly enough, these antibodies were transient and disappeared as the splenomegaly subsided.

Auto-immune phenomena in porphyria have not been previously reported to our knowledge; however, auto-antibodies may not have been searched for, since hemolytic anemia has not been reported in association with porphyria hepatica. Recent reviews of porphyria and of symptomatic hemolytic anemia fail to mention this association (7, 8). Auto-immune phenomena in the absence of increased hemolysis is not uncommon in some diseases associated with alterations of the reticuloendothelial system (9, 10). A positive direct antiglobulin test has been noted in rare instances in apparently normal subjects (11). Although one cannot be certain, the close association of the auto-antibodies in this case with transient

* Kindly performed by Dr. Marjorie Zucker, Department of Physiology, N.Y.U. School of Dentistry.

splenomegaly suggests a pathologic basis for the auto-immune phenomena observed.

SUMMARY

A case of acute intermittent porphyria associated with transient splenomegaly and auto-antibodies is reported.

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THE VECTORCARDIOGRAPHIC AND ELECTROCARDIOGRAPHIC APPEARANCE OF LEFT VENTRICULAR HYPERTROPHY WITH CONDUCTION DELAY

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The sequence of normal excitation of the ventricular musculature is determined by the anatomy of the bundle of His and the Purkinje network (1, 2). This network burrows deeply into the ventricular myocardium to deliver the stimulus to the muscle fibers. The QRS complex represents the spread of the wave of excitation over the ventricles. The normal range of the QRS interval in adults is generally accepted to be 0.06 to 0.10 second (3). When the time for ventricular depolarization is 0.12 second or greater, some type of ventricular conduction disturbance is present.

A host of factors may be responsible for the production of intraventricular conduction disturbances (4, 5). They include anatomic interruption of the bundle branches, functional disturbances in conduction of the bundle branches, ventricular hypertrophy and/or dilatation, drugs such as quinidine and pronestyl, myocardial infarction, electrolyte imbalance, myocardial fibrosis secondary to coronary sclerosis, acute infectious diseases, and supraventricular tachycardias. Excellent experimental and pathologic studies have confirmed the association of the above-mentioned factors with conduction distrubances (6, 7). As a result of these, specific electrocardiographic patterns are recognized as being associated with functional or anatomic blocks in various portions of the conduction system. However, microscopic studies have not always been able to correlate the electrocardiographic findings with specific pathologic alterations (8).

Intraventricular conduction disturbances are recognized in the vectorcardiogram by slowing of the rate of inscription of the time markings which outline the QRS loop (9). Experience has shown that the slowing usually occurs in specific portions of the loop, with other sections inscribed at a normal rate. This produces certain segments of the vector loop in which the time markings are very closely spaced, and other portions wherein the time markings appear at normal intervals. This slowing or "bunching" can be seen in at least two and usually all three of the planes of projection.

In the course of our investigations, we have observed a series of vectorcardiograms in which there are conduction disturbances of an unusual variety. These vectorcardiograms are characterized by terminal conduction delay and a superior orientation of the vector forces. The corresponding electrocardiograms al

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have prolonged QRS intervals, left axis deviation, and unusual precordial leads. To simplify their description they have been divided into two groups. Group A consists of 15 cases which have superiorly oriented vectors and are posteriorly displaced. Group B consists of four cases which have superiorly oriented vectors and are anteriorly displaced.

MATERIAL AND METHODS

The 19 patients studied were chosen from the clinics and wards of The Mount Sinai Hospital and have been followed for periods ranging from six months to five years. A complete history, physical examination, fluoroscopy and/or chest roentgenogram, blood studies, and urinalysis were obtained in each instance. A spatial vectorcardiogram in three planes was recorded using the cube reference system of electrode placement (10). Immediately following this, an electrocardiogram was recorded on a Technicon three-channel direct-writing cardiograph at a paper speed of 50 mm/second at one and one-half times normal standardization.

RESULTS

Clinical evaluation of these patients found them to be a rather homogeneous group. Their ages ranged from 61 to 80 with an average of 69. There were 15 males and four females. A history or findings suggestive of congenital or rheumatic heart disease could not be obtained from any of the patients. Although four had definite angina pectoris, there was no episode compatible with acute myocardial infarction recalled by any individual. Eight patients required digitalis for the treatment of mild congestive heart failure. Notwithstanding, all patients were ambulatory and active. Seven tolerated major abdominal surgery without difficulty. Physical examination revealed diastolic hypertension (above 110) in three and systolic hypertension (above 150) in six others. Atrial fibrillation was the only arrhythmia encountered and that in two cases. Cardiac murmurs were heard in seven.

Flouroscopic or x-ray evidence of cardiac enlargement indicative of left ventricular hypertrophy was present in seven. Atherosclerosis of the aorta as evidenced by calcification and/or marked tortuosity was observed in 14. No chronic lung disease was encountered. Two deaths occurred in the group as a result of neoplastic disease, which was proved by biopsy. Unfortunately, post-mortem examinations were not permitted.

Group A

Those vectorcardiograms which are superiorly and posteriorly oriented have the following configurations in the specific planes of reference (Figures 1, 2 and 3).

Horizontal Projection. The initial forces are directed anteriorly, either to the right or left. The loop is always inscribed in a counterclockwise manner, with the main axis oriented to the left and posteriorly. The terminal portion reveals slowing of the rate of inscription of the time markings indicative of conduction delay.

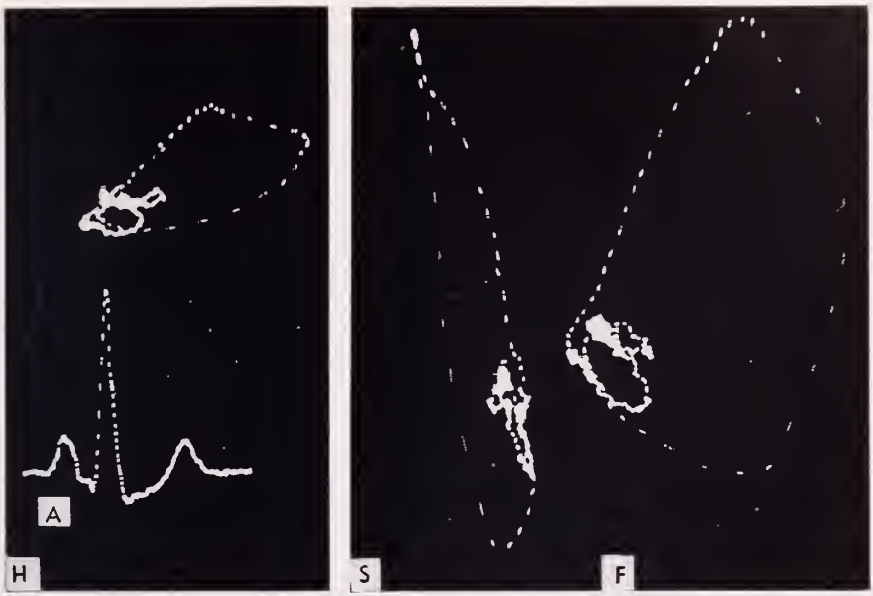

FIG. 1A. A. G., 65 year-old female. Hospital admission for cholecysteetomy because of cholelithiasis. No cardiae symptoms. Blood pressure 150/100 mm Hg. Mild left ventrieular enlargement. The veetoreardiogram reveals superior orientation in the frontal and sagittal planes (F, S). In its terminal part the time markers are more closely spaced. It is furthermore oriented to the left (F, H) and somewhat posteriorly. The ST vector is oriented to the right, inferiorly and anteriorly. The T loop is inferiorly and anteriorly loeated.

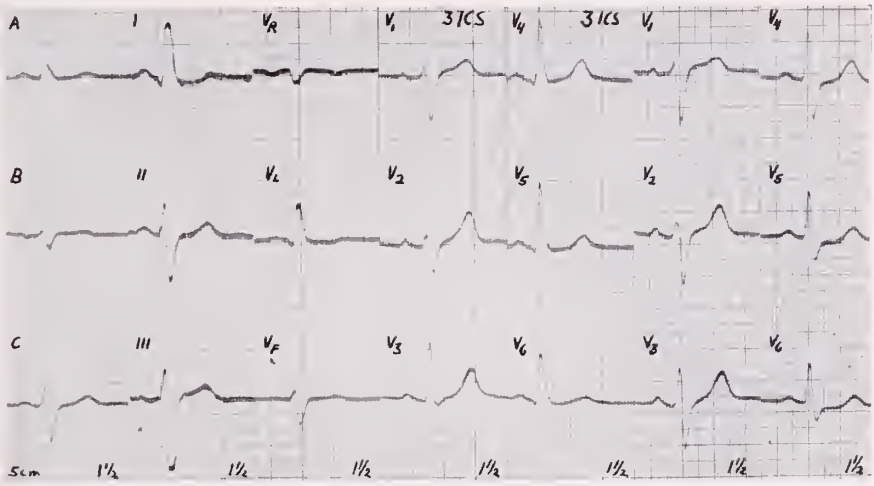

FIG. 1B. Same patient. The electrocardiogram shows a regular sinus rhythm, a marked left axis deviation with a QRS complex duration of 0.13 sec. Two sets of preeordial leads are shown, the first taken at the level of the 3rd intercostal spaee, the second set at eonventional levels. The latter present deep S waves from V4 to V6. Since lead lines for these leads are inferiorly direeted the superior orientation of the cardiac vector projects with deep S waves. When essentially horizontal lead lines are being employed (3rd intereostal space), the ehest leads eorrelate well with the horizontal plane projection of the spatial vectorcardiogram. Leads A, B and C are the vector component leads.

FIG. 2A. H. K., 68 year-old man with a blood pressure of 162/96 admitted for prostatectomy without cardiac symptoms. Radiographic examination of chest suggests somewhat increased transverse diameter of the heart. The VCG is inscribed in a counterclockwise fashion in the frontal and horizontal plane and clockwise in the sagittal plane. The cardiac vector is oriented predominantly superior and to the left and posterior. Its terminal segment reveals a slowed rate of inscription. An ST vector is present, oriented to the right and anteriorly with a similarly oriented T loop (best seen in the lower graph which was recorded at an amplification three times that of the upper one).

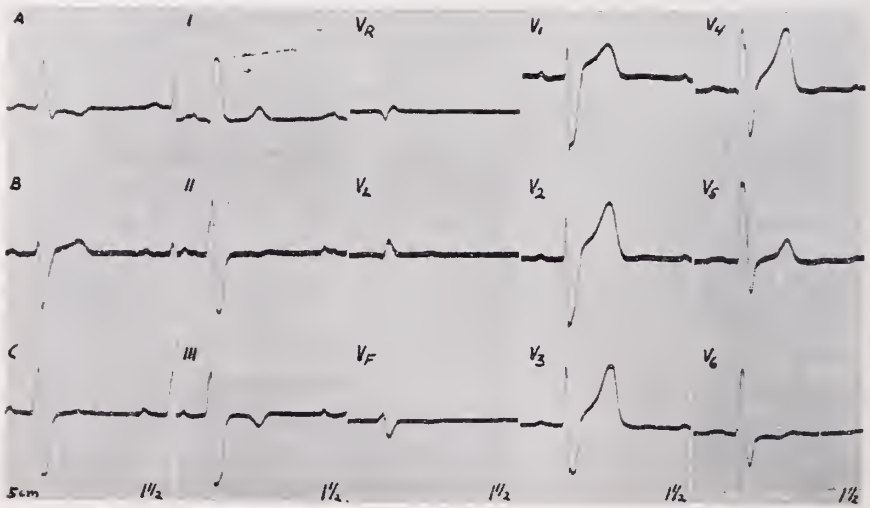

FIG. 2B. Same patient. The electrocardiogram shows a left axis deviation, a QRS complex measuring 0.13 sec. Again, deep S waves are seen in V4, V5 and V6.

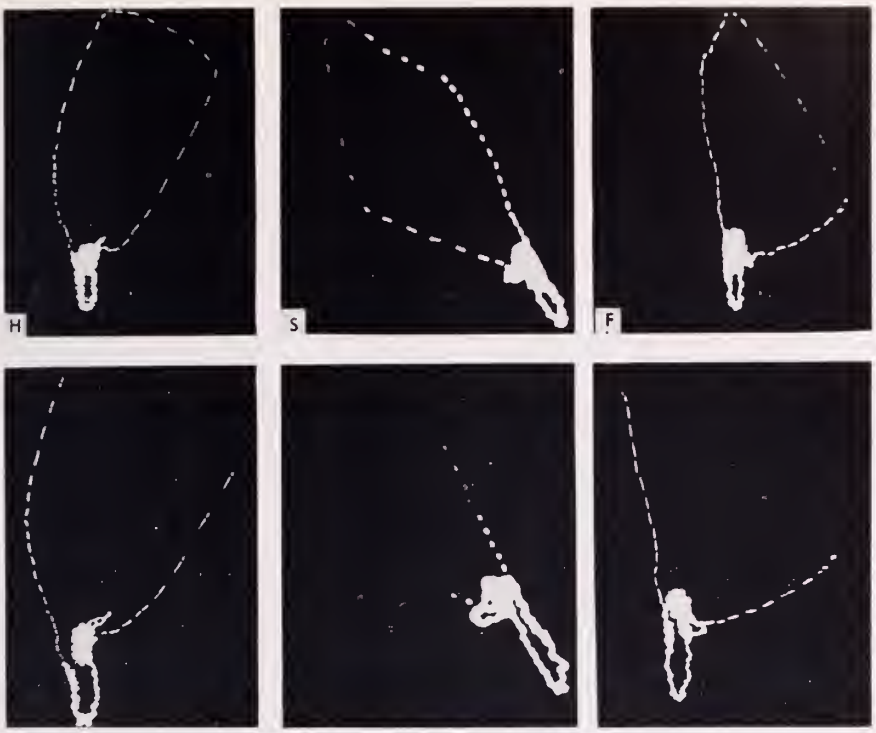

FIG. 3A. I. B., 76 year-old male. Essentially asymptomatic arterial hypertension of 240/110 mm Hg. Radiographic examination of the chest showed no cardiac enlargement and only moderate elongation and tortuosity of the aorta. The VCG is oriented superiorly, to the left and posteriorly, with slowed rate of inscription of its terminal segment. The QRS loop turns initially to the left and slightly inferiorly. The ST vector is oriented to the right and anteriorly associated with a discordant T loop.

Sagittal Projection. The initial forces are directed inferiorly and anteriorly. The loop is inscribed in a clockwise direction in all instances but one and oriented markedly superiorly along the perpendicular axis. Terminal conduction delay is well seen.

Frontal Projection. The initial forces are inferiorly directed to the right or left. The QRS loop is inscribed in a counterclockwise manner in all instances and oriented markedly superior, close to the perpendicular axis. The terminal portion may be to the left or right of the E point with increased proximity of the time markings indicative of conduction delay.

In general, there is an open QRS loop and the ST vector is oriented to the right anteriorly and inferiorly. The T loop is discordant with an inferior and anterior orientation. Occasionally, only an increased QRST angle is present. The electrocardiograms associated with Group A (Figures 1B, 2B and 3B) reveal a left axis deviation in all cases. The QRS duration varies from 0.12 to 0.16 second. In lead 1, nine cases had a qR pattern. In right-sided chest leads, there is an rS pattern with three exceptions which have a QS pattern. In left-sided

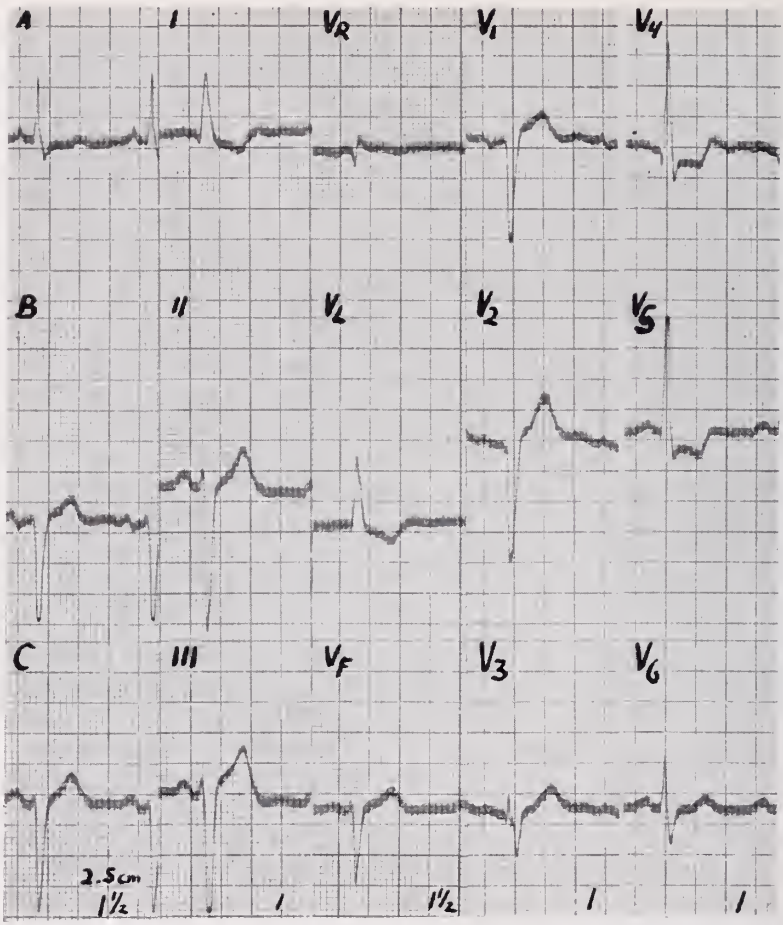

FIG. 3B. Same patient. The electrocardiogram shows regular sinus rhythm, marked left axis deviation with a duration of the QRS complex of 0.12 sec. The initial R wave in V1 is very small, a QS is present in V2 and a deep S wave in V6. The findings in V1 and V2 are not regarded as evidence of a previous anteroseptal infarction.

chest leads, the pattern is that of RS or rS. There is a slurred upstroke in left-sided chest leads in only one instance.

Group B

Those vectorcardiograms which are superiorly and anteriorly oriented have the following configurations in the specific planes of reference (Figures 4 and 5).

Horizontal Projection. The initial forces are directed anteriorly and to the right. Then, the loop is inscribed in a counterclockwise manner posteriorly and to the left, and finally anteriorly and to the right with the conduction delay in the terminal portion.

Sagittal and Frontal Projections. These are identical with the corresponding projections of Group A. This is to be expected since the primary forces in all of these records are superiorly oriented and look alike. Thus, the sagittal projection

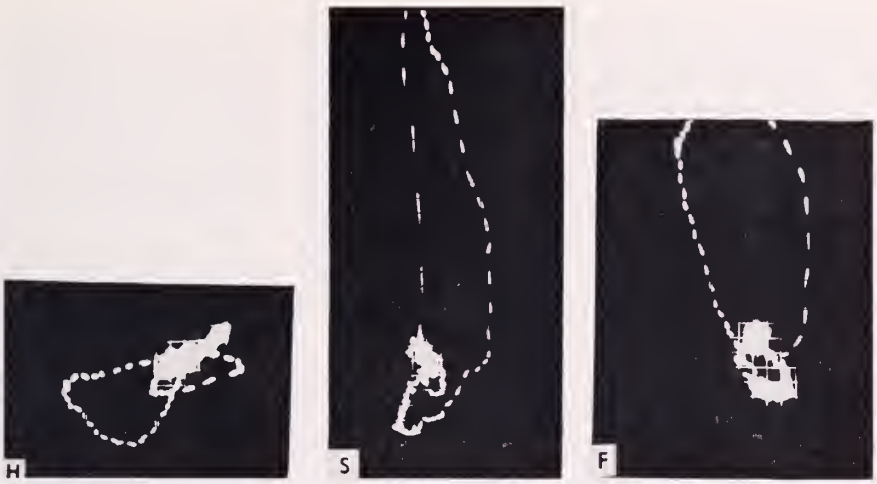

FIG. 4A. A. S., 65 year-old female with metastatic carcinomatosis of the liver. Radiographic examination of the chest reveals a rounded left cardiac contour and an increased cardiac transverse diameter. Marked arteriosclerosis of the aorta. No known hypertension, past or present. Moderately loud apical systolic murmur. No cardiac symptoms. The QRS loop is oriented superiorly, to the right and anteriorly. Its terminal half is more slowly inscribed than its initial segment. The T loop is discordant.

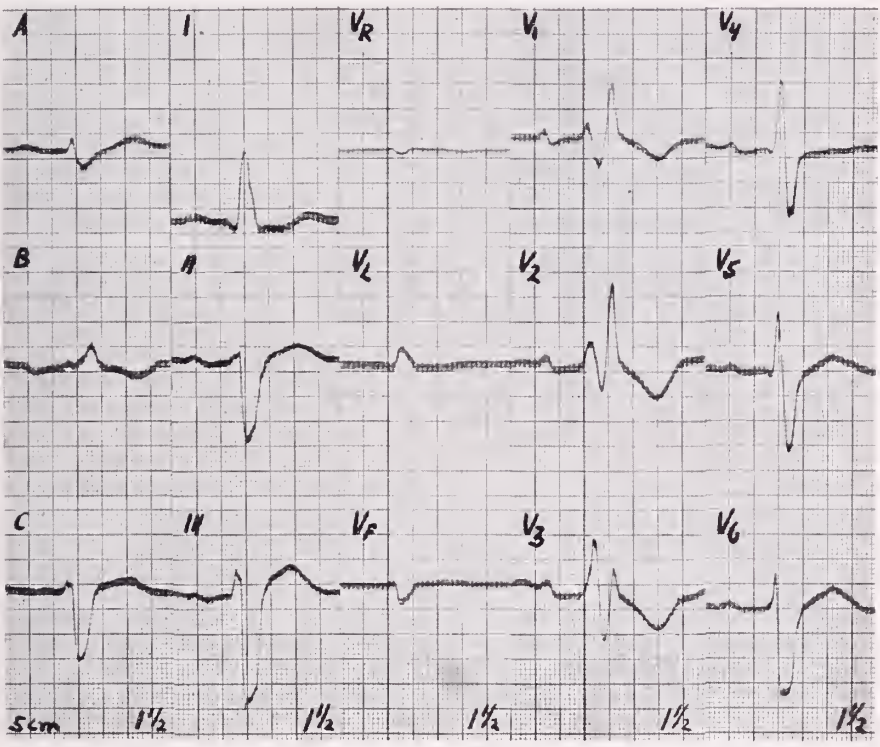

FIG. 4B. Same patient. The electrocardiogram reveals regular sinus rhythm, marked left axis deviation with a QRS complex duration of 0.14 sec. RSR′ complexes are recorded in V1, 2 and 3 with deep S waves in V4 to 6. Note the absence of the S wave in Lead I.

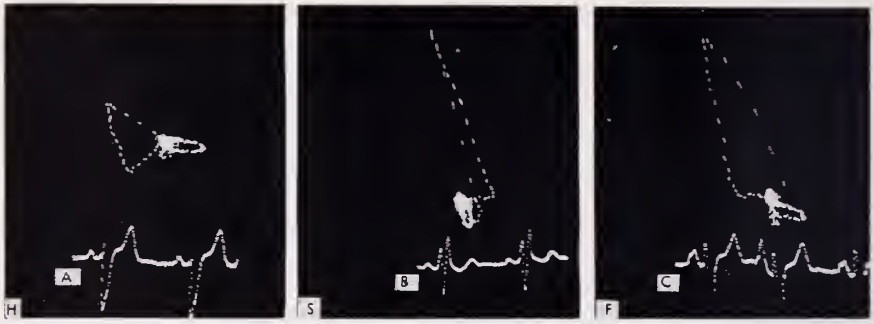

FIG. 5A. B. E., 66 year-old male, suffering from duodenal ulcers for which a gastroenterostomy and vagotomy had been performed. Faint aortic systolic murmur, no cardiac enlargement, Blood Pressure 160/80 mm Hg. No cardiac symptoms. The VCG shows the QRS loop to be oriented superiorly and to the right with a distinctly slowed inscription of its terminal segment. The T loop is inferior and to the left.

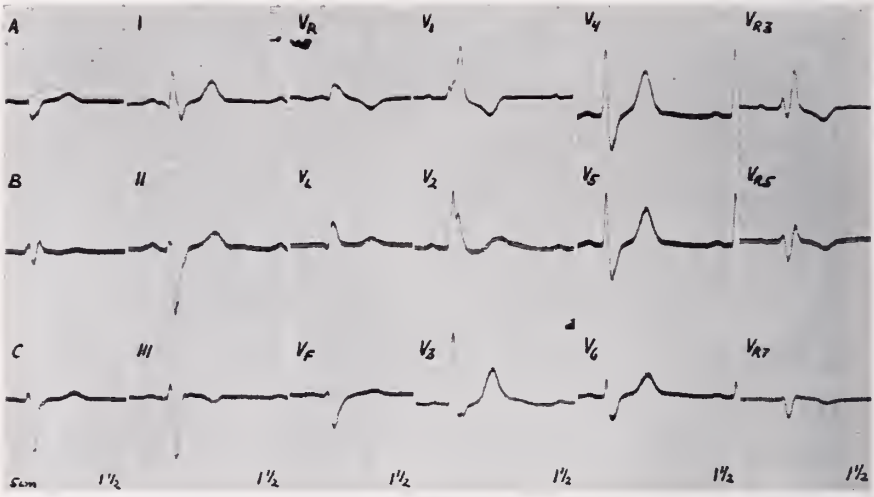

FIG. 5B. Same patient. The electrocardiogram shows regular sinus rhythm, left axis deviation and a QRS complex duration of 0.12 sec. The high R wave in V1 is due to the fact that the superiorly oriented cardiac vector is tilted somewhat to the right and anteriorly. In our opinion left ventricular preponderance with terminal conduction delay is present. We do not believe this to be a form of right bundle branch block.

is inscribed in a clockwise manner and the frontal projection in a counterclockwise manner in all instances. The terminal conduction delay is well seen in both projections.

There was an open QRS loop in only one case. The T loop was rounded, discordant, and oriented to the left and inferiorly in all cases.

The electrocardiograms associated with Group B (Figures 4B and 5B) all have left axis deviation. The QRS duration varies from 0.12 to 0.15 second. In lead 1, there are broad S waves in two instances. In right-sided chest leads, there is an rsR′ in two cases, and a tall R in the other two. In left-sided chest leads, an rS pattern is always seen.

DISCUSSION

In normal individuals, the time markings of the QRS loop are evenly inscribed, with a slight delay often encountered at the very beginning and end of the loop (Figure 6).

The vectorcardiographic findings in right bundle branch block and left bundle branch block have been studied previously (11–18). In right bundle branch block (Figure 7) the major portion of the QRS loop is inscribed in a normal direction in each projection. There is a terminal portion which is irregularly and slowly inscribed so that the time markings are in very close proximity to one another. This terminal portion appears as an appendage which is oriented to the right and anteriorly and has only a minimal component in a vertical direction. The T loop is oriented essentially opposite to the terminal appendage. In left bundle branch block (Figure 8) the most significant alteration is the presence of conduction delay in the middle and late portions of the QRS loop. In the horizontal projection, the loop is clockwise or a figure-of-eight, such that the largest portion is inscribed in a clockwise manner. The initial septal deflection is either absent or minimal.

Comparison of the electrocardiograms and vectorcardiograms of Group A with those of left bundle branch block reveals the following differences.

1. In Group A the initial forces are directed anteriorly, whereas in left bundle branch block the initial forces are posteriorly oriented. This accounts for the presence of q-waves in lead 1 and r-waves in right-sided chest leads in our cases. In left bundle branch block q-waves in lead 1 and r-waves in right-sided chest leads are uncommon.

2. The conduction delay in left bundle branch block is maximal in the middle portion of the loop with terminal extension, whereas our series shows delay only in the terminal portion of the QRS loop. This delay in left bundle branch block produces a plateau at the height of the R-wave in one of the available leads of the electrocardiogram which is not seen in our series.

3. In left bundle branch block, the QRS loop is oriented predominantly posteriorly, whereas in our cases the main QRS loop is superiorly oriented. Because left-sided chest leads are taken below the dipole center, they reflect the superior force as a negative deflection and an rS or RS pattern is inscribed. S-waves in left-sided chest leads in left bundle branch block are not observed.

FIG. 6. H. G., 39 year-old male. No organic disease. The QRS loop is oriented to the left and inferiorly. The rate of inscription is rather even throughout. The QRS and T loop are essentially concordant.

FIG. 7A. E. C., 48 year-old male. Osteoarthritis of spine for which patient received radiotherapy. No clinical evidence of heart disease. The spatial vectorcardiogram shows a terminal right anterior component with slowing (increased proximity of time markers) of the rate of inscriptions. The T loop is discordant to it.

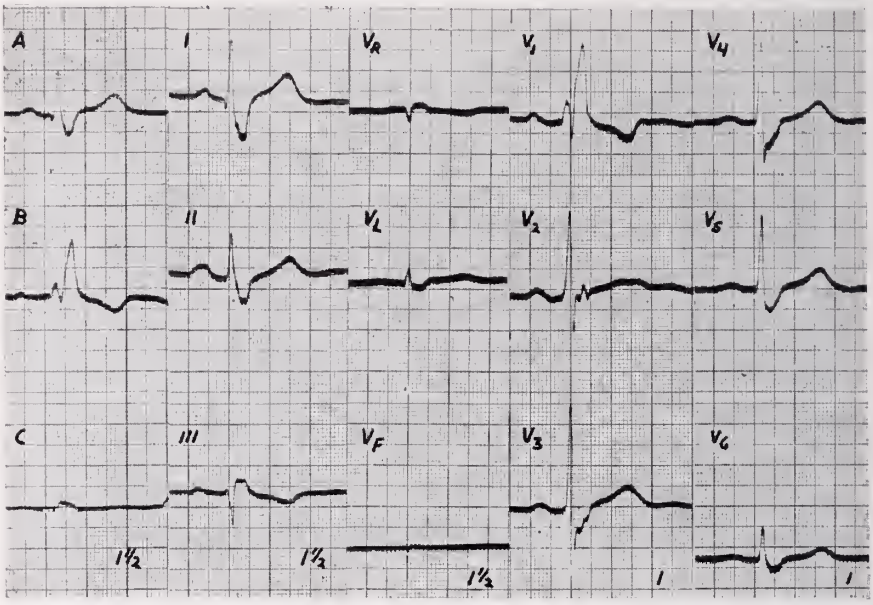

FIG. 7B. Same patient. The electrocardiogram shows regular sinus rhythm with right bundle branch block, the QRS complexes measuring 0.12 sec. A, B, C are the vector component leads (record taken at 5 cm/sec.).

4. In our cases the QRS loop in the horizontal plane is inscribed in a counterclockwise fashion in every instance, whereas in left bundle branch block the inscription is always clockwise.

Inspection of the horizontal projection and precordial leads of Group B reveals no resemblance to those characteristic of left bundle branch block. On the contrary, they resemble right bundle branch block. The vectorcardiographic criteria for right bundle branch block have been enumerated. The terminal forces are oriented horizontally in space, with little or no vertical component. The electromotive forces in Group B which produced this similar terminal delay are not oriented horizontally in space. These slow components represent the return of the superiorly oriented forces to the dipole center and are perpendicularly oriented. The precordial leads do not visualize the fine distinction between the terminal forces in our cases and those of right bundle branch block.

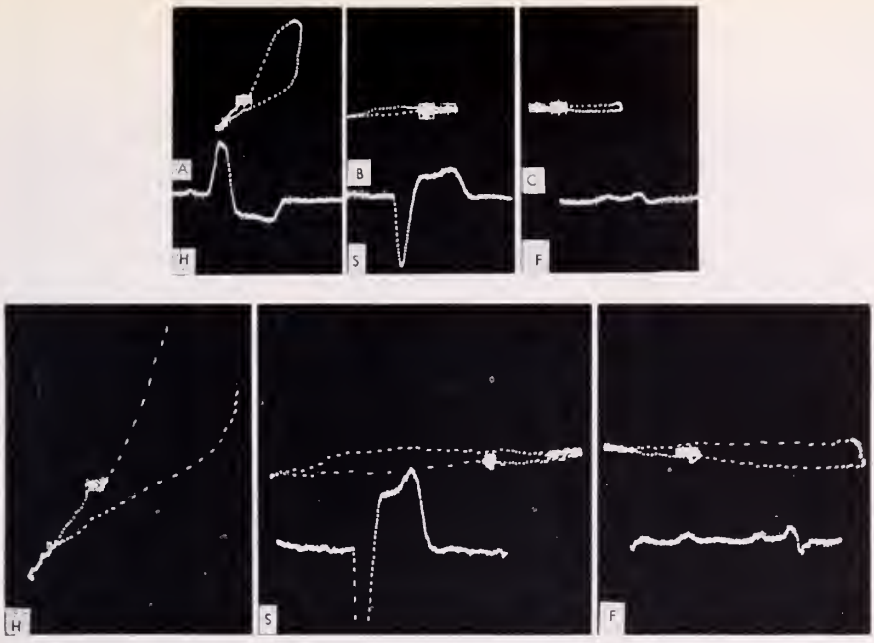

Fig. 8A. A. B., 57 year-old male with essential hypertension, arteriosclerotic heart disease, angina pectoris and diabetes mellitus. The spatial vectorcardiogram reveals left bundle branch block: in the horizontal plane projection the QRS loop is inscribed in a clockwise fashion with distinct slowing of inscription in its middle segment, an ST vector which is oriented anteriorly and to the right and a discordant T loop.

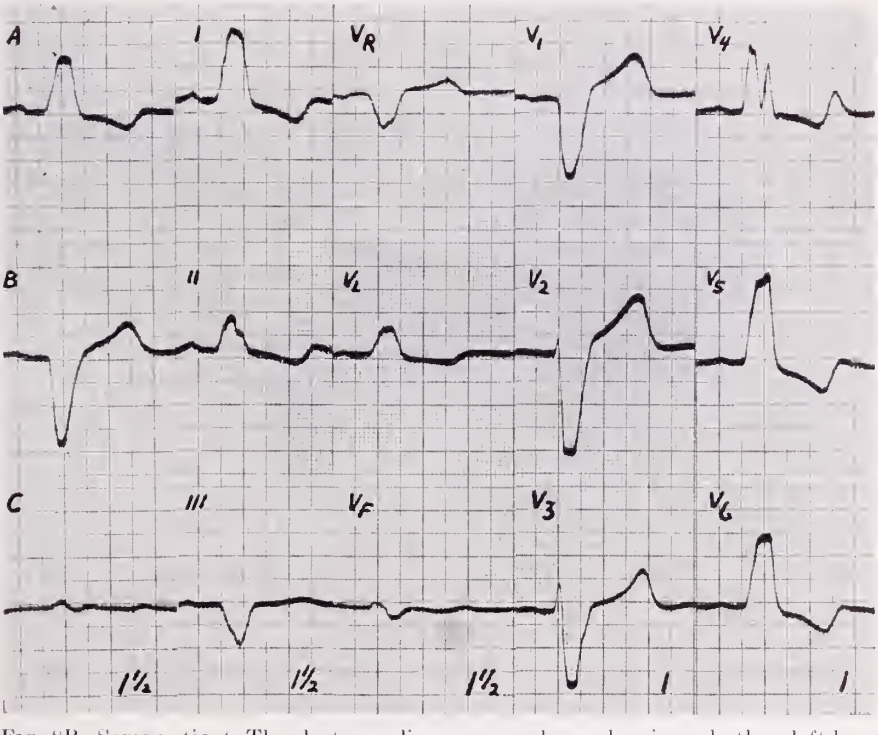

Fig. 8B. Same patient. The electrocardiogram reveals regular sinus rhythm, left bundle branch block with a duration of the QRS complexes of 0.16 sec. A, B, C are the vector component leads. Record taken at 5 cm/sec.

Although by conventional criteria one would consider these records to represent right bundle branch block, we included them in this report for the following reasons: since the bulk of the electromotive forces is directed superiorly, a slight shift in an anterior or posterior direction may cause the horizontal projection to be displaced anteriorly or posteriorly. An analogy can be made between the superior forces of these vectors and a vertical stake driven perpendicularly into the ground. With the stake tilted slightly forward, its shadow will project anteriorly. If the stake is tilted slightly backward, its shadow will project posteriorly (Figure 9). Correspondingly, two similar superior vectors may project differently on the horizontal plane if one is oriented slightly posteriorly (Group A) and the other anteriorly (Group B).

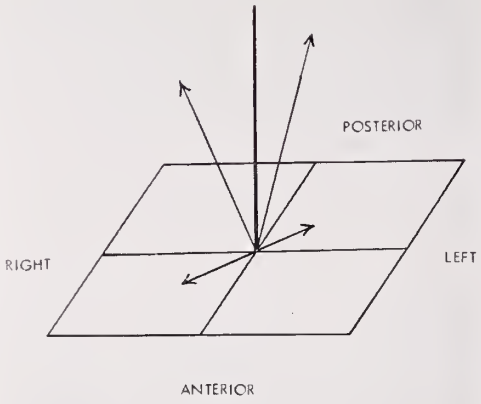

FIG. 9. The diagram illustrates that deviation of only a few degrees from the perpendicular may project the vector either into an anterior or posterior quadrant.

The electrocardiograms of both groups have been compared with the criteria of Wilson, Sokolow and Lyon, and Braunwald et al. for the diagnosis of left ventricular hypertrophy (19–21). Their criteria were not found to be applicable to our cases.

The observations presented concern a group of elderly patients, without a history of clinical myocardial infarction, with a vectorcardiographic and electrocardiographic picture different from those found in left ventricular hypertrophy, left bundle branch block, and right bundle branch block. The electrocardiograms are characterized by features suggestive of left ventricular hypertrophy in the extremity leads (22) without the corresponding pattern in the precordial leads. In most cases, early small r-waves with unusually deep S-waves are found in left-sided chest leads. The QRS duration is increased. The T-waves are partially discordant in most, but not in all cases. In others, late high R-waves or R′-waves were found in right-sided chest leads in association with RS complexes in left-sided chest leads. The vectorcardiograms of both groups were characterized by a predominant superior orientation with increased duration and conspicuously

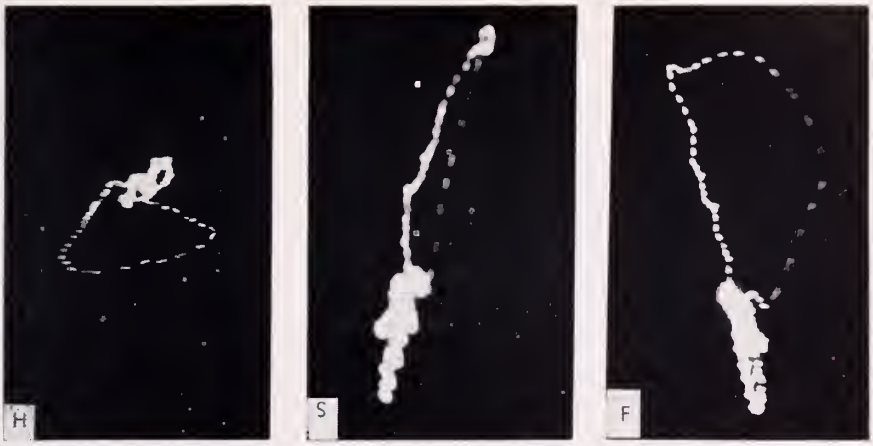

FIG. 10A. B. S., 35 year-old female with a severe form of interatrial septal defect and pulmonary hypertension. The vectorcardiogram is inscribed clockwise in the horizontal plane and counterclockwise in the sagittal and frontal planes. The QRS vector is oriented superiorly and anteriorly with a slowed rate of inscription of its terminal half. The T vector is discordant.

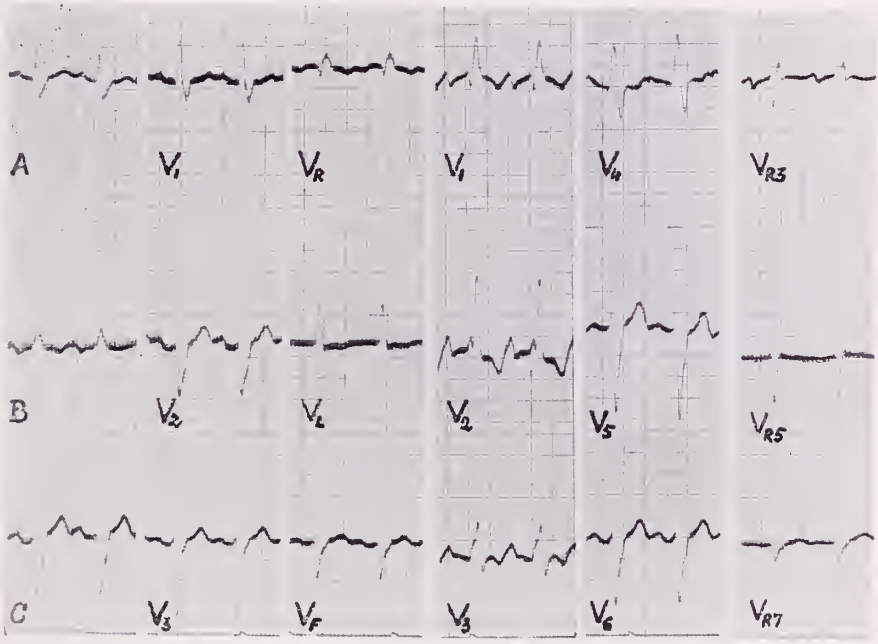

FIG. 10B. Same patient. The electrocardiogram shows regular sinus rhythm and right ventricular hypertrophy with interventricular conduction defect. A, B and C are the vector component leads. The records are taken at 2.5 cm/sec.

increased proximity of the time markings in the latter half of the QRS loop. The QRS loop was open in all cases and the T loop occasionally rounded. Most of the vectors tilted somewhat in the left posterior or lateral direction. Some of them projected in part left posteriorly, right posteriorly, or right anteriorly. It

should be appreciated that minor variations of the tilt from the perpendicular by only a few degrees can greatly affect the resulting horizontal projection (Figure 9). Although their vectorcardiograms are similar, the resulting chest lead patterns are quite different.

Only one case showed suggestive features of the incomplete left bundle branch block as described by Sodi (23). We have seen, however, rare and unusual cases of right ventricular hypertrophy presenting similar features to those in our series (Figure 10). Myocardial infarction may produce localized or even terminal slowing of the QRS loop, the specific alterations still permitting proper recognition (24). This cannot be said for all cases (9). Features commonly encountered in what is referred to as right bundle branch block are not seen in our cases. The slowed segment of the former invariably has a right anterior and horizontal orientation. Our group of cases has an almost perpendicular orientation of its slowed segment.

It has been suggested that vectorcardiographic techniques might indicate the diagnosis of left ventricular hypertrophy when the electrocardiograms fail to do so (25–27).

In the cases herein reported, we believe that these vectorcardiograms occurring in old people are indicative of left ventricular hypertrophy with intraventricular conduction disturbance (9). Castellanos and his co-workers recently published one record similar to those comprising our Group B (28). Their patient came to necropsy and the left ventricular wall was 18 mm thick and the right ventricular wall was 4 mm thick. No myocardial infarction was found. This is suggestive, but further studies and post-mortem material must be accumulated.

SUMMARY AND CONCLUSIONS

1. A series of vectorcardiograms is presented characterized by a superior orientation of the vector forces and terminal conduction delay.

2. The corresponding electrocardiograms all have left axis deviation, an rS or RS pattern in left-sided chest leads, and either an rS or Rs pattern in right-sided chest leads. The QRS duration varies from 0.12 to 0.16 second.

3. The differences between these vectorcardiograms and electrocardiograms and left ventricular hypertrophy, right ventricular hypertrophy, left bundle branch block and right bundle branch block are enumerated.

4. The patients from whom these tracings were derived are all in the older age group (average 69 years), ambulatory, and in reasonably good health. A history compatible with myocardial infarction could not be elicited from any one of these individuals.

5. These vectorcardiograms and electrocardiograms are regarded to be indicative of left ventricular hypertrophy with intraventricular conduction disturbance.

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A CLINICAL SURVEY OF GLOBULIN DISTRIBUTION PATTERNS DETERMINED BY SIMPLE IN VITRO LABORATORY METHODS*

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The selective effects of diverse pathological conditions on the serum alpha, beta, or gamma globulin fractions were initially portrayed by the moving boundary (Tiselius) method of electrophoretic separation of serum proteins. With this method, an increase in the serum alpha globulin concentration was observed as a consequence of infections (1–3), neoplasms, (3, 4) rheumatic diseases (1, 5–7) and conditions associated with tissue injury (8). Relative or absolute increases in beta globulins were frequently demonstrated as a result of biliary obstruction (9, 10), and nephrosis (11, 12) or were often associated with diabetes (3) and less common processes characterized by lipoproteinemia (8). The development of gamma globulinemia due to hepatitis (13), portal cirrhosis (14), lupus erythematosus (15), sarcoid (3), myeloma (8, 16) and other "dysproteinemic" states is well known. Recently congenital agammaglobulinemia (17) has been defined as both a clinical and electrophoretic entity. Secondary or acquired agammaglobulinemia (18) has also been proposed as a factor of clinical importance in a small minority of patients suffering from recurrent infections or advanced neoplastic disease.

Because of the tediousness and impractibility of performing numerous serial Tiselius electrophoretic analyses on serum, there have been relatively few clinical studies which demonstrate the independent and often wide fluctuations which may occur within the major globulin fractions as a result of multifocal, changing, or multiple pathological processes in the individual patient. Luetscher (12) and Thorn, et al. (19) have described several instances of the transition of beta globulinemia into alpha globulinemia during the clinical progression of nephrosis into the nephritic stage of glomerular-nephritis. The development of gamma globulinemia after an initial alpha globulinemia has been reported in such immuno-hematological disorders as infectious mononucleosis (20) and in some patients with rheumatic fever (5) or rheumatoid arthritis (7).

The zone (paper) electrophoresis (21) method of serum protein fractionation has recently become available to the routine clinical laboratory as an alternative to the more cumbersome boundary electrophoresis techniques. The recent critical investigation by MacKay et al. (22) has emphasized the quantitative limitations of paper electrophoresis. The mean per cent error for a single determination of individual globulin fractions approximated 10 per cent for alpha-2 globulin, 8 per cent for beta globulin and 5 per cent for gamma globulin. The resolution of conventional paper electrophoretic methods was unreliable for quantitative measurement of alpha-1 globulin, a fraction related to a number of "acute phase" reactants including mucoprotein, cholinesterase and C-reactive protein. To en-

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hance the reliability of paper electrophoresis, several workers have proposed that the usual methods of staining serum patterns for protein linkages be extended to include separate procedures for staining protein-bound lipids and carbohydrates. Such a triple staining process would provide a more representative picture of changes in the glycoproteins and lipoproteins which are the principal components of the alpha and beta globulin fractions. However, the availability of paper electrophoresis as a routine clinical procedure would thereby be limited. For these reasons, any battery of simple in vitro techniques suitable for the routine detection of quantitative changes among the major globulin fractions would seem to warrant an extended clinical investigation.

During the course of various studies (24–30) on serum proteins in neoplastic, hepato-biliary, and other diseases we have appraised a battery of four simple in vitro procedures which together provide a means of estimating quantitative alterations in the distribution pattern of globulin fractions. Three of these procedures involve the isolation (Fig. 1) and measurement of essentially discrete globulin components, namely: I, the serum alpha-1 mucoprotein (23), comprising about one-fourth of total alpha-1 globulin in the normal subject; II, the acid precipitable globulin (APG), a turbidimetrically measurable protein fraction (28) representing approximately three-fourths of the alpha-2 plus beta globulins; and III, the zinc sulfate (ZS) precipitable globulin (31), representing about 90 per cent of gamma globulin. Estimation of the total protein-bound polysaccharide (Ptp) as galactose-mannose equivalents (32) constituted the fourth procedure

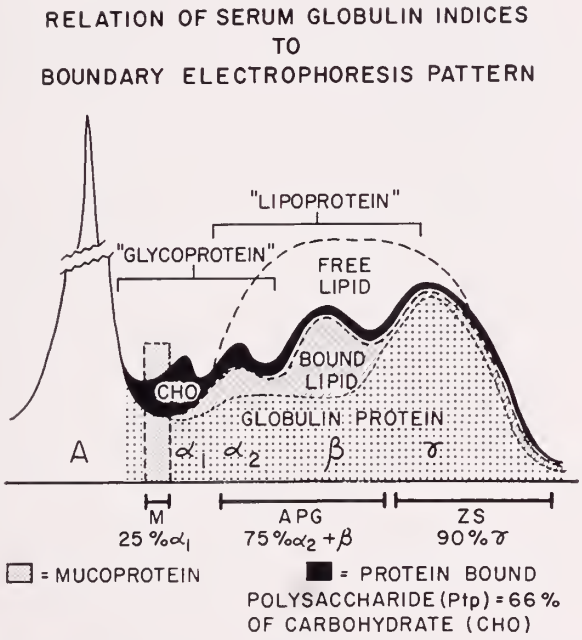

FIG. 1. Diagram illustrating the position of the alpha-1 mucoprotein (M), the acid precipitable globulin (APG), and the zinc sulfate (ZS) precipitable gamma globulin, and the normal distribution of protein-bound polysaccharide (Ptp), the latter representing approximately 66 per cent of total bound carbohydrate. See text for other details.

in this battery of globulin indices. In the normal subject about half of the protein bound polysaccharide is bound to alpha globulins (30) whereas the remainder is distributed (Fig. 1) among beta and gamma globulins (albumin is virtually devoid of polysaccharide). This general distribution of polysaccharide among the various globulins accounts for the numerous reports of increased total bound polysaccharide in a wide variety of the common inflammatory, neoplastic, metabolic, degenerative or traumatic disorders (3, 24, 33). In these pathologic conditions, the increased serum polysaccharide concentration usually results from an increased content of carbohydrate-rich alpha globulin glycoproteins. However, in a number of less common diseases associated with an increase in beta or gamma globulin, an augmented total polysaccharide level may reflect increased increments of beta or gamma globulin polysaccharide, rather than increments from the more usual alpha globulin sources (3). By employing the three simple fractionation procedures in conjunction with the total bound polysaccharide (Ptp) determination, it has been possible to detect a variety of alterations in the distribution pattern of the major globulin fractions, as well to estimate the extent of selective changes within the globulin spectrum. Despite the fact that none of these in vitro procedures could be precisely or stoichiometrically converted into globulin equivalents as measured electrophoretically (or by salt precipitation), there was, nevertheless, a satisfactory correlation (28) between major deviations in the serum electrophoretic pattern and alterations detected by this battery of in vitro procedures.

The four globulin distribution indices were measured in more than 1500 patients with varied pathological disorders. Presented below are data summarizing some of these observations together with a discussion of the potential clinical usefulness of such an in vitro approach for detection of alteration in serum globulin distribution patterns.

MATERIALS AND METHODS

Serum was obtained for study from patients hospitalized at the Medical Service or treated in the Medical Out-Patient Department of the Mount Sinai Hospital. Clinical and pathological diagnoses were established by members of the house or attending staff not primarily concerned with this investigation.

The serum mucoprotein concentration was estimated as biuret peptide by Simkin's method (34) adapted for 2 ml. serum samples. The acid precipitable globulin (APG) turbidity procedure was employed as described by the present author (28). The gamma globulin concentration was estimated by Kunkel's (31) zinc sulfate turbidity method. The total protein-bound polysaccharide was measured as equivalents of galactose-mannose according to Shetlar's modification (32) of the tryptophane sulfuric acid condensation procedure.

RESULTS

The four globulin indices in this clinical study were analyzed with the following range of normal values: Serum mucoprotein (M) measured as biuret peptide,

40–70 mg per cent females, 48–75 mg per cent males; acid precipitable globulin (APG) turbidity, 4–8 units per 0.1 ml serum; zinc sulphate (ZS) turbidity, 4–8 units per 0.1 ml serum; the bound polysaccharide of the total protein (Ptp) measured as galactose-mannose, 90–135 mg. per cent; the ratios Ptp/M 1.2–2.4; and APG/ZS 0.6–1.8.

General Survey

Abnormal values in one or more of the four determinations comprising the serum globulin profile procedure were found in 93 per cent of the initial sera (Table I) submitted from 245 patients, representing about half of the total medical ward admissions during a six-month survey. During this period almost all patients with hepato-biliary disease, hepatomegaly, splenomegaly, "dysproteinemic" disease or difficult or slowly-resolving diagnostic problems were included in this study together with a random sample of infectious, neoplastic, cardiovascular, renal or arthritic cases. In 88 per cent of these 245 patients, the degree and distribution of quantitative changes in the M, APG, and ZS values was

TABLE I

Globulin distribution patterns observed in 245 ward medical patients

Distribution Pattern Type	No. Patients	Quantitative Deviations			
		M mg%	APG u.	ZS u.	Ptp mg%
Alpha	64				
Broad—alpha-1 and alpha-2	43	>80	>9.0	<8.0	+
Narrow—alpha-1	21	>80	<8.0	<8.0	+, 0
APG middle segment	22				
Alpha-2 and beta	4	<70	>8.0	<8.0	+
Beta					
Absolute	8	<70	>8.0	<8.0	0
Relative	10	<45	>6.0	<4.0	0, −
Gamma	76	<70	<8.0	>10	+, 0
With reduced mucoprotein (M)	37	<45	<8.0	>10	+, 0
With reduced APG turbidity	13	<45	<4.0	>10	+, 0
Bimodal	28				
Alpha and gamma	21	>80	<8.0	>10	+
Beta and gamma	8	<70	>8.0	>10.0	+
Trimodal					
Alpha, beta, and gamma	21	>80	>10.0	>10.0	+
Indeterminate or with minor changes	16				
Normal	18				
Total	245				
Reduction in Globulin Component					
Hypomucoproteinemia (M)	45				
Hypo acid precipitable globulinemia (APG)	13				
Hypogammaglobulinemia (ZS)	30				
Total	88				

sufficiently skewed to permit a gross classification (Table I) of abnormal globulin profiles into one of ten patterns. These designations were based on the premise that a selective elevation in the M, APG, or ZS value could be taken as evidence, respectively, for an increase in an essentially discrete alpha-1, alpha-2 plus beta, or gamma globulin component. Increased total serum polysaccharide content, present in over 60 per cent of all sera studied, was not employed in classifying globulin patterns unless the localization of the major polysaccharide increment within the globulin spectrum was apparent by a marked skewing in the M, APG, and ZS value for the individual serum sample. The incidence of the various abnormal globulin profiles as well as the occurrence of deficiency in M, APG, or ZS content is summarized in Table I.

Broad or narrow alpha globulin patterns were found in 64 or 25 per cent of the total sera studied. The broad pattern (Fig. 2a), representing an increase in both alpha-1 and alpha-2 globulin, consisted of elevated M, APG and Ptp values with normal or decreased ZS turbidity. The narrow pattern (Fig. 2a) reflecting a selective elevation of alpha-1 globulin and/or mucoprotein, consisted of an increased serum M content with or without increased Ptp but with normal or low APG and ZS values. These alpha globulin patterns were observed most frequently as a result of infections (Fig. 3), neoplasms, or tissue-reactive processes induced by the common cardio-vascular or renal diseases. In rheumatic fever sera there was no generally consistent pattern despite frequent occurrence (Fig. 3) of high mucoprotein levels. There were no obvious differences in the occurrence of narrow versus broad alpha patterns among the diseases encountered. Potential diagnostic significance was attributed to the absence of hepatitis, portal cirrhosis, lupus, or nephrosis among the group of 64 cases with selective alpha globulin patterns. A selective APG or "middle segment" pattern (34) was represented by a relative or absolute increase in APG turbidity (Fig. 2b) accompanied by relative

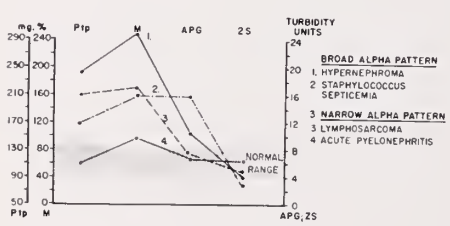

Fig. 2a

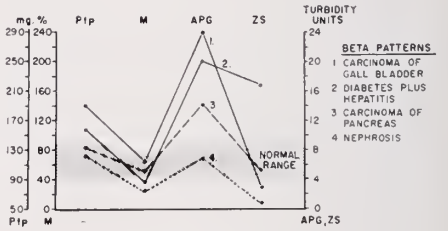

Fig. 2b

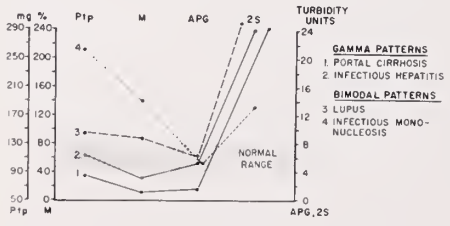

Fig. 2c

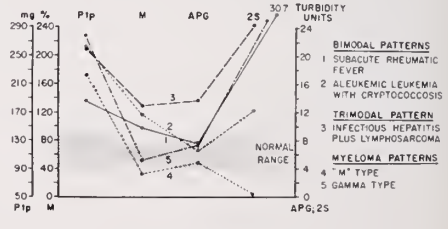

Fig. 2d

Fig. 2a-d. Representative examples of the various types of serum globulin distribution patterns detectable by the M, APG, ZS and Ptp determinations.

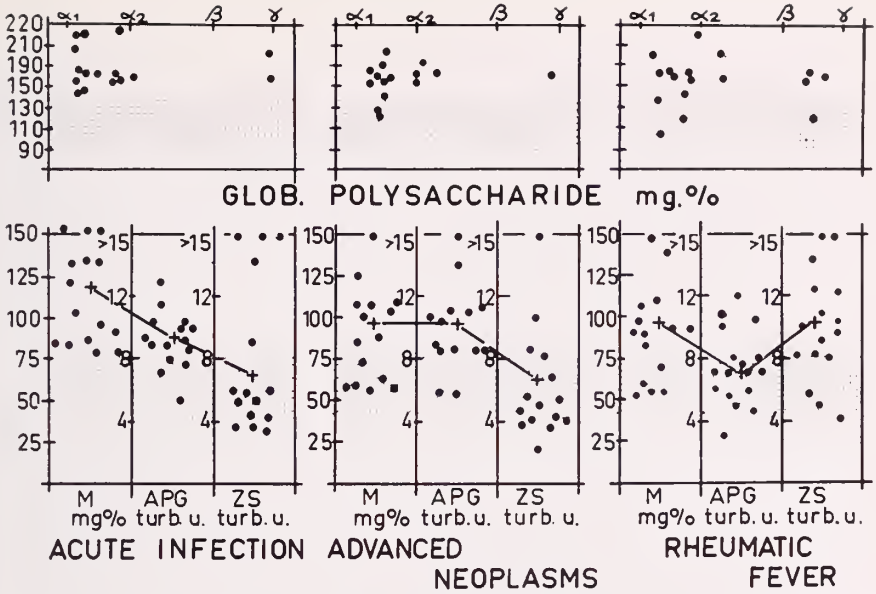

FIG. 3. Globulin indices from patients with acute infection, advanced neoplastic disease and rheumative fever showing the lack of a distinctive pattern despite the frequent occurrence of increased values in the alpha globulin indices. A hypothetical location for the preponderance of bound polysaccharide was postulated after inspection of the M, APG, and ZS values from each individual sample. Normal range in lightly shaded areas.

or absolute reduction in M and ZS values. This middle segment pattern, observed in 22 or about 9 per cent of the total sera in the six month survey, was most frequently associated with obstructive biliary diseases, the nephrotic syndrome, and and diabetes. A selective gamma globulin pattern (Fig. 2c) consisting of an elevated ZS turbidity value (>10 turbidity units) with normal or reduced M and APG concentration was obtained in 75 sera or 30 per cent of those submitted for study. This pattern was associated with infectious hepatitis, homologous serum hepatitis, portal cirrhosis, or post necrotic cirrhosis in 40 patients; with splenomegaly and probably cirrhosis in 5 cases, with disseminated lupus in two instances, and with a variety of disorders in the remainder of cases. There were only six patients with neoplastic disease among the total group of 75 patients with selective gamma globulin patterns. These included two cases of multiple myeloma, one each of leukemia, and lymphoma, one case of diffuse hemangioendothelial sarcomatosis of the liver, and only one case of carcinoma (from a total of 51 sera available from carcinoma patients). Thus approximately 60 per cent of the patients in this survey who showed a selective gamma globulin pattern were suffering from primary hepatocellular disease. When the characteristics of the gamma pattern were further defined to include a low mucoprotein level approximately 80 per cent of patients with such a pattern (or 32 of a total of 37 cases) were found to have hepatocellular disease. If in addition the gamma pattern was characterized by a low APG turbidity, i.e., a low "middle segment", as well as a low mucoprotein, the incidence of hepatocellular disease increased to over 90 per cent (v.i.).

A bimodal alpha-1 and gamma globulin pattern, as indicated by high M and

ZS values (Fig. 2c) with a normal APG turbidity or middle segment, was found in 21 sera or 9 per cent of specimens submitted. This pattern with a marked increase in ZS turbidity (>15 units) was most often due to portal cirrhosis complicated by an active extrahepatic infection or neoplasm, but was also encountered in lupus. Bimodal patterns with only moderate increase in gamma globulin (10–15 units) were seen in several instances each of infectious mononucleosis, lymphoma, leukemia (Fig. 2d ✻2) and rheumatic fever (Fig. 2c, Fig. 3) and in isolated cases of such varied disorders as pancreatitis, sickle cell disease, chronic pulmonary disease, and tuberculosis. A bimodal pattern with normal alpha-1 and high beta and gamma globulin (Fig. 2b ✻2) was detected in only a few sera from cases of hepato-cellular disease (hepatitis or portal cirrhosis) and pre-existing or coincident diabetes or biliary tract disease.

Panglobulinemia or a trimodal pattern manifested by increase in all components measured was found in 9 per cent of sera or 21 cases submitted for study. Most patients in this group were suffering from complicated multiple disorders, as for example hepatitis plus pyelonephritis, cirrhosis and pneumonia, perforated diverticulitis with liver abscesses, and hepatitis plus lymphoma (Fig. 2d ✻3).

The high incidence of abnormal globulin patterns observed in this survey was underscored by the finding that only 8 per cent of sera showed a normal set of globulin profile values and 7 per cent showed minor abnormalities insufficient to warrant designation as a selective alteration in globulin distribution. Because of this diversity and frequency of abnormal globulin patterns, this study was extended with particular reference to the potential value of the globulin indices as aids in the differential diagnosis of hepato-biliary diseases, and such dysproteinemic diseases as disseminated lupus, multiple myeloma, and nephrotic syndromes.

Hepatitis

In Fig. 4 the globulin profiles from the initial sera of 20 unselected cases of infectious or homologous serum hepatitis are plotted. The combination of a low alpha-1, normal or slightly elevated APG middle segment, and the high gamma globulin turbidity occurred in more than $\frac{4}{5}$ of the cases. The opposite pattern, i.e., high alpha, and low gamma globulin observed so often (v.i.) in pancreatic carcinoma and in other biliary obstructive diseases was not found among any of these 20 hepatitis cases nor among a large number studied over a two year period. The serial changes in the globulin profiles of four representative patients with infectious or homologous serum hepatitis of varying severity and duration are shown in Fig. 5. A fall in the alpha-1 mucoprotein (M) level and a rise in the gamma globulin (ZS) turbidity level was the characteristic common to these curves during the first two weeks after hospitalization. This divergent trend, although somewhat delayed, was also observed to occur, as previously reported (26) in several cases of "cholangiolitic" hepatitis. It was again noted that the hepatitis associated with infectious mononucleosis (26) was rarely accompanied by a falling mucoprotein. Thorazine "hepatitis" (Fig. 6) likewise failed to produce the serial changes observed with infectious or homologous serum hepatitis. Approximately 15 per cent of hepatitis sera failed to show a reduced mucoprotein

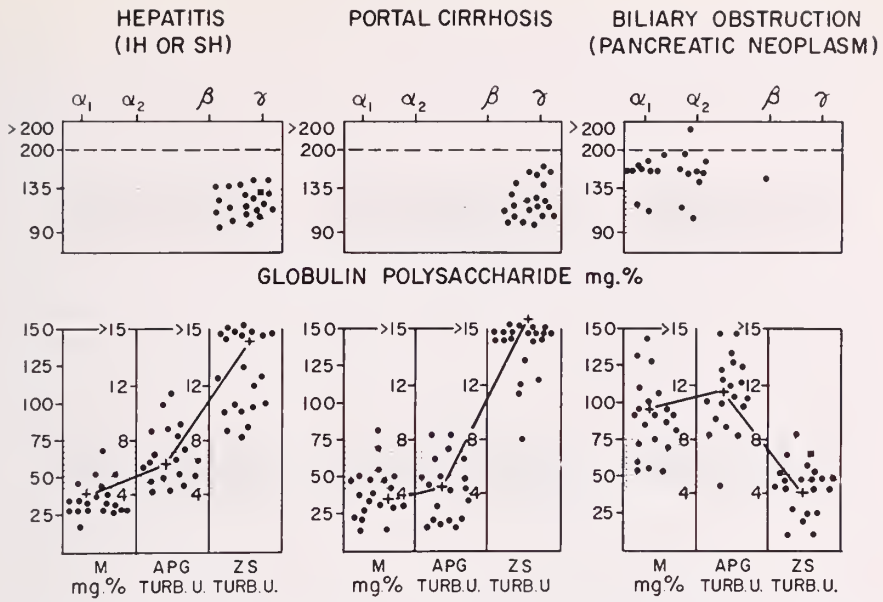

Fig. 4. Globulin indices from initial sera of 60 individuals with hepatitis, portal cirrhosis, or pancreatic carcinoma. See text for discussion of differences in the profiles of these groups.

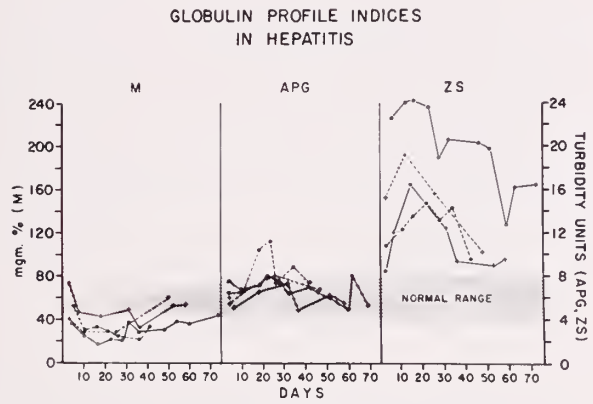

Fig. 5. Serial determination of globulin distribution pattern as estimated by the M, APG, and ZS procedures in four patients with hepatitis.

content on admission. These cases were of two types, either mild hepatitis already in the recovery phase when first studied, or hepatitis complicated by other coincidental pathological processes. Fig. 7 patient #2, illustrates the changes which occurred in the globulin profile in a patient who on admission had a panglobulinemia as a result of the simultaneous occurrence of acute hepatitis and acute pyelonephritis. Divergence in the M and ZS values appeared only after penicillin treatment had suppressed the pyelonephritis. At that time the M level fell from a high range past the normal range into the low hepatitis range while the gamma

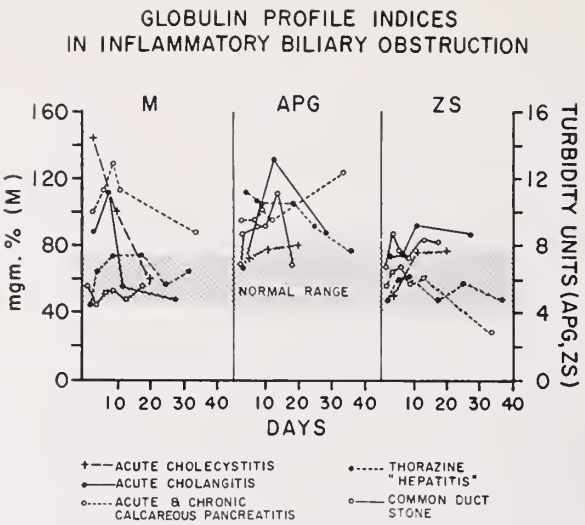

Fig. 6. Serial globulin profile indices of five representative patients with inflammatory biliary obstructive disease of varied etiology.

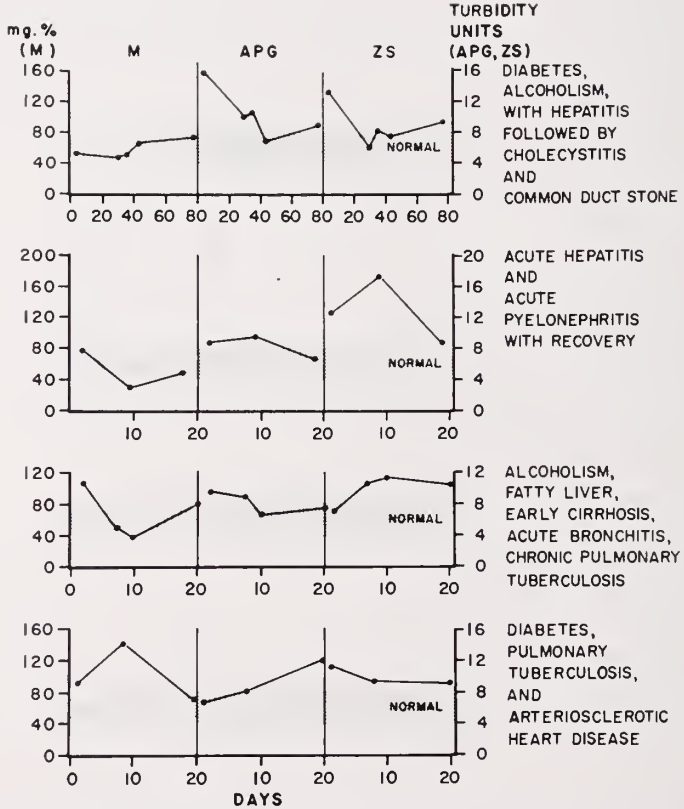

Fig. 7. Serial globulin indices illustrating independent fluctuation of the M, APG, and ZS components in cases complicated by two or more pathologic processes involving hepatic function and inflammatory tissue responses.

globulin continued to increase further. When ultimately the jaundice subsided, the M rose and the ZS turbidity fell, both towards the normal range. The potential for independent change in any of the three globulin components is further illustrated by other serial profiles (Fig. 7) from cases of hepatocellular disease complicated by extrahepatic pathological processes.

Portal or Post-necrotic Cirrhosis

Although the globulin profile in cirrhosis was generally similar to that in hepatitis, it differed in two aspects, namely the presence of a more variable alpha-1 mucoprotein level as a consequence of frequent coincidence of infections and neoplasms in cirrhotic patients and the finding of an absolute reduction in APG turbidity in about a third of the total of 83 cirrhosis cases studied. Fig. 4 shows the globulin profiles from 20 unselected patients with portal or post necrotic cirrhosis. A selective gamma pattern with low alpha-1 mucoprotein, and normal or only slightly increased polysaccharide was observed in about $^4/_5$ of these patients. The random detection of a low APG turbidity, although not specific for hepatocellular disease was found in only 30 patients from a total of over 1500 different sera analyzed in our laboratory from all sources over a two year period. Among these 30 sera with low APG turbidity, there were 27 cases who showed the complete (hepato-cellular dysfunction) pattern of a low alpha-1 mucoprotein, a low APG turbidity, an elevated ZS turbidity, and a normal or moderately increased polysaccharide. Twenty-six of these twenty-seven patients had portal or post-necrotic cirrhosis. The single case without cirrhosis, despite the presence of this cirrhosis-type pattern, was a patient with an unusual diffuse hemangioendothelialsarcomatous replacement of the liver. Of the other three patients with low APG turbidity, two had massive GI bleeding with hypoglobulinemia involving all four globulin components, and one had multiple myeloma with deficiency of M, APG, and ZS but with strikingly high total polysaccharide—a pattern apparently characteristic of the "M" type myeloma protein (v.i.).

Biliary Obstructive Disease

The usual occurrence of selective alpha and/or beta patterns in obstructive biliary disease appeared in distinct contrast to the virtual absence of these patterns in hepatitis or portal cirrhosis. Fig. 6 illustrates the serial globulin profile in representative cases of five different types of inflammatory biliary obstructive disease. It may be noted that in acute cholecystitis and in acute pancreatitis, the alpha-1 mucoprotein responded rapidly to clinical improvement with a reduction in the initially elevated M level. The rapid development of a beta globulinemia is shown with common duct stone, cholangitis and thorazine hepatitis. Thorazine "hepatitis" is illustrated because this new etiological factor for jaundice manifested a globulin profile and biochemical changes similar to those seen with common duct stone or cholangitis. The consistent finding of high APG turbidity with a high APG/ZS ratio in pancreatic carcinoma is seen in Fig. 4 and has already been reported in other biliary diseases described elsewhere (29). In seven cases with advanced biliary cirrhosis the selective gamma globulin pattern so

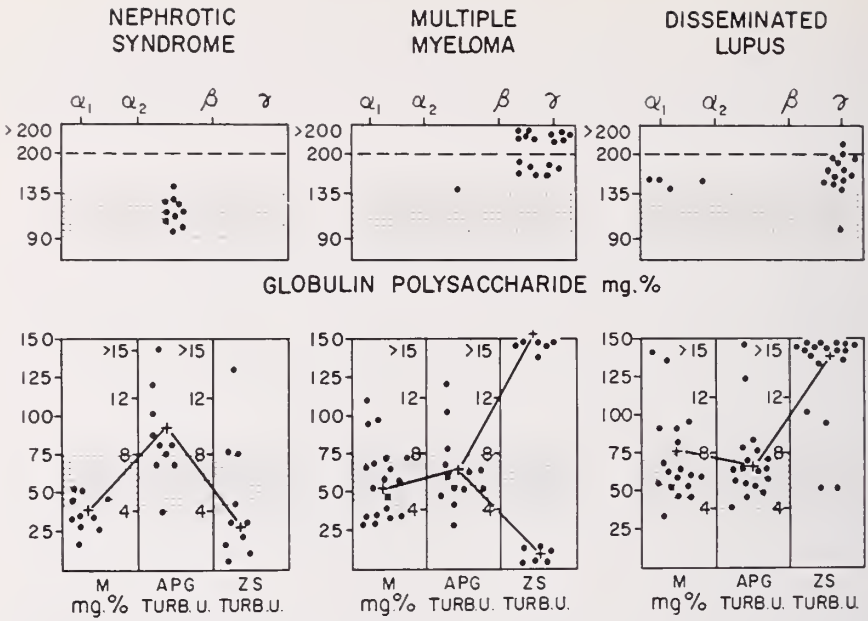

FIG. 8. Globulin profile determinations from initial sera of patients with nephrosis, multiple myeloma and disseminated lupus.

common in portal cirrhosis was not observed. As seen in Fig. 4, there was little overlap when the complete pattern of the M, APG and ZS indices in obstructive jaundice was compared with the pattern due to hepatitis or portal cirrhosis.

Nephrotic Syndrome

A selective "middle segment" pattern consisting of a relative or absolute increase in APG turbidity (beta globulin) accompanied by a normal total polysaccharide and relative or absolute reduction in M and ZS values (Fig. 8) was observed in nine of ten patients in the nephrotic stage of glomerulo-nephritis. None of these patients showed significant urea retention. In one patient, the high APG turbidity was unaccountably accompanied by a moderate increase in gamma globulin. The mucoprotein was subnormal or in the lower normal range in all ten patients. The selective beta pattern of nephrosis contrasted with findings of increased serum mucoprotein and a consistent alpha-globulin distribution pattern among a group of ten randomly selected patients with uremia due to glomerulonephritis or vascular renal disease.

Disseminated Lupus

The most constant alteration in the globulin profile among patients with disseminated lupus was a selective gamma pattern with pronounced gamma globulinemia. This was detected as an increased zinc sulfate turbidity level in 16 of 18 patients with 14 patients showing turbidity levels above 15 units. The two patients who failed to show a high ZS turbidity level were suffering from a

nephrotic syndrome accompanied by low grade azotemia. However, several others with renal involvement maintained a high ZS turbidity level so that it did not appear that a close correlation could be expected between the globulin pattern and the degree and character of renal involvement in disseminated lupus. This contrasted to the findings in the nephrotic syndrome due to glomerulonephritis already mentioned. The alpha-2 plus beta segment, as measured by the APG turbidity, was normal (Fig. 8) in 13 of 18 cases, as was the alpha-1 mucoprotein (M) concentration in 11 patients. The increased total polysaccharide found in 17 of 18 cases reflected the marked increase of gamma globulin polysaccharide. It was noteworthy that no consistent alteration in alpha-1 or alpha-2 components occurred, a finding not in accord with the concept that lupus is a disease in which the circulating blood proteins may be the resultant of derangement in tissue mucopolysaccharides.

Multiple Myeloma

Complete globulin profiles were obtained from 12 patients with multiple meyloma (Fig. 8). Each profile was markedly abnormal, indicating either a distinct alteration in gamma globulin or striking presumptive evidence of an abundant abnormal glycoprotein not precipitable by M, APG or ZS procedures. Six patients showed an extremely high ZS turbidity associated with a high total polysaccharide (Ptp) content which, by inspection of the accompanying M and APG values, could be assumed to be contributed by a gamma globulin rich in carbohydrate. The other six patients showed a pattern consisting of a marked elevation of bound polysaccharide (Ptp) associated with a virtual absence of ZS turbidity and a variable M and APG value insufficient to account for the marked increase in Ptp. This latter myeloma pattern stood out as unique among our entire experience with globulin profiles; and represented an easily recognizable and apparently characteristic pattern produced by an "M" type myeloma protein lying between beta and gamma globulin (confirmed as a spike in each instance electrophoretically). In this series, whenever a profile with a total polysaccharide of over 200 mg per cent was accompanied by a very low or an absent ZS turbidity level ("agammaglobulinemia") without any significant increase in alpha globulin indices it was invariably due to "*M*" type multiple myeloma.

COMMENT

The initial purpose of this survey was to determine whether the combination of the M, APG, ZS and Ptp determinations could detect the varied types of alterations in serum globulin distribution known to occur in diverse pathological conditions studied by established electrophoretic methods. This question seems to be answered affirmatively since the pathological conditions frequently associated with selective influences on alpha, beta, or gamma globulin fractions, as summarized in the introductory analysis of results with other procedures, were also found to produce similar selective globulin profile patterns when the battery of four in-vitro procedures were employed. These clinical observations amplify our previous conclusion concerning the APG and ZS determinations (29) namely,

that despite the fact that none of the four procedures can be equated as stoichiometric equivalents of any given globulin fraction, nevertheless a good correlation can be expected between gross electrophoretic changes in sera and selective alterations in the profile procedures.

The M, APG and ZS procedures precipitate somewhat less than 85 per cent of the total proteins of the normal globulin complex. The presence of any large globulin fraction not directly precipitated from the serum by these three procedures may be detected by an unexpectedly high content of total bound polysaccharides (Ptp). A small but significant alpha-1 globulin not part of the mucoprotein complex or a component in the narrow area between beta and gamma globulin could be missed by this battery of tests. In six sera in which the "M"-myeloma globulin appeared as a spike between beta and gamma globulin, the battery detected the presence of a large polysaccharide-rich component lying between the precipitated M, APG, and ZS proteins.

Although the profile represents in part a device to avoid the more tedious electrophoretic methods, there is evidence that the procedures possess certain intrinsic merits not offered by conventional serum electrophoresis. These advantages, aside from ease of determination, include a) an accurate measurement of a clinically responsive and labile "acute phase" reactor, i.e. the mucoprotein (M) which is not measurable by conventional electrophoresis even though it represents a substantial portion of alpha-1 globulin, and b) the ready estimate of a large glyco- and lipo-protein complex, i.e. the acid precipitable globulin (APG), in the middle globulin segment covering the alpha-2 plus beta globulin. The reduction in serum levels of both of these components as a result of severe hepatic insufficiency due to portal and post-necrotic cirrhosis appears to represent a relatively characteristic alteration in the globulin spectrum. This middle segment deficiency in liver disease, reported by us (29) on the basis of the APG turbidity procedure, has also been described as a "new sign of hepatic coma" in electrophoretic studies by Von Donnelen and Schulte (35). In the present study the reduced APG turbidity, although not usually accompanied by hepatic coma, was consistently associated with severe hepatic insufficiency when found as part of a totally abnormal globulin distribution pattern consisting of a low M, low APG, high ZS, and normal or only moderately increased total polysaccharide. This abnormal profile appears to be characteristic of hepato-cellular insufficiency and as such would seem to warrant further clinical studies.

CONCLUSIONS AND SUMMARY

Alteration in the distribution of serum globulin fractions may be detected by an invitro battery of simple laboratory procedures measuring the serum mucoprotein (M), the acid precipitable globulin (APG) turbidity, the zinc sulfate (ZS) turbidity and the total protein-bound polysaccharide (Ptp). The ease with which independent fluctuation in the various globulin components may be estimated makes feasible frequent serial study of the influence of hepatic and extrahepatic processes in complicated or perplexing cases of jaundice and hepatomegaly. This method of estimating the globulin profile provides data of potential value in the

differentiation of hepatocellular versus obstructive jaundice, and may represent a useful screening procedure in obscure diagnostic problems, as well as a confirmatory aid in such "dysproteinemic" diseases as nephrosis, disseminated lupus, and multiple myeloma. In a survey of over 1500 sera from patients with diverse medical disorders, the pattern of reduced M, reduced APG, and high ZS, with an essentially normal Ptp was found in 27 patients. This pattern, while not absolutely specific for portal or post-necrotic cirrhosis, was consistently observed as a result of severe hepato-cellular insufficiency. The converse pattern of a high M, high APG, and low ZS value was observed frequently in obstructive biliary disease but did not occur among a large series of patients with infectious hepatitis, homologous serum hepatitis, post-necrotic cirrhosis, or portal cirrhosis. A detailed comparison of this in-vitro approach to globulin analysis with other methods for detection of abnormal serum proteins seems warranted.

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UNUSUAL OSTEODYSTROPHY ASSOCIATED WITH RENAL DISEASE

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Bone disease occurring in the presence of longstanding kidney failure is usually, but not invariably accompanied by hyperplasia of the parathyroids present at autopsy. The two main factors concerned in the production of the bone lesions are renal acidosis and secondary hyperparathyroidism. What are the bone lesion causing mechanisms?

In the past the characteristic bone lesion of renal osteodystrophy in adults was considered to be that of osteitis fibrosa generalasata, the bone picture resulting from hyperparathyroidism. Many observers, Rutishauser (1), Albright (2, 3), Jaffe (4), now believe the bone lesions should be ascribed primarily to the renal acidosis and that the parathyroid hyperplasia is secondary. Fairbanks (5) and others emphasize that the early radiologic manifestations of renal osteodystrophy are those of osteoporosis (true bone atrophy). Brailsford (6) states that because of a failure to recognize osteoporosis early by x-ray, the diagnosis in many cases is not made until later secondary hyperparathyroidism has produced the picture of typical osteitis fibrosa with its severe destructive changes and multiple deformities.

The sequence of events leading to the bone disease is usually conceded to be: 1) renal insufficiency 2), diminished excretion of phosphate 3), disturbed electrolyte equilibrium with acidosis 4) elevated serum phosphate level 5) depression of serum calcium level as an adjustment to high serum phosphate level 6) hyperplasia of the parathyroids with hypersecretion to meet this tendency 7) resorption of bone.

It is noteworthy to mention that in a search of the literature, very little is to be found on pathological studies other than those of vertebrae and ribs (routine autopsy specimens), except where frank lesions of osteitis fibrosa have been met with by preceeding roentgen studies. Certainly, there is little to be found on the study of the long bones in these cases.

The report below serves to illustrate some unusual radiological findings in the long bones in this syndrome.

CASE REPORT

A 55 year old colored male was admitted with a fracture of the right femoral neck, sustained when he slipped while mopping a floor.

The past history was significant only in that nocturia two to three times was noticed for an unrecalled period of time.

Physical examination revealed the following positive findings: A slight elevation of the blood pressure (180/80); moderate enlargement of the heart with a

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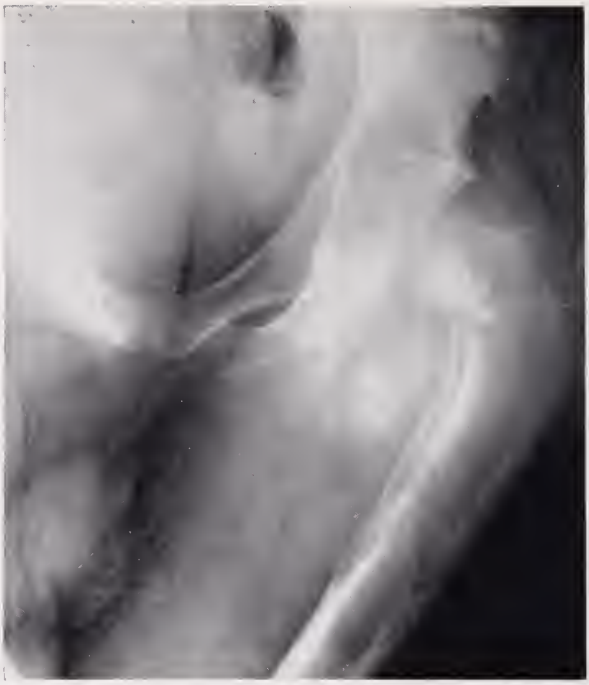

FIG. 1

grade II systolic murmur and a two finger enlargement of the liver; the right lower limb was held in a position of flexion, internal rotation and adduction.

The essential laboratory changes revealed a mild uremia (with persistent 2–4 plus albuminuria, urea nitrogen 37 on admission) severe anemia with a 6.7 Hbg. and 1.9 million R.B.C. and reversal of the albumin-globulin ratio 3.7/4.0. Urological examination: The P.S.P. excretion was 20 per cent in 2 hours, and I.V.P. examination revealed no excretion of dye from either kidney.

X-ray examination. The femur displayed a low basilar neck fracture in a pathological area, (Fig. 1). A sharply delineated porotic area was seen in the upper shaft and distal neck. The cortex was not thickened, the marrow space not narrowed. There was slight osteoporosis, with coarsening of the trabecular structure of all the bones examined. This was especially manifest in the proximal and distal humerus, proximal radius and ulna bilaterally. Most striking was the appearance of transverse radiolucent bands crossing the entire diameter of the bones in the metaphyseal regions of the upper and lower tibiae, distal radius and ulna bilaterally, (Figs. 2, 3, 4). A flat plate of the adbomen showed extensive calcification in the pancreas, (Fig. 5), and in the regions of the right sacroiliac articulations, pelvic blood vessels, and possibly in the ureters.

Course. Because the patient represented a very poor operative risk he was placed in traction. The free extremities were kept constantly active. A needle biopsy of the femoral lesion showed mainly regenerating bone fragments with some osteoclastic activity and fibrotic marrow. A needle biopsy of one of the translucent tibial bands showed sparse trabiculae, normally ossified. On the

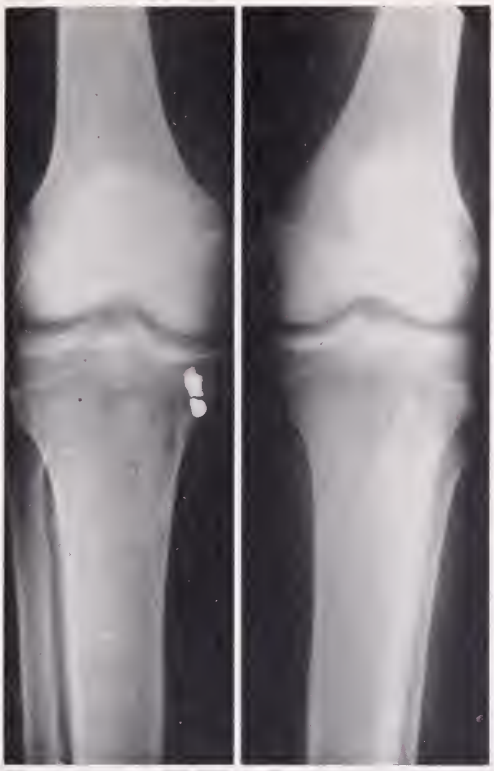

FIG. 2

FIG. 3

26th hospital day, the fracture was fixed with a Jewett appliance (Fig. 6), using low spinal anaesthesia. Material removed from the femur at the time of operation showed dense trabiculae displaying a mosaic formation and a mild degree of both osteoclastic and osteoblastic activity. Considered by itself, this trabecu-

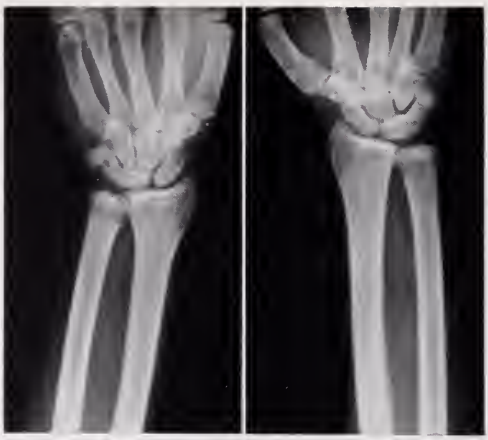

FIG. 4

FIG. 5

lar atrophy with fine fibrosis around the bony spicules, rare osteoclast and fatty marrow, represented findings compatible with secondary osteoporosis.

Although the patient at first responded well to the operation his subsequent medical course was progressively downhill with the onset of severe uremic manifestations.

His blood chemistries are outlined below in Table I. This represented a picture of severe acidosis in renal failure. The calcium fell dramatically to 5.7 mgm per cent just before death from an admission one of 9.3 mgm per cent. The phosphorus rose to 10 mgm per cent from an admission one of 3.1 mgm per

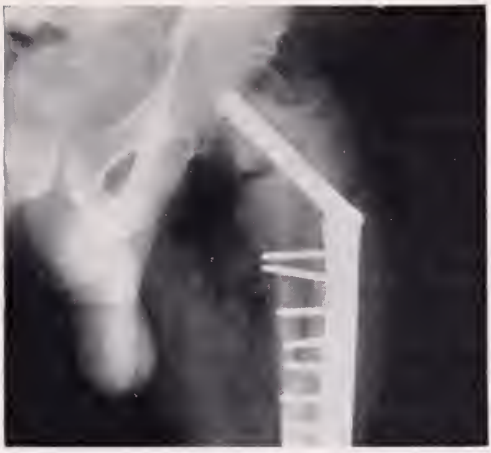

FIG. 6

TABLE I

Date (Hosp. days)	Ca (mgm%)	P	Alk ph'tase K.A. Un.)	Urea N_2	CO_2	K (meq. l.)	Na	Cl
Admission	9.0	3.1	6.5	37				
			11.0					
10th			16.0		49	5.9	136	106
19th	9.3	4.1						
41st	8.5	4.7	14.0	46		5.7		
53rd	8.4	3.9	13.0		33	6.2	135	102
72nd			13.0		33	5.8	137	110
74th	5.7	9.3	7.0	126	26	6.9		108

cent. The alkaline phosphatase was only slightly raised at one point. The CO_2 combining powers showed marked acidosis. Urea nitrogen became markedly elevated. On the 74th hospital day the patient died.

Post mortem examination. The lungs displayed bronchopneumonia. The kidneys were small and contracted showing arterio and arteriolarsclerosis with superimposed metastatic calcification. There was slight enlargement of all four parathyroids grossly and microscopically slight hyperplasia as manifested by the chief cells. Study of the femoral and metaphyseal regions of the bones confirmed the previous findings. Ribs and vertebrae were essentially normal.

DISCUSSION

Though a somewhat similar radiological picture has been seen in osteoporosis of disuse in an isolated immobilized limb, this was ruled out by the symmetrical pattern of changes and the general nature of the case. His upper extremities and the left lower extremity had been kept freely active. Metabolic osteomalacia and senile osteoporosis were eliminated by the clinical and laboratory data as

were Leukemia and Cushing's syndrome. Attempts were made to correlate the femoral lesion with the metaphyseal changes as a single syndrome. It was noted that Paget's in its early porotic stage may simulate osteitis fibrosa. Actually, several observations suggested the possibility that the femoral lesion represented an independent early Paget's disease.

SUMMARY AND CONCLUSIONS

1. Attention is called to the importance of renal function study in any instance of nonspecific osteoporosis or atypical Paget's disease involving the long bones evidenced in x-ray studies.

2. Kidney damage may produce a variable effect upon the skeleton dependent upon the timing and interplay of the effects of both acidosis and secondary hyperparathyroidism. There is no single, clear-cut microscopic picture of renal osteodystrophy.

3. The complexity of renal function damage is such that it may result in the skeletal picture of matrix inadequacy, as in true bone atrophy (osteoporosis); of osteitis fibrosa as is common in basic parathyroid disurbance, or of a combination of the two.

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CRYOGLOBULINEMIA, MACROGLOBULINEMIA, AND THE AMINOACIDURIA WHICH IS SOMETIMES ASSOCIATED WITH MULTIPLE MYELOMA[1, 2]

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Cryoglobulins may be defined as blood proteins which have the property of precipitating from solution when cooled below body temperature and of re-dissolving when raised to body temperature (1). Some of them precipitate at room temperature, and others require a temperature as low as 4°C. or less. Some of them form a flocculent precipitate; others form a gel as a lower layer in a tube of serum or plasma (2, 3). Occasionally, they precipitate in the form of crystals (2, 4, 5). Solubility of these cold-precipitable proteins depends not only on temperature but also on concentration of the proteins in solution, pH and ionic strength. Influence of these factors is various and must be determined for each protein.

Test for cryoglobulins requires precaution of drawing blood into needle and syringe warmed to body temperature, and transportation of sample in a water bath at 37°C. to an incubator where it is allowed to clot. After the clot is formed, the serum is removed, still at 37°. Once the serum is removed, it is placed in the refrigerator at 4° or 2°C. and the tube is examined daily for a period of about seven days for evidence of a precipitate. If a precipitate is formed, the tube is heated to 37°C. The precipitate re-dissolves if it is cryoglobulin.

Cryoglobulinemia has been observed in a number of different diseases which, for convenience, may be divided into four groups. The first is composed of diseases of the plasma cells and lymphocytes and includes multiple myeloma (1), plasmacytosis (5), lymphocytic leukemia and lymphosarcoma (5–7). The second, the vascular disease group, consists of Raynaud's syndrome and Buerger's disease (1). Raynaud's syndrome may actually be a secondary manifestation of the cryoglobulinemia. The third group consists of what are loosely called the collagen diseases and includes disseminated lupus erythematosus (1), periarteritis nodosa (4), rheumatic fever (7), and rheumatoid arthritis (8). The fourth group includes a large number of infectious processes: subacute bacterial endocarditis (7, 9), hepatitis (1, 10), kala azar (11), lymphogranuloma venereum (1), bronchopneumonia (7), and bronchiectasis (7).

Cryoglobulinemia has been accompanied by a variety of symptoms, the severity of which is not readily attributable to the concentration of the abnormal

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[2] Read before a symposium on Hematology, The Mount Sinai Hospital, New York, N. Y., February 16, 1955.

[3] Markle Scholar in Medical Science.

protein (1, 12) but perhaps more to the critical temperature of the precipitation. Sensitivity to cold is usually noted. With proteins that precipitate at temperatures only slightly below 37°C. small reduction in environmental temperature may be accompanied by sudden circulatory disturbances of great severity. The list of symptoms includes purpura and edema of the skin similar to that encountered in hypersensitivity reactions, Raynaud's syndrome with bluish discoloration of extremities, tip of nose, and ear lobes, formation of ulcers with little tendency to heal, and sometimes extensive gangrene of the extremities. Most of these symptoms may be prevented by protection from exposure to cold.

A number of different studies have been performed in an effort to characterize the cryoglobulins. By electrophoresis it has been shown that these proteins migrate as gamma globulins usually in distinct peaks (1, 10, 13, 14). On ultracentrifugation, cryoglobulins usually have a sedimentation constant similar to that of gamma globulins, 7 Svedburg units, although in some instances the molecules have had higher sedimentation constants (1, 13–15). Studies of aminoacid content have revealed a composition similar to that of gamma globulin (5). A recent report states that hydroxyproline has been found in one cryoglobulin (16). This aminoacid has not been found in any other serum protein. The N-terminal aminoacids of eight cryoglobulins have been studied (13, 27). Normal

TABLE I

Adult Fanconi syndrome: chemical abnormalities probably as a result of proximal renal tubular failure

	Blood	Urine
Glucose	Normal	*Present*
Protein		Present
Amino acids	Decreased	Increased
Phosphorus	*Decreased*	Increased
Potassium	Decreased	Increased
Bicarbonate	Decreased	Increased
Uric acid	Decreased	Increased
Alkaline phosphatase	*Increased*	

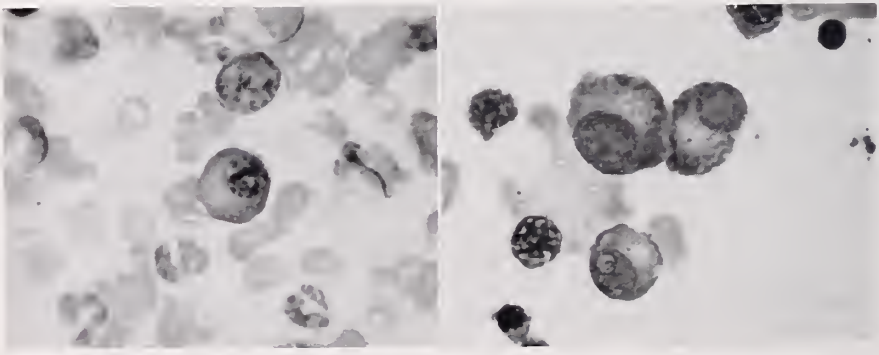

FIG. 1. Plasma cell from the bone marrow of a patient with acute rheumatic fever.
FIG. 2. Plasma cells from the bone marrow of a patient with multiple myeloma.

gamma globulin has about equal amounts of aspartic acid and glutamic acid. The cryoglobulins usually have either aspartic acid or glutamic acid, although in some instances both aminoacids but in twice the normal amount are present as endgroups. Immunologic studies, although only few have been done, would also indicate that cryoglobulins are very closely related to gamma globulins (17). In summary, I think that we may state that the physical, chemical, and immunologic properties of cryoglobulins are quite similar to the unusual proteins that are found in multiple myeloma and that are called myeloma proteins.

The site of origin of the cryoglobulins poses another very interesting problem. We don't have a definite answer, but it is of interest to observe the appearance of the plasma cells that are frequently found in the bone marrow when cryoglobulinemia is present. In figure 1, is pictured a normal appearing plasma cell from a patient with rheumatic fever; in figure 2, a myeloma cell (plasma cell) from a patient with multiple myeloma. The normal cell reveals a greatly increased basophilia of the cytoplasm and a decreased perinuclear clear zone. The nuclear chromatin is more homogeneous, and some of the nuclei contain nucleoli. The term myeloma cell does not imply that this type of cell is seen only in the disease multiple myeloma. Figures 3 and 4 show two cells from a patient with cryoglobulinemia. These cells were present in the bone marrow in fairly large numbers. One can see the very unusual vacuolated character of the cytoplasm of these cells. Some of them are so bizarre that it is impossible to decide whether they should be called plasma cells or reticulum cells. One cannot help but wonder whether these might not be the cells where cryoglobulins are formed. It is of interest that Abrams, Cohen, and Meyer (18) have isolated a cryoglobulin from lymphoid tissue. This cryoglobulin had many of the physical properties of a plasma cryoglobulin from the same patient, raising the question again as to whether or not these proteins are produced in cells of the plasma cell and lymphocytic series.

Attention was focused on macroglobulinemia by Waldenström (12). Although his patients had many features that simulated multiple myeloma and lympho-

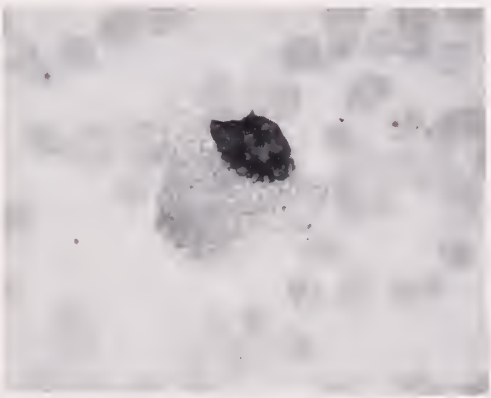

FIG. 3. Plasma cell from the bone marrow of a patient with plasmacytosis and cryoglobulinemia.

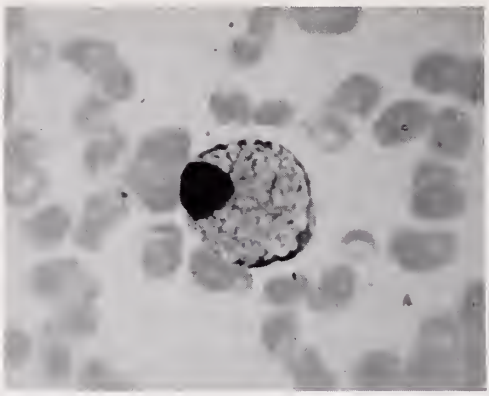

FIG. 4. Plasma cell (?reticulum cell) from the bone marrow of a patient with plasmacytosis and cryoglobulinemia.

sarcoma, he believed that he could clearly differentiate the three conditions. The most characteristic feature is the presence in the serum of a protein of high molecular weight, and a sedimentation constant of about 20S in the ultracentrifuge. The symptoms include anemia with bleeding from the mucous membranes, lassitude and fatigue. Unlike myeloma, the condition usually causes no bone pain. Lymphoid hyperplasia results in enlargement of lymph nodes and sometimes in hepatosplenomegaly.

Laboratory examination reveals severe anemia and a leukocytosis with lymphocytosis which frequently constitutes 50 to 60 per cent of the total. There is a moderate thrombocytopenia to which bleeding episodes are only partially attributable. The sedimentation rate is markedly elevated. There is a high serum viscosity and elevated serum globulin, which usually has an electrophoretic mobility quite similar to that of the various myeloma proteins, that is, a peak in the beta or gamma region or possibly between the beta and gamma. On ultracentrifugation these proteins have a sedimentation constant from 14S to 28S. Not infrequently several peaks are found. It is not unusual for the macroglobulin to be also cold precipitable. In the bone marrow, instead of plasma cells there are a large number of lymphocytoid cells. There is sometimes difficulty in distinguishing these, however, from typical plasma cells. Most cases show no Bence-Jones urinary protein, although there have been cases with this protein described. X-ray films of the bones usually show only slight osteoporosis, rather than the punched-out lesions of multiple myeloma.

I think that the macroglobulinemia of Waldenström constitutes a fairly clear-cut syndrome, although individual cases have characteristics not easily distinguishable from multiple myeloma and lymphosarcoma. Diagnosis can be established by ultracentrifugation. It has been claimed also that macroglobulinemia may be recognized by immunologic methods (19). The question as to whether these macroglobulins are aggregates of molecules or are true giant molecules has not been definitely answered. Studies by Petermann and Braunsteiner (15) of a macroglobulin that was also a cryoglobulin indicate that the protein acted in

every respect as if it were an aggregate of molecules. Not only have primary forms of macroglobulinemia been described, but macroglobulins have also been found in patients with malignant processes such as carcinoma of the uterus (20). Other patients with macroglobulinemia have been reported by Mandema (21) and Mackey (22).

Aminoaciduria has also been reported in only a very few cases of multiple myeloma (23). Dr. Lila Wallis and I have examined for aminoaciduria the urines of about twenty-five patients with multiple myeloma. We were surprised to find that aminoaciduria could be found in only one. This happened to be a patient who was excreting large quantities of Bence-Jones protein. The technique used for demonstration of the aminoaciduria was two-dimensional paper chromatography. In this procedure a small quantity of urine is placed near the corner of a large sheet of filter paper. A solvent, in this case phenol, is allowed to move by capillary attraction through the paper carrying with it the various aminoacids that were present in the urine spot at different rates. It takes about thirty-six hours for this solvent to wet the paper completely. The paper is then dried and turned 90° and another solvent, this time lutidine, is allowed to pass through the paper. This also carries aminoacids at different rates. The paper is then dried and stained with ninhydrin. The aminoacids show up as individual spots, one for each aminoacid. This is a semiquantitative procedure, the quantity of aminoacid being determined by the size and intensity of the spot. On examining normal urines, one finds only a very few and very light spots on the paper. These spots are usually caused by alanine, glutamine, glycine, and occasionally cysteic acid. In this one patient with multiple myeloma, however, there were a large number of spots representing at one time or another just about every aminoacid, and many of these spots were extremely dark. The aminoaciduria was confirmed by alpha amino nitrogen determinations. In examining the spectrum of the aminoacids being excreted by this patient, we were struck by the similarity to the spectrum found in the adult Fanconi syndrome (24, 25) and for this reason decided to investigate the possibility that our patient might also have this condition. You will recall that in the adult Fanconi syndrome a number of chemical abnormalities occur probably as a result of an abnormality of the proximal convoluted tubule of the kidney. As a result of this defect, several substances normally reabsorbed are excreted into the urine (Table I).

In the adult Fanconi syndrome there is a glycosuria, although blood glucose level is usually normal. Proteinuria is common. Aminoacids are decreased in the blood and increased in the urine. Phosphorus is decreased in the blood and increased in the urine. Potassium, bicarbonate, and uric acid are all decreased in the blood and increased in the urine. It is of interest that the alkaline phosphatase is usually increased. In our patient we found all of these abnormalities. We were particularly interested in the presence of glycosuria, low serum phosphorus, and the elevated serum alkaline phosphatase, because it would be most unusual for these to occur in an uncomplicated case of multiple myeloma. In looking for the adult Fanconi syndrome in any patient with multiple myeloma, one should be alerted by the presence of any of these changes. As a result of

these chemical abnormalities, the patient has considerable bone pain. X-ray films, however, usually show only bone rarefaction with pseudo-fractures. The patient has a waddling gait and frequently has polydipsia and polyuria. In reviewing the literature we were able to find only one other case wherein the adult Fanconi syndrome with aminoaciduria occurred in a patient with multiple myeloma. This was a patient reported by Sirota and Hamerman (26) from the Mount Sinai Hospital. They mentioned that the two diseases were probably unrelated. We feel that the adult Fanconi syndrome with aminoaciduria may well be of a secondary type; secondary to the multiple myeloma. Both of these patients had marked Bence-Jones proteinuria. Our patient had the very interesting additional finding of unusual rod-shaped crystalline bodies in the plasma cells. Since in some patients with multiple myeloma crystals of Bence-Jones protein have been found at autopsy in the epithelial cells of the kidney tubule, one wonders whether or not this could produce the renal defect responsible for Fanconi syndrome. I think it is important to point out that this association must be quite rare, as one usually does not find such things as an elevated serum alkaline phosphatase, a decreased phosphorus, and glycosuria in patients with multiple myeloma.

When a patient has both multiple myeloma and adult Fanconi syndrome, symptoms may be related chiefly to the latter condition, and several therapeutic measures may be employed. A normal electrolyte balance may be restored. The effect of estrogens, androgens, vitamin D, and alkalinizing agents may be tested. By such expedients the patients may be kept comfortable for a much longer period of time than if therapy is directed at the multiple myeloma alone.

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MOBILIZATION OF STAPES (ROSEN)

Simple Procedure for Otosclerotic Deafness

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One of the most important and dramatic developments in otology in the past century has been the evolution of the surgical treatment of deafness due to otosclerosis. The first attempts to improve hearing in stapes ankylosis resulting from suppuration were made in 1876 by Kessel (1) who first removed the drum, malleus and incus. Later he tried stapes mobilization and stapedectomy at a time when the nature of otosclerosis was unknown. His approach and technique were modified and improved upon by many during the ensuing 25 years, when mobilization and stapedectomy were abandoned as worthless and dangerous. Attention was centered next on the creation of a labyrinthine fistula which became the accepted technique employed to improve hearing in otosclerotic deafness. Passow (2), Jenkins (3), Barany (4), Holmgren (5), Sourdille (6), and Lempert (7) were the pioneers in this field.

Inspired by his observation of Holmgren's work in 1924 (5), Sourdille developed his labyrinthine fistula operation, which he performed in several stages. In 1937, Sourdille described his technique at the New York Academy of Medicine (6). The following year Lempert published his first report of fistulization of the lateral semicircular canal with a dental burr by a one-stage endaural technique (7), a brilliant advance. Since 1938 the fenestration operation has been improved by Lempert and other otologists all over the world and much has been added to our knowledge of the physiology of hearing. We have in the Lempert fenestration operation an exciting example of scientific progress, in which each contributor, standing on the shoulders of his predecessors, utilized their work as a basis for his.

The development of the original Rosen technique for mobilizing the fixed stapedial footplate was largely an accident. In quest of a minor procedure to determine beforehand a patient's suitability for the formidable fenestration operation, a technique was devised in 1952 for palpation of the stapes to determine its degree of fixation (8). The technique consisted essentially of lifting the drum out of its sulcus with six to seven millimeters of attached skin of the external auditory canal and exposing the incudo-stapedial joint and the stapedial tendon through an ear speculum. Gentle pressure was applied in a posterior direction against the incus close to the neck of the stapes to determine whether ankylosis of the footplate was present (Fig. 1).

The determination with certainty that there was stapedial fixation before performing the fenestration operation seemed indicated, since in some cases of "clinical otosclerosis" palpation of the stapes during the fenestration operation after removal of the incus revealed the stapes to be freely movable. The hearing in these cases did not improve after fenestration. Had the stapes been known to

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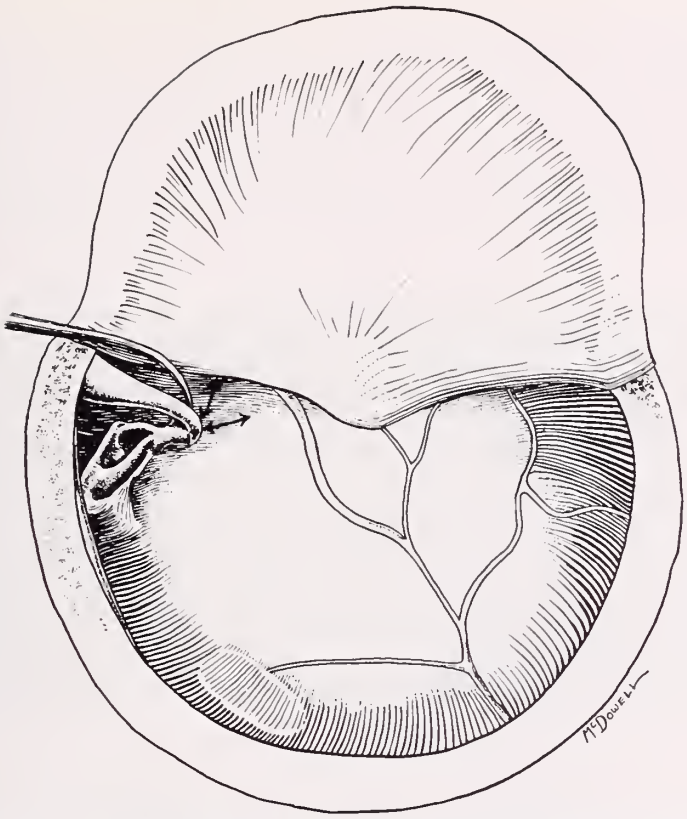

FIG. 1. Drum and skin are reflected and a wide exposure of the long process of the incus, stapes and stapedial tendon is made after the edge of the bony canal wall is removed. Palpation in the direction of the arrows is then made to determine stapedial fixation.

be freely movable, the fenestration operation might not have been performed since, in the main, it is designed only for those with stapes ankylosis.

In April, 1952, in one of a series of cases in which palpation of the stapes for fixation was being performed to determine whether or not fenestration was surely indicated, slight pressure applied posteriorly on the incus at the incudo-stapedial joint revealed slight movement of the incudo-stapedial joint and the stapedial tendon. Intermittent pressure against the incudo-stapedial joint caused the patient's hearing to return suddenly and dramatically on the operating table. Three weeks later the hearing in the operated ear had reached the line of normal hearing by pure tone and speech audiometry, from a pre-operative loss of 40 decibels. The hearing has remained at the normal level for 45 months to date. This patient had previously been examined in various audiologic centers in America and had been advised by all to have the fenestration operation.

It seemed that by the manipulation described, the partially fixed stapedial footplate was rendered freely mobile and hearing was thus restored. This accidental mobilization justified the assumption that the fixed footplate of the stapes could in fact be mobilized and result in excellent hearing, since the intact ossicular chain is preserved for its normal function of sound transmission. A

technique was therefore devised to mobilize deliberately all degrees of stapes fixation for the restoration of hearing in otosclerotic deafness (9–17).

The question of whether a completely fixed stapes could be mobilized by pressure against its neck was investigated extensively on the cadaver. Thirty-one stapes were fixed in cement in order to approximate the otosclerotic rigid stapes (Fig. 2). Various weights were suspended from the neck of the stapes and the maximum weight noted before fracture of the crura occurred. The arithmetic mean of the weights was 166 grams (Fig. 3). Pressure applied against the neck

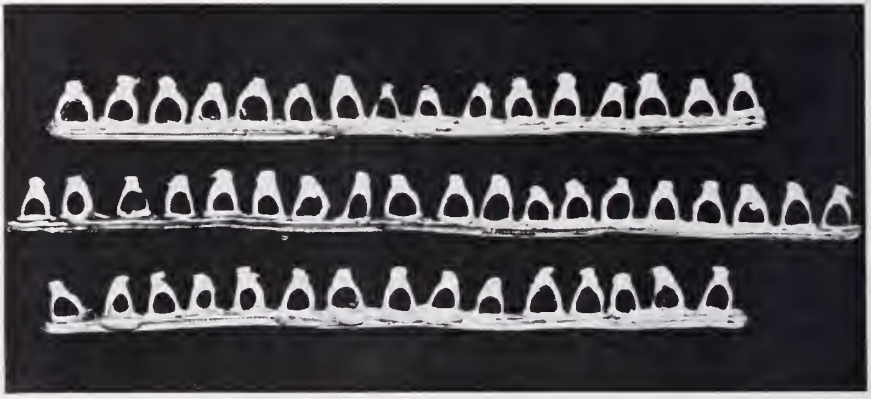

FIG. 2. Stapes removed from fresh cadavers with the footplate fixed in cement to approximate the otosclerotic rigid stapes.

FIG. 3. Eight-ounce weight suspended from the neck of the stapes indicates the amount of force which the neck of some stapes can withstand without fracture of the crura.

of the stapes in order to mobilize the rigid footplate is in a similar direction as that exerted by the suspended weight, while the force used in surgical manipulation is considerably less.

The Rosen technique for mobilizing the fixed stapedial footplate has been employed continuously since 1952 with gratifying results (17). Otologists in many parts of the world employing this technique have been successful in mobilizing the rigid footplate of the stapes with marked improvement in hearing (18–23).

HISTORY OF MOBILIZATION OF THE STAPES

Kessel in 1876 was the first to advise mobilization and even extraction of the stapes in stapes ankylosis resulting from suppuration and other causes unknown at the time (1). This procedure consisted of perforating the tympanic membrane and introducing an explorer into the cavity, probing against the incudo-stapedial articulation in an effort to free the stapes in the oval window. His method, with slight variation of the instruments, was adopted by Michel (24) and Schwartze (25), both of whom reported some good results. Miot (26) characterized this method and that of Gelle' as being too difficult and not to be recommended because of the narrowness of the view. He stated that "Mobilization of the stapes is too delicate an operation to risk without seeing what one is doing".

Boucheron (27), in 1888, excised the posterior half of the drum and in most cases separated the incus from the stapes. He tried with a special hook to mobilize the stapes using a movement similar to the traction of the stapedial muscle. Boucheron also excised the malleus and incus as did Burnett (28) in America. In this procedure the chorda tympani nerve often was cut inadvertently.

Miot in 1889 performed stapes mobilization through a myringotomy (26). He exerted pressure under the incudo-stapedial articulation parallel to the crura and if that failed to render the stapes mobile, he gently manipulated the anterior edge of the incudo-stapedial articulation. He also tried pressure on the crura but found it impractical because they withstand little pressure. Miot also attempted to mobilize the malleus before trying to mobilize the stapes. Whenever he did not succeed in mobilizing the stapes because of the degree of fixation, he excised the malleus. Miot also re-operated his cases two and three times within a brief period. In 1900 he reported 74 successful results out of 126 with his methods.

According to Miot, the problem was not whether mobilization of the fixed stapes could improve hearing, for of that there was ample proof. But he warned of the dangers of mobilization procedures because of possible accidents resulting from poor view, insufficient lighting, lack of technique and inadequate post-operative care. He attempted to evaluate the various techniques of stapes mobilization and stapedectomy and to mark out the indications and contra-indications of their use and results.

Faraci (29) in 1899 reported limited success with stapes mobilization. He too stated unequivocally that mobilization of the fixed stapes could restore hearing and predicted that a great stride in scientific progress would be made when the technique of stapes mobilization was ultimately perfected.

In America, Blake (30), Jack (31), and Burnett (28) turned to stapedectomy after attempting mobilization.

In 1900, Siebenmann (32), Politzer (33), and others declared that all operations on the stapes, whether mobilization or stapedectomy, were useless and even harmful. Stapedectomy, after resulting in temporary improvement, actually aggravated deafness they found, while lesions and accidents occurring during attempts at stapes mobilization made the results uncertain.

By the end of the last century, all operations on the stapes were abandoned. When it is considered that such a delicate procedure was performed through a myringotomy, with insufficient view of the stapes, without magnification or adequate lighting, coupled with the difficulty of achieving hemostasis and preventing post-operative infection, it is not surprising that these efforts to restore hearing were finally abandoned. Fistulization of the labyrinth, from which the present-day fenestration operation of Lempert is derived, then became the accepted approach for the restoration of hearing in otosclerotic deafness.

TECHNIQUE FOR MOBILIZATION OF THE FIXED FOOTPLATE OF THE STAPES (ROSEN)

The operation is performed under local anesthesia through an ordinary ear speculum in the external auditory canal, using the Zeiss-Cameron loupe. One to two cubic centimeters of a mixture of three parts two percent xylocaine and one part adrenaline chloride 1/1000 is injected subcutaneously into the skin of the posterior wall, roof, anterior wall and floor at the junction of the cartilage and bone.

An incision is made through the skin over the bony canal wall six to seven millimeters external to the drum, beginning postero-superiorly at the point of junction of the pars flaccida and pars tensa of the drum. (It is always best to begin the incision higher rather than lower.) The incision is carried downward along the posterior wall, floor, and anterior wall as far as the point where the pars tensa and pars flaccida meet antero-superiorly using instrument № 1 shown in Figure 4.

Starting at the beginning of the incision, the skin is separated from the bone as far as the edge of the drum with instruments № 2 and № 3 shown in Figure 4 (previously used by Lempert in tympanosympathectomy). The tympanum is first entered with instrument № 3 (Fig. 4) at the middle of the posterior canal wall about a millimeter or two below the beginning of the incision. From this point of entry into the tympanum, the drum is progressively lifted out of its sulcus. It is reflected upward upon itself like an apron with instrument № 4 (Fig. 4). This is essentially the same approach to the tympanum as that used by Lempert in his tympanosympathectomy operation for tinnitus (34).

In over 85 per cent of the cases, most of the incudo-stapedial joint is seen at once. The stapes, however, cannot yet be seen sufficiently to allow safe manipulation (Fig. 5). Therefore about two to three millimeters of the very edge of the posterior bony canal just external to the incus and stapes must be removed with instrument № 5 (Fig. 4) in order to get a full view of the long process of the incus, the incudo-stapedial junction, the head, neck, sometimes the crura and the footplate of the stapes, facial canal, the entire length of the stapedius tendon,

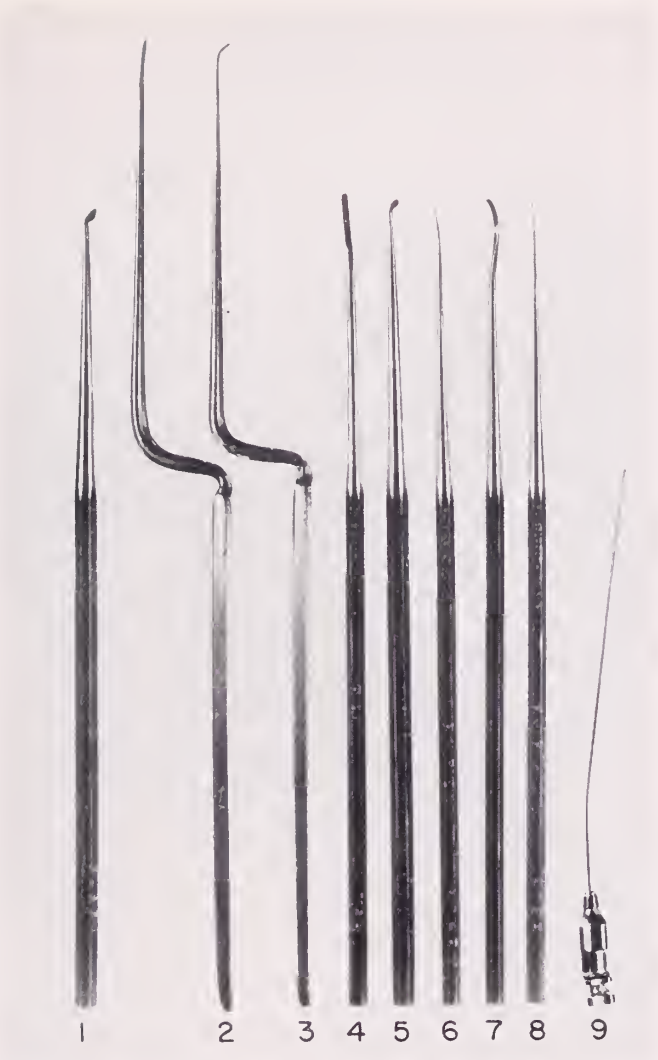

FIG. 4. Instruments numbered in the order in which they are used in mobilization of the fixed stapedial footplate (Rosen).

chorda tympani nerve, a portion of the incudo-malleolar articulation and the inner aspect of the hammer handle (Fig. 6). In some cases the chorda tympani must be sacrificed because it obstructs the view necessary for safe manipulation of the stapes.

To test for mobility of the stapes, a finely pointed probe (instrument #6 shown in Figure 4) is placed against the long process of the incus close to its articulation with the stapes and moved gently posteriorly for a distance of about a half-millimeter (Fig. 1). When the normal footplate of the stapes is freely movable in the oval window, the gentlest pressure of the probe against the long

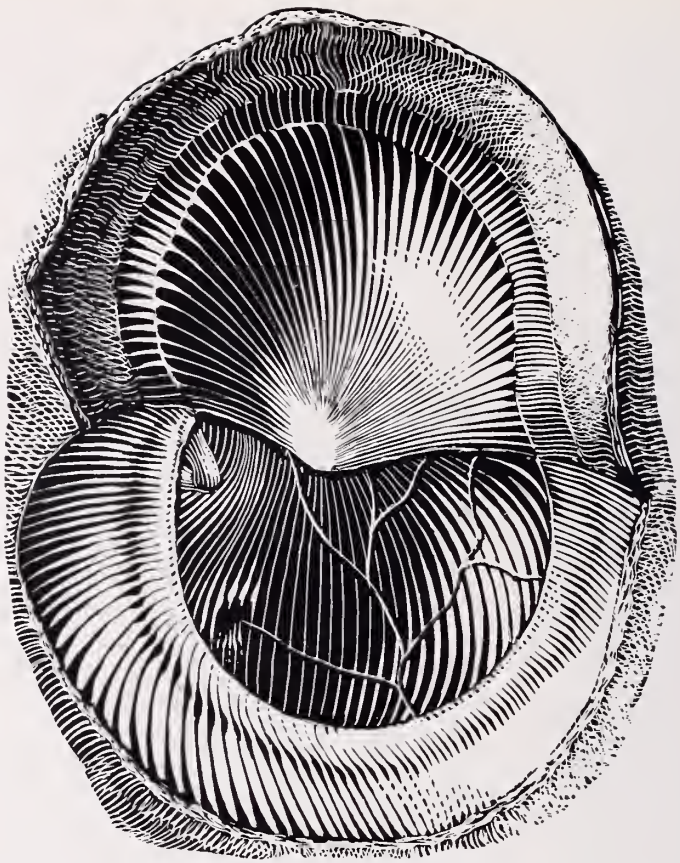

FIG. 5. When drum and skin are reflected upward, in over 85% of the cases more or less of the incudo-stapedial joint is seen. This is, however, an inadequate view of the stapes that does not allow safe manipulation.

process of the incus causes free and unimpeded movement of the incus, the incudo-stapedial joint, the head, neck, crura of the stapes and stapedial tendon. The tendon of the stapedius is the structure to watch at all times, since its movement is the reflection of the footplate movement. The footplate of the stapes moves invariably whenever the head and crura move and when this happens, the tendon invariably moves in proportion to the movement of the stapes.

These structures can all be seen to move together as one. The operator can also feel these structures moving. This associated sight and feel must be experienced often to master the technique. When the stapes is partially or incompletely fixed, it takes greater pressure of the probe against the long process of the incus to move these structures even slightly, as measured again by the degree that the tendon can be seen to shorten and lengthen. Again, these structures can be seen to move together as one, however minutely; but when the footplate of the stapes is completely fixed, very firm pressure of the probe against the long

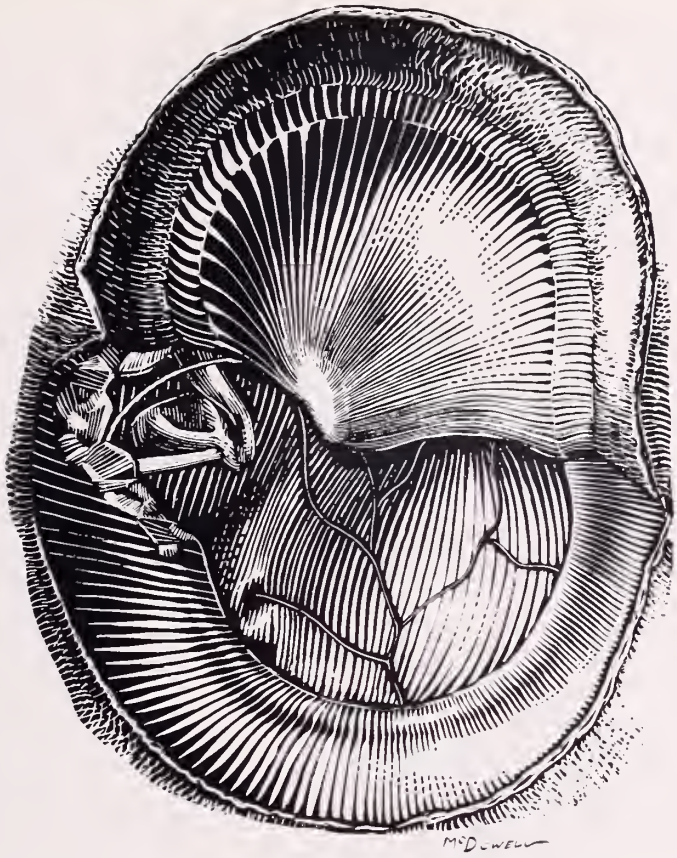

FIG. 6. After 2–3 millimetres of the very edge of the posterior bony canal just external to the incus and stapes is removed, a full view of the long process of the incus, the incudo-stapedial junction, the head, neck of the stapes and the entire length of the stapedial tendon, etc., is obtained. This exposure is absolutely necessary for stapes mobilization.

process of the incus causes the incus alone to move, but there is no movement whatever of the head, crura, footplate or tendon of the stapes.

When the stapes is rigidly fixed (stapes removed from cadavers and fixed in cement offer good practice to get the feel of the otosclerotic rigid stapes) variable pressure downward against the anterior aspect of the neck (only the neck, because it is the thickest and strongest part of the stapes) may suddenly loosen the footplate with immediate improvement in hearing. For this purpose a specially curved, narrow mobilizer was devised (instrument ✻7 in Figure 4). The palpating edge of the mobilizer is first inserted over the incudo-stapedial joint and is carried inward until one can feel the anterior crus of the stapes close to the footplate. The instrument is pulled gently upward and outward hugging the anterior crus until one suddenly feels a dent or depression, which is the neck of the stapes. At this point the stapes withstands the greatest pressure without fracture of the crura (Fig. 7).

FIG. 7. Pressure of the mobilizer (instrument #7) against the neck only of the stapes mobilizes the footplate without violating the incudo-stapedial joint.

Pressure against the neck of the stapes in a posterior direction in the line of the stapedial tendon is made until the stapes is mobilized. The direction of the stapedial tendon roughly follows the same direction as the crura and the long axis of the footplate; however, when one or both crura can be seen, the direction of the pressure against the neck of the stapes is in the line of the crura. Very slight pressure laterally (inferiorly) against the neck of the stapes may help to mobilize it (Fig. 1). The amount of pressure which can be exerted on the neck of the fixed stapes without fracturing the crura is considerable (Fig. 3). The muscles involved in the actual pull of the mobilizer against the neck of the stapes are the small muscles of the fingers and hand; never the larger muscles of the elbow or shoulder.

When a drop of saline solution is placed in the round window niche and the mobilized stapes is moved back and forth at its neck, a light reflex can sometimes be seen of this fluid moving in the round window niche. The movement of the saline solution in the round window niche is the result of the pressure transmitted through the cochlea from the movable stapedial footplate. This is seen best with the microscope.

If during the procedure adhesions or granulations involving the ossicles or round window are encountered, they may be dealt with using instrument #8 (Fig. 4). Rounded and slightly bent spinal tap needles of different calibers are used for suction (instrument #9 in Figure 4). When the operation is finished, the drum and the attached skin of the external auditory canal are replaced in their original positions. The ossicular chain remains intact.

Procedures of this kind should be performed only by those skilled in endaural surgery. Even the skillful surgeon should perform the mobilization operation on at least fifty fresh cadavers before the first patient is operated on, because of the

great number of anatomical variations. One must learn to do the operation skillfully through external auditory canals which are wide, tortuous or narrow. Also in many specimens the posterior bony canal wall is concave and the anterior wall is convex. Separating the skin from the bony wall without tearing it or injuring the drum in such cases is difficult and should be learned on the cadaver.

This operation appears deceptively simple, but learning to perform it skillfully is not, because all maneuvers are restricted by the limits of the external bony canal. In some cases the incus and the stapes are completely hidden by the posterior bony canal wall. The edge of the bony canal wall must therefore be removed cautiously to expose the ossicles. Care must be taken not to separate the incudo-stapedial joint during the mobilization or to dislocate the stapedial footplate by too sudden and too great pressure against the neck. It is well therefore, to discover these pitfalls on the cadaver.

Mobilization of the stapes is a minor operation and a short one, with little or no surgical shock. The patient is ambulatory following the operation, on full diet and leaves the hospital the following morning. Regular activity may be resumed in a few days. The skin of the canal is healed in about two weeks following the operation and the drum, which had been red and swollen, begins to take on its normal appearance. There is no postoperative vertigo or disequilibrium. In many cases the tinnitus disappears the instant the footplate is mobilized. Once the healing process is completed, the patient may swim, dive, travel by air, etc. without restriction.

Complications following the operation are few and of a minor nature. Of the 211 cases recently reported (17) none showed any evidence of labyrinthitis, facial paresis, erysipelas or perichondritis. Upper respiratory infection shortly after the operation depresses the hearing markedly, sometimes causes middle ear suppuration and should be avoided.

FURTHER DEVELOPMENT OF THE ROSEN TECHNIQUE OF STAPES MOBILIZATION

Mobilization of the Fixed Stapedial Footplate by Applying the Mobilizing Force to the Footplate Itself (Direct Method)

When pressure against the neck of the stapes fails to mobilize the fixed stapedial footplate and therefore fails to restore the hearing, the direct method of footplate mobilization is employed. This method consists in applying the mobilizing force directly to the footplate itself, the site of the pathological fixation.

Only after thorough skill has been acquired in the technique of mobilization at the stapedial neck should the advanced technique of mobilization at the footplate itself be attempted.

The preliminary steps in this technique are identical with the steps of the original Rosen technique. It must be emphasized that "two or three millimeters of the very edge of the posterior bony canal wall just external to the incus and stapes must be removed with instrument #5 of Figure 4 (Fig. 6) in order to get a full view of the incus, the incudo-stapedial junction, head, neck, sometimes the crura and the footplate of the stapes, facial canal, the entire length of the stapedius tendon, the chorda tympani nerve, a portion of the incudo-malleolar

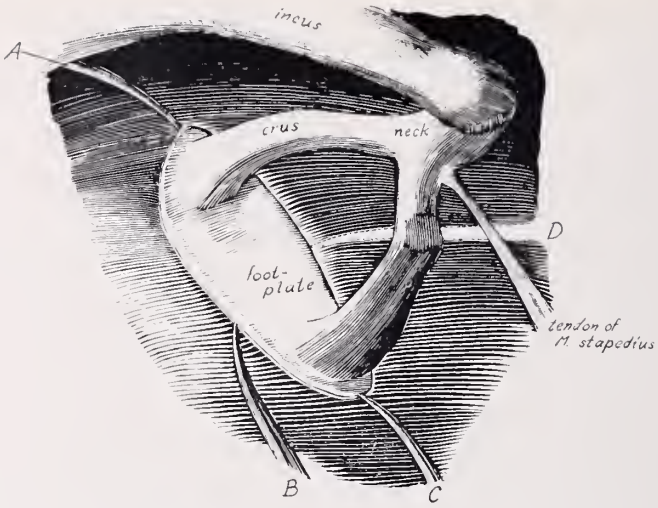

FIG. 8. "A" and "B" show the pointed explorer used anteriorly and inferiorly to mobilize the footplate. Occasionally the explorer is used at the posterior edge of the footplate "C" and rarely at the anterior edge "D".

articulation and the inner aspect of the hammer handle." This exposure is absolutely necessary for mobilization of the stapedial footplate, at the footplate.

Instrument #6 (Fig. 4), the explorer, is used exclusively to exert the necessary pressure against the peripheral margins of the footplate to pry it loose and render it mobile.

The explorer is inserted over the incus onto the anterior crus of the stapes, which is then followed inward until the footplate is reached. At this site, the anterior aspect of the stapedial footplate, only the very point of the explorer is gently wedged in between the bony rim of the oval window and the periphery of the footplate (Fig. 8A).

One can feel the point of the explorer entering this rather soft area between the periphery of the footplate and the bony rim of the oval window. The point of the explorer penetrates this area for a distance less than the thickness of the footplate. While moving the explorer ever so slightly in and out against the edge of the footplate, as if one were prying loose a lid, the entire footplate itself can be seen to loosen and move. The explorer is then withdrawn.

In many cases, the hearing returns as soon as the explorer is removed. If the hearing does not seem to improve or the tendon does not yet move, the point of the explorer is then inserted between the bony rim of the oval window and the edge of the inferior aspect of the footplate (Fig. 8B). This area of the footplate can easily be seen. The above sites have been utilized most often to mobilize successfully the stapedial footplate. Much less commonly, it is necessary to insert the point of the explorer at the posterior or superior margins of the footplate in order to mobilize it (Figs. 8C and D). Moving the footplate at one or

more of the above points suddenly causes a return in hearing. Occasionally, vertigo occurs for a few hours after the operation.

This method of direct footplate mobilization should be used only after thorough trials of pressure against the neck of the stapes fail to mobilize the rigid footplate. It was first used in an unsuccessfully fenestrated ear in April, 1954, and is indicated as well for virgin ears with a profound degree of stapedial rigidity. Direct footplate mobilization has restored hearing to as high as 10 to 15 decibels by pure tone and speech audiometry from pre-operative audiometric levels of 60 decibels (35).

AUDIOLOGIC ASPECTS

The degree of success in a series of cases operated upon for otosclerosis depends largely upon the selection criteria used. Careful, complete audiologic work-up is essential. Modern audiology provides a variety of tests which can be carefully controlled and which can be repeated with a high degree of reliability if certain basic rules are obeyed.

The Test Area. Audiometric rooms used for the selection of cases and for follow-up evaluation of results must have relatively stable, low ambient noise intensity levels, preferably no higher than 30 decibels. Noise levels up to 40 decibels are usually accepted for pre-operative testing due to the patient's hearing loss. For the evaluation of hearing in the most successful cases, however, where the post-operative hearing is normal or near-normal, the lower noise level is desirable. The intensity level of sound can be measured with commercially available sound level meters.

Equipment. Pure tone and speech audiometers constitute the basic test equipment. Air conduction tests require the use of two earphones, one for each ear, held securely to the ears by a double head band. For bone audiometry a bone "receiver" or oscillator should be available with a head band which will press the oscillator firmly to the mastoid bone with pressure that is uniform from patient to patient. A masking noise is essential, with adjustable intensity which can be read on a calibrated dial.

All test equipment, including pure tone air and bone and speech audiometers must be kept in calibration. Reference levels of normal hearing or "zero hearing loss" must be checked periodically for electrical and acoustic output. A simple calibration for pure tone air conduction levels can be accomplished by testing the thresholds of a group of young persons with known normal hearing. A satisfactory method of calibrating the bone conduction circuit of the audiometer is as follows: Select a series of audiograms made with the audiometer of the hearing of about six patients with pure inner ear deafness. Find the average deviation, in decibels, of the bone thresholds from the air thresholds for each test frequency. These average deviations are then applied as corrections to bone readings arrived at on each patient tested with that audiometer.

Test Personnel. It is desirable to have the tests performed by professional audiologists. The administration of modern tests of hearing requires consider-

able clinical skill and judgement, based upon thorough, specialized training in hearing and in the measurement of hearing function. Tests performed by the audiologist allow the surgeon to evaluate his results objectively.

Tests. Pure tone air and bone conduction audiometry along with speech audiometry provide the necessary information concerning the degree and type of deafness.

Since the determination of suitability for the mobilization procedure is generally based upon the estimated reserve of hearing in the inner ear, the bone conduction test results are of primary importance. The bone audiometry must therefore be accomplished with very careful attention to such details as placement and pressure of the oscillator and the amount and kind of masking employed.

Speech audiometry should include, in a minimum test battery, the speech reception threshold and the discrimination score. The speech reception threshold provides quantitative information about a change in the acuity of hearing for speech following mobilization of the stapes. The discrimination score aids in the determination of suitability, which is predicated on the understanding that poor discrimination indicates inner ear involvement, which reduces the chances for successful results from surgery of the middle ear.

Additional testing should be administered in cases in which the diagnosis is in doubt. Such testing may include examination for the presence of recruitment and tolerance tests. The presence of recruitment tends to indicate an inner ear lesion, usually cochlear.

RESULTS OF MOBILIZATION

Indirect Method (Pressure Against the Stapedial Neck Only)

The first careful statistical analysis on the results of mobilization of the stapes (Rosen technique) was presented in the Spring of 1955 (17). Two hundred and eleven consecutive patients were followed audiologically for periods ranging from three months to over two years following mobilization surgery. The cases were divided into categories based upon the pre-operative pure tone bone conduction thresholds at 500, 1000 and 2000 cycles per second as follows: "A" category included patients with bone conduction losses no greater than ten decibels; in "B" category the bone conduction losses did not exceed 20 decibels and in "C" category the maximum bone conduction loss for the three critical frequencies was 30 decibels. All cases with bone conduction losses greater than 30 decibels were grouped together in "D" category.

Two separate criteria were used to evaluate the success of the operation: 1) social adequacy of hearing and 2) significant improvement of hearing regardless of the post-operative level achieved, including cases in which the improvement permitted more successful use of the hearing aid. Since the exact level of social adequacy of hearing is not yet universally agreed upon, figures were given for the percent of cases reaching a post-operative level of 30 decibels as well as those reaching 35 decibels.

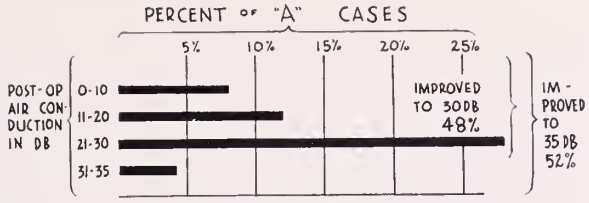

Fig. 9. Percent of 25 "A" cases showing improvement to the various pure tone threshold levels following mobilization at the neck of the fixed stapes (indirect method).

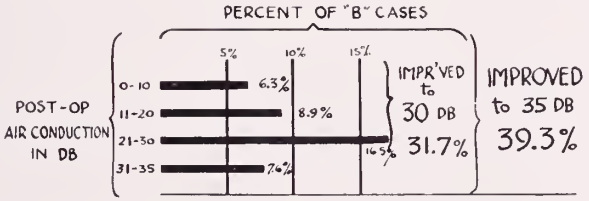

Fig. 10. Percent of 79 "B" cases showing improvement to the various pure tone threshold levels following mobilization at the neck of the fixed stapes (indirect method).

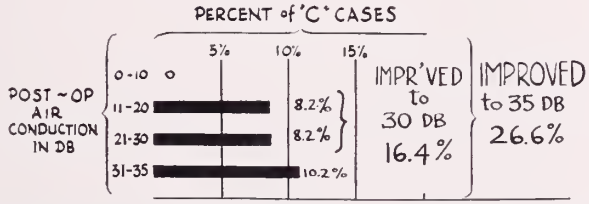

Fig. 11. Percent of 49 "C" cases showing improvement to the various pure tone threshold levels following mobilization at the neck of the fixed stapes (indirect method).

The results reported were as follows:

In Class A cases 52 per cent achieved pure tone levels of hearing between normal and 35 decibels and 64 per cent reached these levels by speech audiometry. Forty-eight per cent reached the 30 decibel level or better by both pure tone and speech audiometry (Fig. 9).

In Class "B" cases 39.3 per cent achieved pure tone levels of hearing between normal and 35 decibels and 41.4 per cent reached these levels by speech audiometry. Thirty-two per cent reached the 30 decibel level or better by pure tones and 34 per cent by speech audiometry (Fig. 10).

In Class "C" cases 26.6 per cent achieved pure tone levels of hearing between normal and 35 decibels while 16.4 per cent reached the 30 decibel level or better by pure tones (Fig. 11).

The per cent of cases in all four categories in which hearing was improved significantly without regard to levels of social adequacy were as follows: In 189 cases, 57.1 per cent improved from 10 decibels to 40 decibels or more over their pre-operative hearing, while 42.9 per cent remained unimproved.

Post-Operative Improvement in Hearing for Speech in Groups "A", "B", "C" and "D"

Improved (in db)	*No. of Cases (Total, 189)*
40 or more	11
39–30	23
29–20	22 (Improved, 57.1%)
19–15	23
14–10	29
Total improved	108
Unimproved	81 (Unimproved, 42.9%)

An important measure of the success of surgery for middle ear deafness is the extent to which the conductive portion of the deafness can be eliminated. In theory the mobilization procedure can restore hearing up to the level of the cochlear reserve as indicated by the bone conduction threshold. Following successful mobilization of the stapedial footplate, 50 per cent of the patients who reached the 30 decibel level or better are able to hear within 15 decibels of their cochlear potential, as measured by bone conduction (Fig. 12).

Direct Method (Pressure at the Footplate Itself)

The following cases illustrate some of the results achieved by the direct method of mobilization, i.e., mobilization at the footplate itself, months after the indirect method (mobilization at the neck of the stapes) failed to improve the hearing.

R. C., a 35 year old female, had bilateral progressive deafness for over five years. She had no tinnitus and heard better in the subway. On March 5, 1954, a mobilization operation was performed on the left rigid stapes. Pressure against the neck of the stapes failed to mobilize the footplate. The hearing did not improve on the operating table. Repeated audiological testing over a thirteen month period after the operation revealed that the hearing was only slightly improved, reaching a level of 40 to 45 decibels from the pre-operative level of 55 decibels. The surgical note at the time of operation stated that the crura may have been fractured.

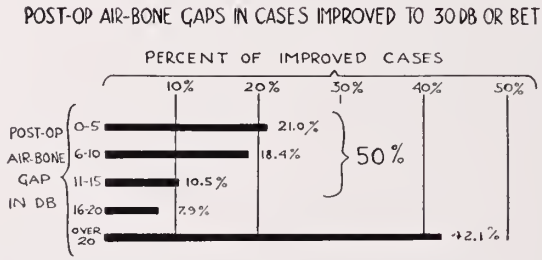

Fig. 12. Residual air-bone gaps following successful mobilization in "A", "B" and "C" cases. Fifty percent of all cases reached a level within 15 db or better than the pre-operative bone conduction.

On April 6, 1955, the same ear was re-operated on. At the second operation, no technical difficulties or significant changes were encountered in the external canal or the middle ear. Very slight pressure on the neck of the stapes revealed free movement of the stapedial tendon but without improvement in the hearing. This freely moving tendon was probably due to fracture of the crura at the initial operation. The point of the explorer was then placed between the bony rim of the oval window and the inferior edge of the footplate (Figs. 8B and 13B). With a slight prying motion the footplate itself could be seen and felt to loosen and move. The hearing improved dramatically on the operating table. Three months later the hearing reached the 10 decibel level by pure tone and speech audiometry (Fig. 14). The restoration of essentially normal hearing in this case indicates that the second operation caused the fixed footplate to become freely mobile.

A. F., a man 58 years of age, had bilateral progressive deafness for 15 to 20 years. The right ear was much deafer than the left. There was no family history of deafness. He wore a hearing aid in his right ear for many years. The preoperative hearing loss was 60 decibels by pure tone and speech audiometry.

On September 21, 1954, a mobilization operation was performed on the right rigid stapes. Persistent pressure against the neck of the stapes finally caused the crura to fracture, leaving the rigid footplate. The hearing remained unimproved.

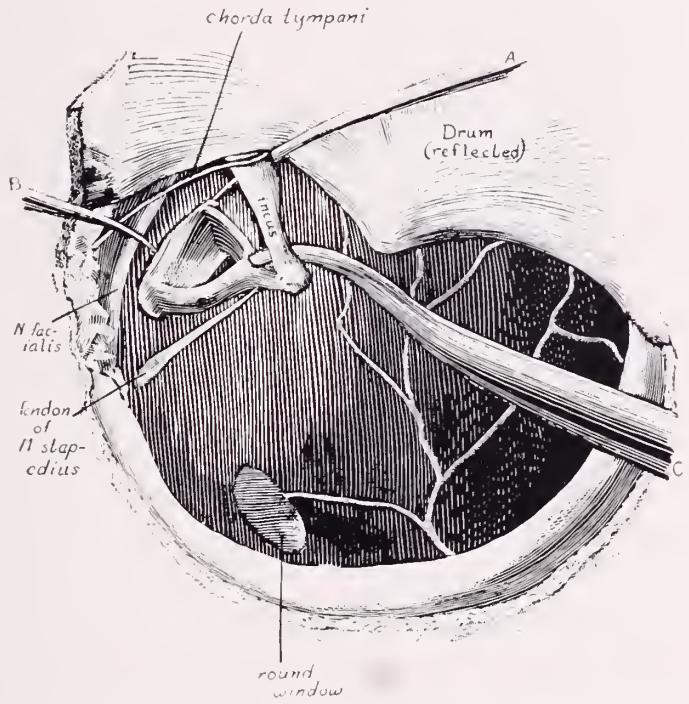

FIG. 13. First the mobilizer "C" is pressed in a posterior direction against the neck of the stapes (indirect method) in the line of the crura or in the line of the stapedial tendon when the crura are not distinctly seen. When this maneuver fails to mobilize the footplate, the explorer is used at "A" and "B" in the positions indicated to pry loose the rigid footplate.

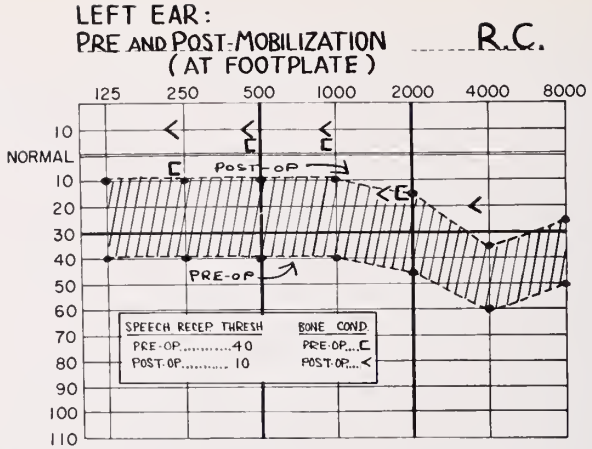

FIG. 14. Successful mobilization at the footplate (direct method) 13 months after mobilization at the neck of the stapes (indirect method) failed to mobilize the footplate and restore the hearing.

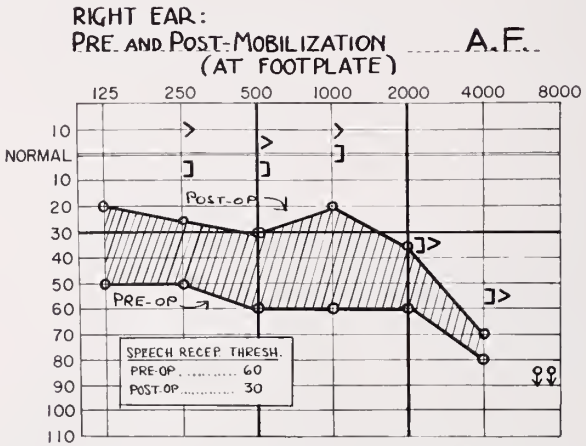

FIG. 15. Successful mobilization at the footplate (direct method) 8 months after mobilization at the neck of the stapes (indirect method) failed to mobilize the footplate and restore the hearing.

On May 2, 1955, eight months after the original operation, the same ear was re-operated on. The crura were found still fractured from the previous operation. The explorer was first inserted anteriorly and then inferiorly (Figs. 8 and 13, A and B) between the bony rim of the oval window and the edge of the footplate. Using a prying motion, the footplate could be seen and felt to move. Eight months later the hearing reached the 30 decibel level by pure tone and speech audiometry (Fig. 15). In this case, the explorer penetrated slightly deeper than the thickness of the footplate. Since the hearing improved so markedly despite the presence of crural fracture, it seems that the equivalent of a fenestration of the oval window at the site of the insertion of the explorer was achieved.

K. N., a woman of 47 years, had bilateral progressive deafness for three years and intermittent ringing tinnitus. On May 5, 1955, at operation the right stapes

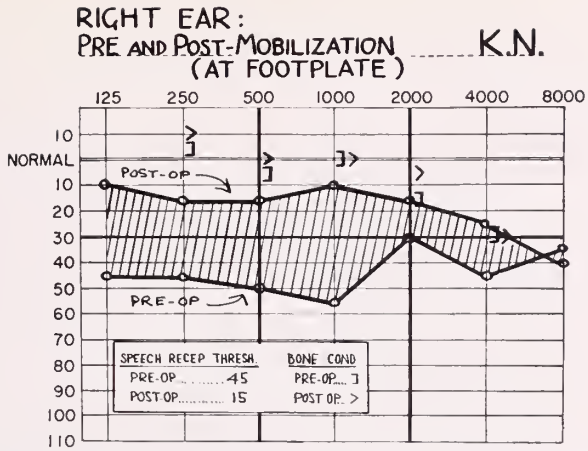

FIG. 16. Successful mobilization at the footplate (direct method) 5 weeks after mobilization at the neck of the stapes (indirect method) failed to mobilize the footplate and restore the hearing.

was found rigid. It seemed that pressure against the neck caused the stapedial tendon to move very slightly, yet the hearing did not improve. The pre-operative loss of 45 decibels did not improve. Five weeks later the right ear was re-operated on. The tendon still moved only very slightly on pressure against the neck, yet the hearing did not improve. Then the point of the explorer was inserted between the bony rim of the oval window and the edge of the footplate anteriorly, posteriorly and inferiorly (Figs. 8 and 13, A, B & C). With a slight prying motion of the explorer the footplate was seen to move and the stapedial tendon moved markedly. Seven weeks after this second operation at the footplate the hearing reached the 15 decibel level by pure tone and speech audiometry (Fig. 16).

In the following illustrative cases operated for the first time, the footplate was so rigid that extreme pressure against the neck failed to cause any movement whatever of the footplate or the stapedial tendon. In these cases direct mobilization of the footplate itself was therefore performed at once.

C. B., a 50 year old woman had bilateral progressive deafness for 10 years with intermittent hissing tinnitus. The pre-operative loss for pure tones was 55 decibels and 65 decibels for speech. On May 6, 1955, the left stapes was found rigid. Considerable pressure against the neck of the stapes seemed to cause the stapedial tendon to move very slightly but the hearing did not improve on the operating table. The point of the explorer was then inserted at the inferior margin of the footplate (Figs. 8 and 13B). With a slight prying motion the footplate and tendon could be seen to move and the hearing improved. Eight months later the hearing reached the 25 decibel level by pure tone and speech audiometry (Fig. 17).

D. H., a 50 year old woman, had bilateral progressive deafness for 10 years with intermittent buzzing tinnitus. The pre-operative hearing loss by pure tone and speech was 60 decibels. On May 10, 1955, the right stapes was found to be extremely rigid. Great pressure against the neck of the stapes did not cause any

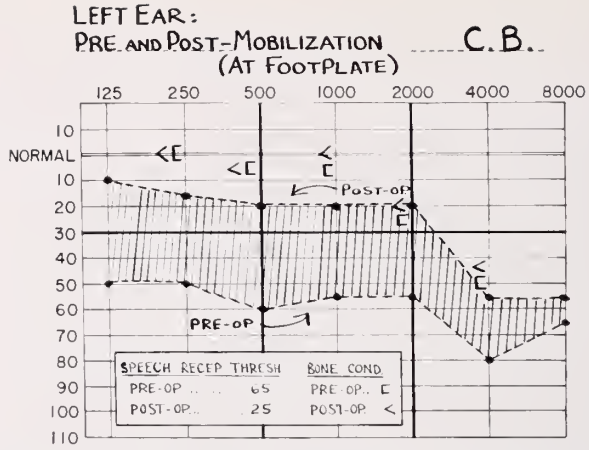

FIG. 17. Successful mobilization at the footplate (direct method) immediately after mobilization at the neck of the stapes (indirect method) failed to mobilize the footplate.

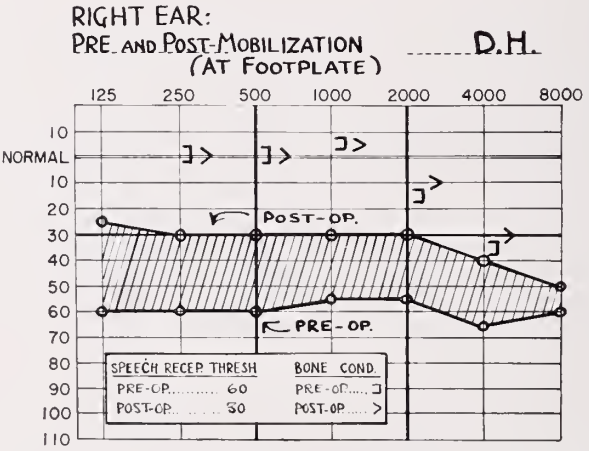

FIG. 18. Successful mobilization at the footplate (direct method) immediately after mobilization at the neck of the stapes (indirect method) failed to mobilize the footplate.

movement of the stapedial tendon and the hearing did not improve. Then the point of the explorer was placed against the posterior and anterior edge of the footplate and with a prying motion the footplate was loosened and the stapedial tendon was seen to move (Fig. 8A and C). The hearing improved at once. Eight months later, the hearing reached a 30 decibel level by pure tone and speech audiometry (Fig. 18).

Indications

At present, it can be stated that all patients with progressive conductive deafness, in whom the history, physical and audiological examinations indicate a fixed stapedial footplate due to otosclerosis, are suitable for the mobilization operation.

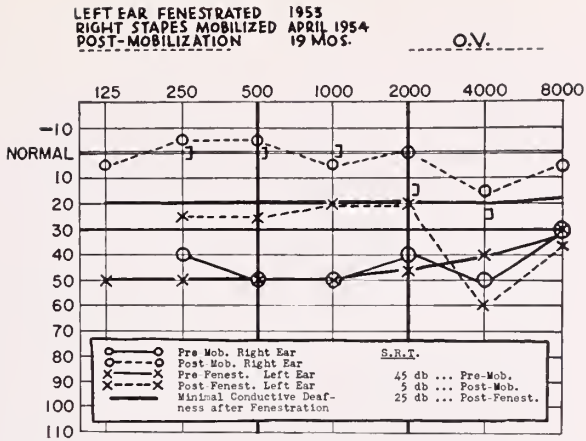

FIG. 19. Normal hearing 19 months after mobilization of the fixed stapes. This audiogram represents the comparative maximum effects from fenestration and mobilization.

The age of the otosclerotic patient is apparently unrelated to the success or failure of the operation. The average age of the patients in the least suitable categories, who by definition show more cochlear involvement is, however, greater than that of patients more ideally suited for the operation. In general, the longer the duration of deafness, the more fixed the stapes is apt to be.

ACHIEVEMENTS OF MOBILIZATION

While the goals of mobilization vary with each patient's hearing potential, the ultimate goal of any treatment for otosclerotic deafness is the restoration of normal hearing. Where there is as yet no cochlear involvement, mobilization of the fixed stapedial footplate is capable of achieving this goal, since in the operation there is no significant alteration or reconstruction of the anatomical structures of the middle ear. The following are some of the achievements of mobilization of the stapes with cases to illustrate:

1. *The Attainment of Normal Hearing*

Normal hearing is usually accepted as hearing within 10 decibels of zero loss for pure tones and speech. Seven patients out of 44 successful cases, or 16 per cent, whose pre-operative bone conduction loss did not exceed 20 decibels, achieved normal hearing following mobilization of the fixed stapedial footplate. These results are possible because the ossicular chain remains intact, thus permitting the complete restoration of the normal function. The following case illustrates this anatomical principle:

O. V., a 38 year old seaman, had bilateral progressive deafness for three or four years. In June, 1953, a left fenestration was performed by another surgeon. The post-fenestration hearing in the left ear had reached its maximum (20 decibels) from a pre-operative loss of 50 decibels. In April, 1954, the right rigid stapes was mobilized and within three weeks the right ear had gained maximum improvement to the five decibel level. Normal hearing has been maintained for 19 months to date (Fig. 19).

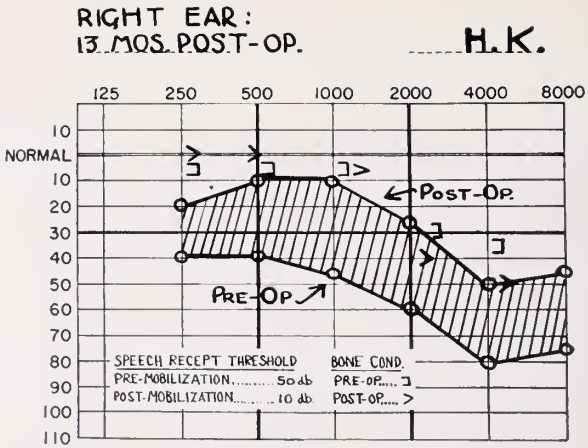

FIG. 20. Post-mobilization audiogram showing post-operative improvement to the level of the full cochlear reserve.

2. *Restoration of Hearing to an 11 to 20 Decibel Level in Patients with Some Evidence of Perceptive Loss in Whom Normal Hearing is Not Possible*

Otosclerotics with a hearing loss between 11 and 20 decibels by pure tone and speech audiometry rarely experience any hearing difficulties. In the following case, the 10 decibel level by speech audiometry was realized through mobilization of the stapes despite significant cochlear involvement:

H. K., 39 year old male, had progressive bilateral deafness for 18 years. He wore a hearing aid continuously for 10 years. His pre-operative loss for pure tones was 48 decibels in the right ear and 43 decibels in the left. His speech reception threshold was 50 decibels in the right ear and 45 decibels in the left. On October 16, 1953, the right rigid stapes was mobilized. The hearing has remained at the 10 decibel level for speech ever since (Fig. 20).

3. *Restoration of Useful Binaural Hearing*

Patients with unilateral deafness, where the hearing in one ear is normal or shows only a slight loss, often complain of difficulty in hearing speech in a noisy environment. This is also true for patients who wear hearing aids since they too are hearing unilaterally through the hearing aid. The understanding of speech against a background of noise requires the ability to locate the source of competing sounds, which can be accomplished only by binaural reception where the two ears hear about equally. Localization and separation of speech from surrounding noise permits the cerebral centers to suppress with facility the undesired noise in favor of the desired speech. Thus, while it is well known that otosclerotics often hear better in noisy places, this is true only when the hearing loss is relatively equal in both ears.

With the aim of achieving binaural hearing it was decided in the case of E. E. to mobilize the right stapes (52 decibels average loss by pure tones and 55 decibels loss for speech in the right ear) in the hope that the hearing in this ear would

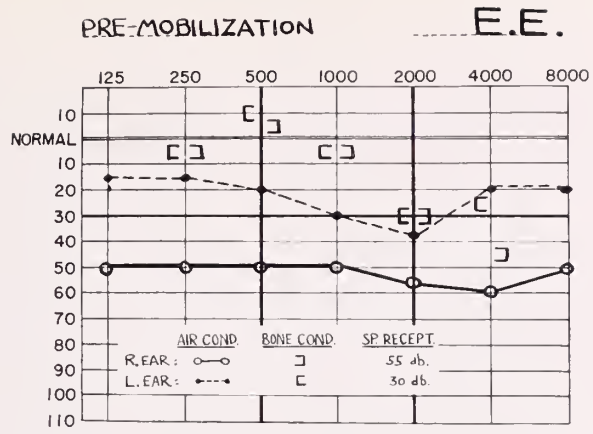

FIG. 21. Pre-mobilization audiogram of patient with much better hearing in the left ear. Mobilization was performed to raise the level of hearing in the poorer ear to that of the better left ear to achieve binaural hearing.

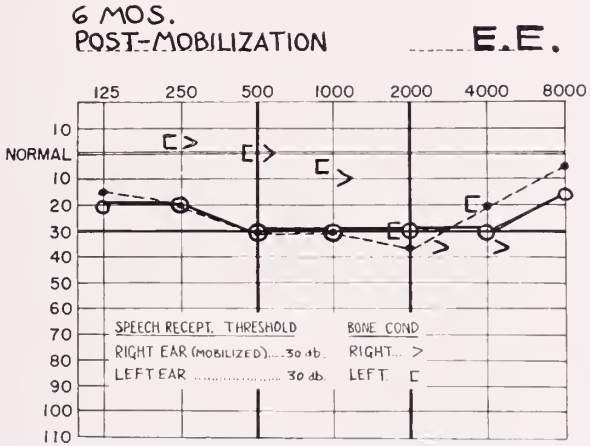

FIG. 22. Post-mobilization audiogram of right ear. Binaural hearing was achieved by successful mobilization of right stapes.

reach or surpass that of the better left ear (28 decibels average loss for pure tones and 30 decibels loss for speech) and thus result in unaided, binaural hearing. This was accomplished successfully. The case history follows:

E. E., 51 year old female, had a history of deafness in the right ear for 14 years and in the left for one year. On September 20, 1954, the right rigid stapes was mobilized and the hearing in that ear was raised to the level of the better left ear (Figs. 21 and 22).

4. *Removal of the Conductive Component (Stapedial) in Mixed Deafness (Cochlear and Stapedial)*

The following case best illustrates a severe mixed deafness where the hearing loss due to stapedial fixation was completely eliminated by mobilization, leaving

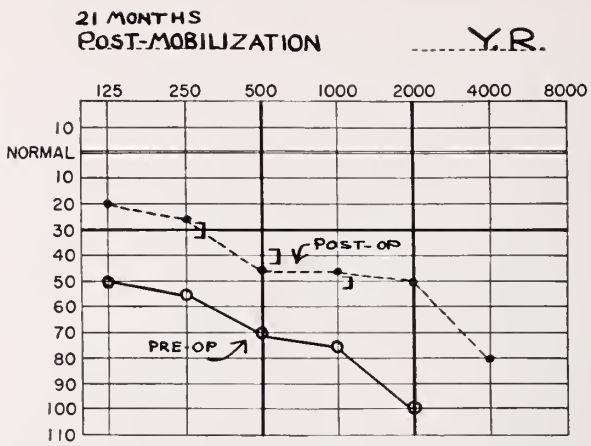

FIG. 23. The solid line indicates air conduction audiogram just before mobilization of the stapes (left ear). The dashed line shows the air conduction audiogram 21 months after mobilization. The air-bone gap present before mobilization appears to have been closed. The nerve deafness remains unaffected. Speech audiometry was not performed due to a language problem.

the cochlear deafness. The improved hearing following elimination of that portion of the deafness due to stapedial fixation allowed more effective use of the hearing aid.

Y. R., male, age 28 years, had bilateral progressive deafness for over 10 years. An unsuccessful right fenestration performed in Bucharest in 1945 was followed by facial palsy which recovered in six months. There was severe tinnitus in both ears. On August 10, 1952, the left stapes was mobilized. Hearing dramatically improved on the operating table. The hearing by air conduction in the left (unfenestrated) ear pre-operatively showed an average pure tone loss of 82 decibels. Hearing by bone conduction, though poor, indicated the possibility of improving his hearing to the degree that the conductive element might be removed. The hearing by air conduction post-operatively showed an average loss of 47 decibels for 500 through 2000 counts per second, with hearing at 20 to 25 decibels at 125 and 250 counts per second respectively. The improvement is significant in terms of the value to be derived from the use of a hearing aid (Fig. 23).

5. *To Permit Successful Use of the Hearing Aid in Extreme Deafness*

The gain or amplification of the strongest commercial hearing aids currently available is insufficient to provide comfortable hearing for ordinary conversation in a patient with a hearing loss in the better ear greater than 85 decibels. Any significant improvement in hearing in such profound deafness increases greatly the benefits to be derived from the use of a hearing aid.

C. W., a 45 year old woman, had bilateral rapidly progressive deafness since the age of 18 years. The speech reception threshold was 100 decibels in the left ear and 95 decibels in the right. The speech discrimination test had to be performed at only 10 and 15 decibels above the speech reception threshold of the right and left ears respectively. At these low sensation levels her discrimination

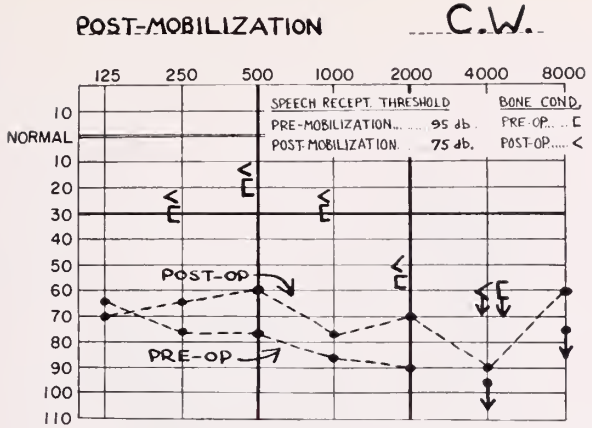

Fig. 24. Post-mobilization audiogram. The pure tone average rose from 83 db loss to 68 db loss and the speech reception threshold rose from 95 db to 75 db. The patient can now use her hearing aid with greater usefulness.

scores were relatively high (58 per cent and 62 per cent) which suggested the feasibility of mobilization. The patient complained of her inability to hear adequately with maximum amplification of her hearing aid.

On November 10, 1954, her very rigid left stapes was mobilized. The pure tone average in the operated ear rose from 83 decibels loss to 68 decibels loss and the speech reception threshold rose from 95 decibels to 75 decibels. The discrimination score in the operated ear rose from 62 per cent to 94 per cent at the same testing level used pre-operatively, 110 decibels above zero hearing loss for speech. Since mobilization, the patient reports greatly improved hearing with her hearing aid (Fig. 24).

6. *Improvement in Hearing Through Mobilization of the Stapes on an Unsuccessfully Fenestrated Ear*

It is fruitful to attempt mobilization of the fixed stapes in an ear in which the final result of fenestration was failure to improve hearing because of closure of the fenestra. An example of this follows:

H. C., a 50 year old housewife had a left fenestration performed ten years ago. Since the fenestration, the hearing in this ear had fallen to 50 decibels in the speech frequencies. The operative cavity was healed. The fenestra was closed osteogenetically, since repeated mechanical irritation all around the fenestral site failed to evoke any vestibular reaction. In August, 1954, the mobilization technique was used in elevating the drum and skin. About six to eight millimeters of the lower portion of the skin flap was also elevated along with the above. The incus, of course, had been removed at the time of the fenestration operation. The stapes was thus exposed in its entirety (Fig. 25). It was found rigid on palpation and was mobilized. The hearing improved to the 30 decibel level in the speech frequencies and has been maintained (Fig. 26).

After all the possibilities of multiple attempts at successive mobilization opera-

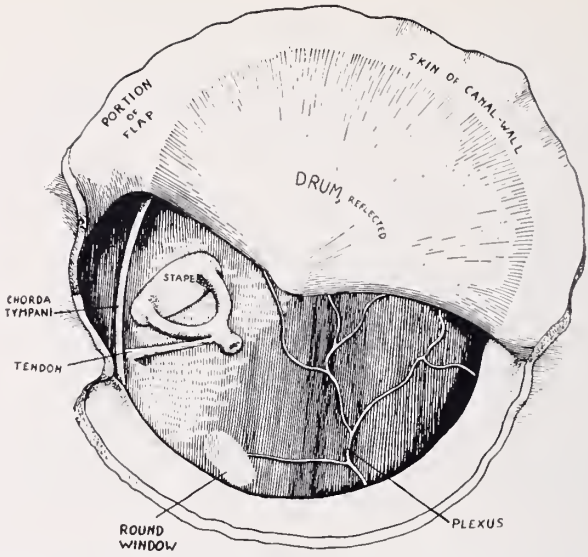

FIG. 25. Drum, skin of canal and a portion of the skin flap made at fenestration are lifted upward. The stapes can be seen in its entirety. Stapes is then mobilized as in non-fenestrated ears.

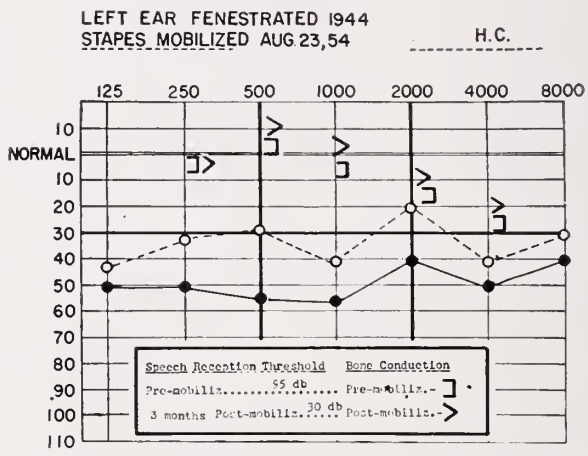

FIG. 26. Left ear, previously fenestrated unsuccessfully in 1944. The solid line shows the air conduction audiogram taken just before mobilization of the stapes. The dashed line shows the air conduction audiogram for the same ear 17 months after mobilization. The speech reception thresholds and pre- and post-mobilization bone conduction thresholds are also shown.

tions have failed to produce the desired result, it is fruitful to attempt the more formidable fenestration operation as a last resort to restore the hearing in otosclerotic deafness. Evidence at hand indicates that the mobilization operation does not impair the chances of a successful fenestration later.

Werth (36) in a report to the Audiological Congress in Paris in January, 1955, and at the Turkish Congress of Oto-Rhino-Laryngology in Istanbul in September, 1955 (20) stated that in the past two years he has had successes in 14 of 16

fenestration operations performed after unsuccessful mobilization. His results in these cases show that of the 14 successful fenestrations, seven were better and seven worse than the Shambaugh prediction (37); the average improvement was 28 decibels as against 26 decibels predicted. These fenestration results are similar to those obtained in virgin ears. Werth found no special difficulties in performing fenestration in these cases. Other otologists have reported successful fenestration results after unsuccessful mobilization (38).

It is apparent that for otosclerotic deafness the mobilization operation, in which the ossicular chain is preserved, should always precede the fenestration operation, in which the ossicular chain is permanently broken.

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ELEVATION OF SERUM ACID PHOSPHATASE IN GAUCHER'S DISEASE

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Serendipity has frequently been the handmaiden of discovery, in medicine as in other disciplines. One of the authors, H. S., saw our first case, L. L., a woman of 52 years, because of acute mid back pain. Investigation demonstrated collapse of the 12th dorsal vertebra and fish mouth appearance of the 11th dorsal vertebra. Eighteen years earlier she had been subjected to splenectomy at The Mount Sinai Hospital and a definitive diagnosis of Gaucher's disease was made. She was well, and taught school until the onset of back pain ten weeks prior to admission to the Maimonides Hospital for study. Roentgen findings and the past history posed the problem of differential diagnosis between a neoplasm with bone involvement and skeletal extension of the Gaucher's disease. Alkaline phosphatase determinations were done and were found to be within the normal range, i.e. 5.4 Bodansky units. Acid phosphatase studies were also done and a report of 7.2 King-Armstrong units was obtained. She was then seen in consultation by another of us, L. T., and when the acid phosphatase determination was repeated at the Mount Sinai Hospital because of the unexpectedly high value, a reading of 9.8 was obtained. It was then decided to study the serum acid phosphatase in other cases of proved Gaucher's disease, with the results to be presented.

METHOD

Serum acid phosphatase was determined by the King-Armstrong method (1) as modified by Carr (2). With this modification, in our hands, normal values range from 0 to 4 units; and it has proved to be a dependable, reproducible, clinical method. Particular care was taken to avoid hemolysis and subsequent contaminations by red cell phosphatase, and standing with consequent decrease in enzyme activity.

RESULTS

Eight cases of Gaucher's disease showed serum acid phosphatase figures ranging from 4.8 to 14 units (see Table I). pH activity curves obtained in two cases showed maximal activity at pH 5.0 (one half pH units plotted), as is typical of an acid phosphatase, excluding the possibility that the findings can be ascribed to red cell phosphatase. Three cases were females, three were boys under ten, one a symptom-free young adult of 22 with no urinary symptoms, and the last

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TABLE I

Case	Name	Sex	Age	Diagnosis Confirmed by	Anemia	Evidence of Hemolysis	Evidence of Bone Involvement	Acid Phosphatase (King-Armstrong units)
1	L. L.	Female	52	Splenectomy 18 yrs. ago. Sternal puncture recently	Slight	None	Collapse of 12th dorsal vertebra	9.8
2	M. L.	Male	7	Prominent hepatosplenomegaly. Sternal marrow aspiration	None	None	Femoral epiphyses involved simulating Perthes' disease	11.7
3	H. S.	Male	$5\frac{1}{2}$	Sternal marrow aspiration	None	None	Femoral epiphyses involved simulating Perthes' disease	7.1
4	A. K.	Male	$9\frac{1}{2}$	Splenectomy	None	None	None	10.8
5	I. L.	Male	75	Sternal marrow aspiration	None	None	Bone survey not done. No symptoms of bone involvement	8.3
6	L. H.	Male	22	Hepatosplenomegaly. Sternal marrow aspiration	None	None	Bone survey not done. No symptoms of bone involvement	8.1
7	J. D.	Female	50	Splenectomy	None	None	"Erlenmeyer flask" bulging of femora	7.0
8	R. G.	Female	45	Splenectomy	None	None	Negative skeletal survey	4.8

was operated upon for prostatic hypertrophy and the microscopic findings showed benign adenoma. Metastatic neoplasm did not come in question in any case. Alkaline phosphatase determinations were done in three cases and were normal.

COMMENT

The finding of an elevation of a serum acid phosphatase in Gaucher's disease is provocative, and requires further investigation and elucidation. Since the fundamental work of Gutman and Gutman (3, 4) an increase of serum acid phosphatase has been considered strongly suggestive of, if not pathognomonic of, metastasizing carcinoma of the prostate. Sobotka, Glick, Reiner and Tuchman, (5) in an investigation of the lipoids of liver and spleen in Gaucher's disease, described a decrease in the percentage of phosphatides in spleen and liver. Whether this decrease in phosphorus-containing lipid can be related to an increase in serum acid phosphatase remains to be determined.

SUMMARY

Eight cases of Gaucher's disease confirmed by splenectomy and pathological study or by sternal marrow aspiration are presented. Elevation of serum acid phosphatase is demonstrated in all.

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THE EDWIN SMYTH PAPYRUS* (PART I)

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In classical times, the Egyptians had a great reputation for their medical knowledge. Homer writes in the Odyssey that physicians of Egypt were skilled beyond all others, and Herodotus several times mentions the medical practitioners of Egypt, each of whom he says was a specialist applying himself to the study of one particular branch. The wisdom of the Egyptians was indeed proverbial, and even though they were not so far advanced in more abstract thought, there is no question that they were a highly gifted people with great capacity for practical achievement. There is no longer any doubt that the foundations of medical science originated in Egypt more than fifty centuries ago. Although modern writers have credited the Egyptians with scientific medical knowledge of profound extent, other scholars have denied this claim almost to the point of asserting the non-existence of any such knowledge. The truth lies somewhere between these two extremes and even the most severe critics grant that a nation which had evolved sufficient knowledge and skill to plan and execute feats of architecture and engineering as early as 3000 years B.C. and whose mathematical knowledge involved the principles of cubic capacity, angles, fractional notation and the square root, must compare favorably with any contemporaries in intellectual capacity. We have considerable evidence as to just what the Egyptians could do in medicine and surgery, in the large number of original documents, the medical papyri which had been found and preserved. The contents of these papyri fall into two main groups; those which may claim to be called medical books, and those which are magical in content or are collections of popular recipes. Tradition has ascribed the authorship of these treatises to various gods, to certain early kings and to ancient sages in general.

These documents constitute the oldest body of medical literature in the world. We shall mention briefly a few of the more significant ones. The longest and most famous of these documents is the so-called Papyrus Ebers which was found in Thebes in 1862, the same year and place in which our subject for the present discussion, the Edwin Smyth Papyrus, was found. The Ebers Papyrus is now preserved in almost perfect condition at the University of Leipzig. It was written about the beginning of the 18th dynasty, which would place it around 1600 years before Christ. There is evidence that it was copied from a series of treatises many centuries older, presumably dating back to the time of the pyramids. It is not really a book, but a miscellaneous collection of extracts, recipes and jottings collected from at least forty different sources. These extracts relate to diseases of the stomach, to the action of the heart and to the surgical treatment of boils, carbuncles and abscesses. Freely interspersed among these elements are magical spells and incantations.

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* Presented at a Seminar on the History of Surgery.

Another important document is the Papyrus Hearst which was discovered in Upper Egypt in 1899 and is now preserved at the University of California. The papyrus is somewhat later in date than the Ebers but its contents are very similar. The Kahun Papyrus was discovered in Lower Egypt in 1889 and is older than any other medical papyri extant, belonging probably to the 12th dynasty, about 1900 B.C. The Kahun Papyrus contains 34 sections, all dealing with one subject, gynecology, which circumstance makes it quite unique.

The Edwin Smyth Papyrus, which is now in the Rare Book Room at the New York Academy of Medicine, is devoted to the surgical treatment of wounds, dislocations, tumors and fractures. It contains 48 long sections, each dealing with a particular case involving a particular organ or region. In addition, it contains thirteen magical incantations and prescriptions on its "verso" side. The magical element can be readily appreciated when we consider that Egyptian medicine had its origin in magic and that magic never lost its hold on medicine, even when science was pervading it to a greater and greater extent. Illness was believed to be due to possession, and the art of the physician stemmed from the various attempts that were made to coax, charm, coerce, or forcibly expel the demon from its involuntary host. This idea persisted even until after the Christian era when we have the writers of the New Testament thoroughly convinced that disease, at least mental disease, was caused by possession. Jesus is credited with having driven out demons from many persons whom he healed. It was originally only in cases of injury due to an evident or palpable cause that purely rational methods of treatment were employed. If it was obvious that a wound had been inflicted by some mechanical means, it was dealt with by more or less rational therapeutic methods, but diseases and internal pains were submitted more often to magical than to medical therapy.

In the Edwin Smyth Papyrus as well as the other medical papyri, prescriptions are each headed by a title which instead of employing a phrase such as, "prescription for treating such and such a disease", more often has some such heading as, "prescription for driving out, banishing, terrifying, or killing" this disease. In the more rational surgical treatment of wounds, a formula commonly used by surgeons reads, "It is a condition I may contend with" or "will wrestle with". The therapeutic treatment of cases that are not frankly surgical consists of liquids, pills or powders for internal consumption or ointments or lotions for external use.

When we come to the terms used in the papyrus to describe pathological changes, we encounter all manner of difficulties. The text is full of problems of lexicography, and it is often very difficult to find English equivalents for the Egyptian names of the diseases. A number of anatomical and pathological terms have been identified with certainty and a still larger number with considerable probability. We can conclude that in general the maladies with which the medical papyri are concerned include those which still plague mankind today, e.g., intestinal troubles, ophthalmia and other eye disorders, boils, sores, animal bites, dermatitis, intestinal worms, naso-pharyngeal diseases. These were the more common ones mentioned. We have descriptions of treatments for alopecia, for

diseases of the mouth, tongue, ear, teeth, nose and throat. In one of the medical papyri there is a long series of remedies for arthritic complaints and gynecological problems. Always included with the medical prescriptions are household remedies for getting rid of fleas, flies, snakes and vermin.

The Edwin Smyth Papyrus deals primarily with wounds of the head and thorax. It was found in 1862 by natives from whom it was purchased by the man whose name it bears. Edwin Smyth, who came from Bridgeport, Connecticut, was an Egyptologist who spent a good deal of his life searching the ruins of Egypt for just such material.

The surgical tests are drawn up according to a definite formula, consisting of five parts. Number one is always the title. Number two is the physical examination of the patient. Number three is the doctor's diagnosis. Number four is an opinion or a verdict, and number five is the treatment. From the rational and almost methodical way in which these texts are drawn up, Professor Breasted, who has done the most extensive work on the Edwin Smyth Papyrus, claimed that the emphasis on magic, so evident in the earlier medical documents, was now minimal, and that the Edwin Smyth Papyrus was, therefore, a truly scientific book. In other words, he felt that the great emphasis on cases which could not even be treated proved that this was a scientific work, perhaps analogous to a clinical pathological conference of today which is intended primarily for the education of the doctor.

The Papyrus deals exclusively with injuries of the head, neck and thorax including spinal column and breaks off abruptly in the midst of a discussion of the treatment of an injury to the spine; in fact, in the middle of a sentence. It is unfortunate that we do not possess the entire work from which this Papyrus was copied as it undoubtedly also dealt with injuries of the pelvis and lower extremities.

We may infer something of the way surgery was taught in Ancient Egypt. The Edwin Smyth Papyrus gives directions to the surgeon, but they do not necessarily deal with techniques of surgical practice. The matter of technique was left to the teacher, the individual surgeon who served as a kind of preceptor in his relationship to the younger man. The presentation of cases is extremely interesting. The title is usually brief and named after the chief symptoms. For example, case number 15 of the 48 cases presented in the Edwin Smyth Papyrus is entitled, "Instructions concerning a perforation in his cheek." Case number 5 reads, "Instructions concerning a deep wound in his head, smashing his skull." Then comes the physical examination in which the surgeon was given instructions on how to examine the case and probe the wound. The surgeon was even told what symptoms he should look for, listing and describing and evaluating them in a way not found in any other ancient medical text. The diagnosis which follows is usually a repetition of the title. Then comes the verdict. This is an extremely interesting part of the documents. It is a statement by the surgeon author as to his further course of action. There are always three possibilities: it was either "an ailment which I shall treat", "an ailment with which I shall contend", or "an ailment not to be treated." The interesting thing here is that when the surgeon

felt that the injury or the disease defied treatment or was untreatable, he simply abandoned the case and nothing at all was done for hopeless cases, not even to alleviate symptoms. In 14 of the 48 cases presented, the surgeon after careful examination and discussion of the symptoms concluded that he would not treat the condition. Professor Breasted advances this fact as conclusive evidence for the scientific interest of the Egyptian surgeon. Sigerist, the medical historian, disagrees and comments as follows: "The book in all probability is a textbook, a manual of surgery written for the instruction of other surgeons. A number of typical injuries are discussed and the surgeons told which ones responded to treatment and what this treatment should be. How could the instructor make clear which injuries are fatal and should not be touched by the surgeons unless he discussed them in detail? The unfavorable verdict was a very severe one, since it left the patient without treatment, and no conscientious surgeon made it unless he had examined the case very carefully; but he had to be taught what symptoms to look for and what they meant before he could reach a verdict that was correct. Hence, I fail to see why this group of cases should have a significance different from the others. Its purpose is just as practical."

Diagnosis and verdict are followed by the indication of the treatment, the application of dressings and nursing care and diet. Of immeasurable help to historians are the glosses or explanations of technical terms which are found in 29 of the 48 cases. These are actually a commentary to the text. Case number 4 uses the term "splitting the skull", which sounds simple enough, but the commentator is more specific about it and wants us to know, "It means separating shell from shell of his skull while fragments remain sticking in the flesh of his head and do not come away".

There are five cases devoted to the clavicle, the scapula and the shoulder joint. In speaking of the soft tissues of the clavicular area, the ancient writer casually adds, "There are two canals under it. One on the right side and one on the left side of the neck. They lead to the lungs." The operations for a dislocated scapula and clavicle are both described. In both, the patient is laid out on his back and his arms are stretched alongside of him. It is very interesting that he is put into this position of hyper-extension to repair the shoulder.

In the section of the Papyrus devoted to the skull, two cases are presented, one involving a knife wound in the forehead and the other a laceration through an eyebrow. The cut on the forehead is to receive a plaster made of "physicians skin." This is a kind of linen bandage prepared by the embalmer. The cut in the eyebrow is to be carefully held together by a special double bandage "so as to cause the two lips of the wound to join one to the other". Thus, we find that the "butterfly" tape was used for approximation of wound edges nearly 5000 years ago.

The Edwin Smyth Papyrus was written on both sides. It is about fifteen feet long and there are seventeen columns on the front, and four and one half or five on the back. The front is called the "recto" and the back the "verso". The text is written in horizontal lines, always from right to left and these are arranged in the columns of the scroll. The material on the back had nothing to do with the

material on the front; in fact, it is a magical piece of writing in contrast to the text appearing on the front. The incantations that appear on the "verso" include eight against the pest or plague, a prescription or recipe curing proctitis and a prescription for some kind of female disease. Most enticing of all is a prescription for making a young man out of an old man.

There are many instances where the text would be completely unintelligible were it not for the glosses. Thus, the expression "moor him at his mooring stakes" is explained as meaning "putting him on his customary diet without administering to him a prescription." This argues that the text originated many years before the glosses were added. The scribe who copied text and glosses many centuries later committed a number of errors, but was not at all ashamed to admit that he had made an error in copying onto the papyrus. We have very good evidence as to just where he made his mistakes. The introduction to any paragraph or section was always written in red ink; these were the so-called rubrics and from then on the text continued in black ink. If there was an error, the scribe merely corrected in red ink over the portion originally written in black, and conversely, if an error had occurred in the rubric he wrote over it in black ink. In the large Breasted edition of the Edwin Smyth Papyrus one can see these evidences of the errors of the scribes. However, every technical language develops terms that are obvious at the time, but may not be so centuries or millenia later. We take for granted today such terms as Billroth II or Wolf-Parkinson-White syndrome, but how much meaning will they have 1000 years hence without some accompanying explanation?

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THE EDWIN SMYTH PAPYRUS* (PART II)

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We may look at historic documents such as the Edwin Smyth Papyrus because of our interest in the subject matter of their text and also because of their language and form. We must first be able to decipher them and to understand their language. In the case of such specialized texts as the one with which we are dealing at present, the palaeographer and philologist will find their task greatly facilitated by cooperation with the medical specialist.

I do not want to go deeply into the philological aspects of this Papyrus, but I should like to convey some idea about the chronological sequence of Egyptian documents.

The element antimony is symbolized by the letters Sb, which stand for the Latin equivalent "stibium". Stibium goes back to the Greek word for antimony "*στιμμι*" and when one tries to trace the origin of this word, one comes upon the Coptic "stim CTHM". The Coptic language was derived directly from the Egyptian that was current about the time of Christ. It incorporated many Greek words, especially of Christian lithurgic content. It subsequently remained the language of those Egyptians who were not converted from Christianity to Islam and whose descendants are still existing, but gradually have accepted the Arab language. Coptic died out as a living language not later than 1400, when it fell into disuse except in the Coptic church in Egypt, where some Christians still survive through the Moslem period, and in Abyssinia where Coptic is used as the language of the State church. Coptic is written with modified Greek characters to which have been added a number of letters from demotic script, ultimately derived from hieroglyphs.

When one goes further back, one finds e.g. in the Edwin Smyth Papyrus on its "verso" side in one of the prescriptions an Egyptian word, which I can not pronounce, because no one can pronounce any old Egyptian words. All we know of them is the sequence of the consonants; it is as if there were no tradition for the pronounciation of written unpunctuated Hebrew and one had only the consonants so that one would not know for sure how to assign the vowels. Egyptian hieroglyphs were written in both directions. In most of the old written documents it runs alternatingly, like a plough right to left and left to right.

In the present example one meets a combination of letter symbols, syllabic symbols and other signs, the so-called determinatives. Fig. 1 shows from left to right the syllable MS, the letter sign for S, a hand which is D, then a bird M, then T, which is a little hill, and a few little points which means that the word signifies a powder; finally, there are three lines indicating that it is a collective noun; while it is grammatically in the singular it means a mass of things. So there is M-S-D-M-T and it is a convention of Egyptology to interpolate the vowel E

* Remarks made at the Seminar on History of Surgery.

between these letters to make the word pronounceable: MESDEMET, which is the precursor of Coptic "stim". This word is then 5000 years old and it appears remarkable that one can follow its history and that of many other words through the old Egyptian, Coptic and modern languages. Going through our vocabulary one can find quite a number of words that are considered to be Greek, but are really Egyptian words. Names of Saints like Paphnutius and Onophrius, which is a frequent given name in Southern Italy, are of Coptic origin. The word "Chemistry" is most likely of Egyptian origin, since its Arab forerunner Alchemy was derived from Egyptian KM, meaning black and specifically the country of Egypt with its black earth; "Chemistry" is the Egyptian science.

Coptic flourished during the first millenium of our era; going back in history one finds the Ptolemeic dynasty up to the time of Christ, say, from 330–30 B.C., and before that Alexander the Great, preceded by a short Persian reign, which had followed the dynasty of Sais, named after their capital in the delta of the Nile; one of the Saïtic kings was Necho, who sponsored the first circumnavigation of Africa. But all this is rather recent history compared to the period when the Edwin Smyth papyrus was written. Tracing our steps further back, there was a time of Ethiopians and other barbarian tribes invading, conquering, and

Fig. 1

ruling Egypt for centuries. They had succeeded a period of national greatness, which we like to call the Egyptian Empire, which flourished from 1600–1100. That was the time when Egypt dominated the Eastern Mediterranean and when, about 1300, the Jews served in Egypt, eventually to leave under Moses. The language that was spoken at this time is known to Egyptologists as "New Egyptian". Before this so-called New Kingdom, there was the period of the Hyksos, savage tribes from Syria. From 2100 to 1800 we count the Middle Kingdom and in this epoch the rich classical Egyptian literature was written. Upon it most of the later inscriptions are based, comparable to the use of Latin during the Middle Ages. One may compare this stage of the language to Attic Greek and to the Golden Period of Latin literature. Before that we have the Old Kingdom from 2700 to 2100. That still leaves the mythical first two Dynasties, the "Pyramid" kings. All the kings of Egypt were systematized in 30 Dynasties by a historiographer at the time of the Ptolemaic kings.

When one looks at these hieroglyphs, they changed a great deal throughout the ages; at last they became very bizarre and people did not understand them anymore. From the Middle Kingdom on, one finds the longhand writing such as in the Papyrus Smyth, the so-called Hieratic writing, which the priests used on papyrus, a tissue of plant fibers pounded together and evidently exceedingly

durable. The Papyrus Smyth and the Papyrus Ebers have been quite accurately dated at 1600 B.C. plus or minus 50 years. Later on, the hieratic script was even more simplified in the so-called Demotic writing, which requires a separate study.

The Papyrus Smyth was found in a tomb near Thebes, the capital of the Middle Kingdom of Egypt. Edwin Smyth was an American Egyptologist, who lived there for about 20 years; he knew the Arabs and Copts and one of them sold him this Papyrus. A little while later he sold him a second one; although Smyth saw at once that the second one was mostly a roll of cardboard on the outside of which part of a Papyrus had been pasted, he gladly paid the price because no matter how much he paid, it certainly was less than its value to science. This second part which was wrapped around the roll of trash consisted of the fragments of an additional page of the Edwin Smyth Papyrus and they have been put together by Smyth and by Breasted to give a fairly complete continuous text. It is actually the first page of the original scroll with only the title missing.

When one comes to the 48th case, one can see that the Papyrus was not torn off and the rest lost, but the scribe who copied it must have been told by his Master "You have got to stop now, for we have some more important incantations here, turn the papyrus around and copy them on the back". Looking at the papyrus one observes that there is an unused portion of about 50 cm. which confirms the fact that the papyrus is complete and that only the copying was incomplete.

This 17th century scribe copied the text from a much older document, which was written in the style of textbooks such as existed for mathematics, agriculture, and other sciences. This accounts for its rather pedantic organization: title, diagnosis, treatment, verdict, etc. From the style of the language Egyptologists can tell that the original text was literally followed; whenever the scribe made mistakes he erased them or inserted corrections. The original text dates from the early part of the Old Kingdom i.e. from the 30th or 29th century B.C., in other words, it was composed about 1300 years before the present copy was made. Thus, it is as if a modern physician were to study medicine today from documents from the time before Charlemagne.

The man who wrote the very interesting commentaries or glosses was also still using the Egyptian language of the Old Kingdom; he must have added these glosses around 2400 or 2500 and within those 500 years some terms had already become obsolete. For instance Case 7 deals with a wound in the scalp that penetrates deeply; the author says "Don't treat it" and he gives as one of the symptoms that the wound smells like—then follows a word which does not occur in any other papryus or document preserved today—it is BKN and we shall pronounce it BEKEN. Fortunately, we have a glosse which says "When he says BKN of sheep, he means the WSST" a more modern word meaning "urine" and known from other Egyptian documents. If the glosse did not exist, we would have no idea what BKN means; there are of course a number of words in the papyrus, the meaning of which is not known and may only be conjectured.

One of them is particularly interesting in our case; it occurs six times in this

papyrus and twice elsewhere in the preserved literature. It consists of a leaf of bamboo (J), then a hand (D), and an open mouth representing (R). It also has a so-called determinative hieroglyph at the end. Egyptian script cannot be called purely alphabetical, but in general every letter responds to a sound consisting of one, two or more consonants and semi-vowels; in cases of more than one sound it also symbolizes the specific vowels. All these signs, individual letters and syllabic symbols, were originally word symbols. This is common to all ancient forms of writing such as Chinese, Cuneiform, and according to a recent discovery, to Greek. In hieroglyphs many such word symbols were still used for the entire word, particularly for those designating concrete objects. At the beginning of historic times, one had already started to use word symbols as syllabic and letter symbols and to combine them to form longer words, grammatical derivatives with prefixes and suffixes, and abstract expressions. Subsequently, one added at the end of a word, to avoid ambiguities, other symbols, so-called determinatives, which indicate categories e.g. a human figure after the name or designation of a human being. In the present case, the alphabetic spelling IDR required some further explanation, since by this time the two liquidae R and N had been confused. In order to show how the word should be pronounced the scribe added the ear of a

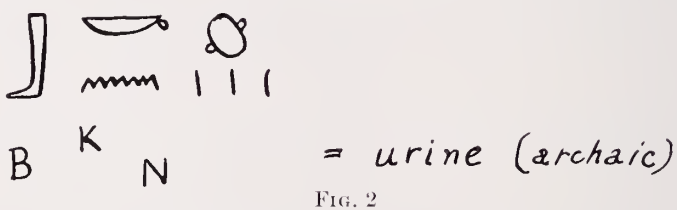

Fig. 2

calf known to be pronounced IDN. Besides there follows a determinative which may mean a textile or metal object. Breasted suggest that the word IDN in the present text may mean either a verb or a noun, signifying "to sew a gaping wound" or a suture.

In some of the cases the ancient physician gives not only one examination, but follows up with a second examination and in one case he has as many as five examinations; on repeated examinations he often changes his prognosis. In this manner, he uses the history of a single patient to offer various alternatives of the outcome. This confirms the assumption that we are dealing with a medical textbook. In these re-examinations, he says in three places: "If the IDN has become loose, then you should" do this or that, for instance, "you should not try to sew it again, but put some meat on it". Raw meat was frequently used as a poultice. IDN fits the word "suture" very well, but I would not consider this translation definitive, as the word might as well mean some metal clamps which the Egyptians certainly had the technical knowledge to make. If you use metal clamps, you could say the same things about them: you put them on, you see if they are loose, you are told what to do, if they become too loose.

Of all these cases, we find that 47 out of 48 are treated rationally. But take Case No. 9. Suddenly, the magic spirit gets the upper hand. There is a man with

a wound in his skull. The author compares the skull to the shell of an ostrich egg and in adumbration of the medieval signet theory, he promptly treats the patient with a poultice from ostrich eggs and incantations to boot. But in the same case, he also talks of the bindings, or bandages. Apparently, the Egyptians had some very fine bandages, such as may be seen in mummies very artfully wound around the body. The doctor is advised to go to the embalmer for these bandages.

On the first, slightly fragmentary page, in the description of Case No. 1, we find a very long digression on the heart. There is a decrepancy in interpretation between Breasted, who considers this as part of the subject of the manuscript, and Sigerist, who believes that this passage was brought in by accident. It refers to a book on the action of the heart as follows; it is the first glosse to the first case: "As for: 'thou examinest a man'" it means counting . . . like counting things with a bushel . . . one in whom an ailment is counted like measuring the ailment of a man in order to know the action of the heart. There are canals (or vessels, MT) in it (the heart) to every member". The MT were the blood vessels, the tendons, and the nerves, which neither the Egyptians nor the Greeks clearly distinguished. There are "canals" to the heart in every member of the body. "Now if the priests of Sekhmet or any physician put his hands or his fingers upon the

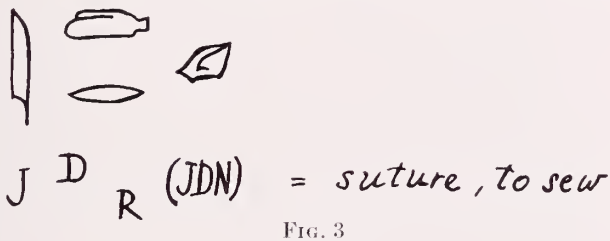

Fig. 3

head, upon the back of the head, upon the two hands, upon the pulse, upon the two feet, he measures . . . to the heart, because its vessels are in the back of the head and in the pulse; and because its pulsation is in every vessel of every member". This is a somewhat halting translation, because of the incompleteness of the page and our ignorance of certain terms, but I think we can go along with Breasted, who insists that the Egyptians, while unaware of the circulation of the blood in the sense of Harvey, certainly believed that the blood was starting out from the heart and going into all directions. A parallel quotation, obviously from a treatise on the heart is found in Papyrus Ebers, where 22 of 46 veins are described as symmetrically distributed; some are said to go to the bladder and to make the urine, and some to go to the testicles and to make the semen and some to go to the nose and to make the nasal mucus. They definitely had the right idea about communicating vessels within the body and this constitutes the most interesting physiological statement in this document.

As far as the wounds are concerned, which are treated by the surgeon and the orthopedist, Breasted was perhaps biased by a search he had made involving 5–6000 old Egyptian cadavers, found in some mass burials. They evidently had been battle casualties and he shows illustrations of battered skulls and an arrow

in situ where it had penetrated the orbit. Hence, Breasted suggests that the Papyrus Smyth was composed by a surgeon who followed the army in the war. We do not think that this argument is quite cogent; some of the wounds described are probably war wounds, but the greater part of them look more like industrial accidents. One should keep in mind that the original text goes back to the time of the pyramids, the construction of which must have been accompanied by numerous accidents in piling up blocks of stone by primitive means. Workers must have fallen down and cracked their vertebral column projecting one vertebra into the other as described in Case 33. Many of the wounds to the skull and the upper extremities point to surgery practiced on workers who had suffered accidents in construction work.

Besides, the Egyptians, while culturally more advanced at this early age than most any other of their contemporaries, were rather a harsh race. It is difficult to say how they compared with other nations, but certainly the Egyptians meted out and took many beatings. They beat not only the slaves, but their own children, which one would consider hardly typical for primitive people, considering for instance the kindness to children by the Central American Indios or the Polynesians. The Egyptian criminal code abounds with cruel beatings which may have resulted in some of the wounds described.

In case of an unfavorable diagnosis, the physician, acting according to the advice in the Smyth Papyrus, would have abandoned the patient, which also speaks for an industrial medicine of very cruel and crude type. If the patient could be restored to make him work again, it was worthwhile doing so, but if he could not be restored, let him die. However, in some cases with the verdict "This is a case I will not treat", some form of palliative treatment is indicated just the same and the physician is advised to wait until the patient reaches "a decisive point"; this foreshadows the idea of a crisis in certain disease, as was later on elaborated by Hippocrates.

At some other point, in a case of a dislocated mandible (Case 25), the surgeon is advised to put his thumbs symmetrically into the mouth and let the jaw fall back into its natural location similar to the technique shown in a much later illustration from Greek days.

The recent excavations in Egypt have again focussed the eyes of the Western world upon the spot where the first civilization originated. Anything we may learn about its origin and progress from monuments and documents, present and to be found in the future, will advance our understanding of the historical development of the human mind.

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In Memoriam

EUGENE N. SCADRON, M.D.
1907–1956

Dr. Eugene N. Scadron was born in New York in 1907. His early education was completed in the private schools of that city. He then went to Dartmouth College, where he received his A.B. in 1930 and his M.D. from Duke University Medical School in 1934. He spent six years in postgraduate training at Duke, Bellevue and finally at the Boston Lying-In, where he finished as resident in obstetrics.

After a short period of practice he entered the U. S. Army in 1942 and was discharged a Major in 1946. Following this Dr. Scadron went into practice here in New York City, sharing offices with his father, who had already been an eminent leader in the field of obstetrics and gynecology for more than a quarter of a century. At the same time he joined the teaching staff of the Medical School of New York University. He rose to the rank of an attending in obstetrics and gynecology at Bellevue Hospital. When the obstetrical department was opened at

The Mount Sinai Hospital in 1952, he was nominated assistant attending, a position which he occupied with credit until his untimely death on January 19, 1956.

During his all too brief connection with the Department of Obstetrics and Gynecology, Dr. Scadron made a vital contribution by his expert clinical knowledge, by his ability to teach and by his special interest in the fields of x-ray pelvimetry and toxemia of pregnancy. He attended most of the department conferences and could be counted upon to contribute sage and timely comments.

Dr. Scadron was a delightful companion and those of us who had the happy opportunity of knowing him well will miss him sorely. His lively mind, his keen sense of humor, his warm friendship, made such a strong impression, that it is hard to realize so vital a life has been terminated.

For the Editorial Board

EXPERIENCES WITH PULMONARY TUBERCULOSIS IN PREGNANCY

HENRY L. DORFMANN, M.D., ALAN F. GUTTMACHER, M.D., AND IRVING J. SELIKOFF, M.D.

New York, N. Y.

The rapid therapeutic advances for pulmonary tuberculosis in recent years promise to make obsolete many of the still unresolved problems of tuberculosis in relation to pregnancy. It is perhaps academically regrettable that the last several decades have not produced clear answers to the then important questions which beset both obstetrician and phthisiologist because it is very unlikely that the natural history of pulmonary tuberculosis during pregnancy, will, in the future, be able to be observed unmodified by therapy.

One can find ample support in the writings of the past several decades for almost any point of view. For example, those whose clinical impressions indicate that pregnancy often leaves pulmonary tuberculosis to run its own course, unaffected by the gravid state will find numerous, albeit not unanimous, support among the many who have written on the subject in the past twenty years. Their theme has been that where the prognosis is bad in tuberculosis with pregnancy, it would be just as bad without pregnancy. Criticism of the data upon which such opinions are based is easy—almost all the studies are retrospective in character; are based upon select material often from sanatoria; usually have inadequate follow-up observation, contain inadequate evaluation of the pulmonary disease; and often compare groups which are not comparable.

Nevertheless, similar criticism may be made of those studies which hinted of disastrous consequences to tuberculous pregnant women if their pregnancy were allowed to go to term, and which found expression in the oft quoted dictum "for the virgin, no marriage; for the married, no pregnancy; for the pregnant, no confinement; for the mother, no suckling."

Even within the past several years, the pendulum continues to swing, although perhaps not in so great an arc. For example, Cromie (1) reporting the experiences of the Northern Ireland Tuberculosis Authority, recently reviewed 101 cases of tuberculosis and pregnancy. The experiences in this group were not sanguine. Of 45 active cases only 23 remained unchanged or improved, while 22 became worse or died. Of 56 inactive cases, 42 remained unchanged while 14 became worse. From these observations, that approximately half the mothers with active pulmonary tuberculosis will suffer an extension of their disease in association with pregnancy and that approximately one-quarter with inactive disease will similarly have an extension of their tuberculosis, he concludes that "the frequency of extension of tuberculosis in this series is higher than most in the literature. A danger of extension does exist and should not be ignored or minimized as seems to be the modern tendency." Although this data might be criticized in that it was

From the Departments of Obstetrics and Medicine, The Mount Sinai Hospital, New York, N. Y.

not a consecutive case study and was retrospective from hospital and clinic records, the incidence of spread of disease, and the mortality rate, must make one take pause.

Similar data has recently been made available from Glasgow. Audrey Freeth (2) x-rayed all patients coming to an ante-natal clinic in a working class area; all women known to have tuberculosis were excluded from this particular series. 541 women were routinely x-rayed and evidence of tuberculosis was found in 29 (5.3%). However, 12 showed only calcific foci of primary infection while 17 (3.1%) showed active or inactive disease. There were four active cases and these remained active after delivery. Of the 8 inactive cases, two became active, two had doubtful reactivation, two remained unchanged, and two could not be traced.

Rich (3) presents pathological data which would indicate an altered tissue and perhaps immunological response to tuberculosis during pregnancy, with lessened resistance to both local and generalized spread. Such pathological experiences have been, however, only sparsely reported and are not easily translated into clinical experience.

After weighing the varied opinions, it is perhaps easy to agree with Jones (4) that "there is an impression among those treating tuberculosis that pregnancy exerts an influence on the course of the infection and that the influence is unfavorable. While not entirely satisfying scientifically, such impressions cannot wisely be disregarded."

One of the areas of conflict of opinion which can perhaps be most easily resolved is the question of the *incidence* of tuberculosis in pregnancy. Here, the disagreements appear to be largely based upon the thoroughness and finesse of the technique utilized in case finding. For example, clinical examination, alone, without the use of fluoroscope or x-ray, yielded an incidence of approximately one case of tuberculosis for each 1,000 women examined (0.1%). Fluoroscopy gives an incidence of 1–2% tuberculosis. Miniature radiography similarly gives an incidence of somewhat over 1%. This increase in diagnostic acumen with improved technique was well illustrated at the New York Lying-In Hospital where, following the institution of photo-roentgenographic survey films, the incidence rose from a maximum of 0.7% to 1.85% (5).

The most exact presently available technique has been full-scale radiography. The data in the various series does not permit of exact comparison because of the variations in incidence of tuberculosis in the various population groups studied. For example, 10 years difference in the time of study of the various series would make a significant difference in the incidence of tuberculosis reported, due to the declining case rate in the last two decades, particularly in the last ten years (6). Variations in such factors as socio-economic status, geographic location, age groups, racial derivation, etc. would also make comparison difficult. Nevertheless, the significant incidence of pulmonary tuberculosis on routine surveys of pregnant women in widely scattered areas even within recent years would indicate that the problem is a serious one.

Our experiences at The Mount Sinai Hospital with regard to the incidence of

pulmonary tuberculosis in pregnancy are reported below. In the area and patient population which we serve, it will be seen that the problem is a frequent and significant one.

PRESENT STUDY

Shortly after the Obstetrical Department of The Mount Sinai Hospital opened its wards to patients, an Obstetrical Chest Clinic was organized and has functioned since. Although all chest problems of obstetrical patients are managed by this clinic, tuberculosis has been its chief problem. From April 1, 1953 to the present writing (Jan. 31, 1956), 4,740 patients have been registered in the Obstetrical Antenatal Clinic. Of these, 338 were seen in the Obstetrical Chest Clinic. Almost half —162 patients—attended because of pulmonary tuberculosis and the remainder for a variety of other conditions including asthma, bronchitis, mediastinal tumors, sarcoidosis, bronchiectasis, diaphragmatic hernia, or were seen for chest x-rays which required evaluation only but which on review had no significant abnormality. Parenthetically, that over 7% of obstetrical admissions required chest consultation emphasizes the value and importance of an Obstetrical Chest Clinic.

As stated, prime concern was the problem of pulmonary tuberculosis. Therefore, it has been the rigid rule of the Obstetrical Department that every antenatal clinic admission have a chest x-ray. This is a full-size 14 x 17 chest film and is taken immediately upon registration in the clinic. All films are reported by the X-ray Department and any patient with an abnormal film is then referred to the Obstetrical Chest Clinic for evaluation. Also, careful review of the patient's history is made and all patients with history of pulmonary disease are referred to this clinic, as are those with abnormal findings on physical examination. Actually, it has been our experience that x-ray examination is almost the sole requirement for case finding in our patients since those with some history of tuberculosis also had abnormal chest films, while the reverse was by no means true. Clinical examination was responsible for finding but one case during our study.

INCIDENCE OF PULMONARY TUBERCULOSIS, THE MOUNT SINAI HOSPITAL ANTENATAL CLINIC, APRIL 1953–JANUARY 1956

From April 1, 1953 to January 31, 1956, 4739 antenatal patients were examined by routine chest x-ray. Pulmonary tuberculosis was found in 161. Another patient was found to have tuberculosis on clinical examination. Thus, in this group of apparently well young women, an incidence of tuberculosis of 3.4% was found (table 1). This does not include 25 instances of calcified primary complexes seen on x-ray, which were classified as normal films, but does include 16 instances of 2nd pregnancies and 2 instances of 3rd pregnancies, in this series.

Of considerable clinical importance was the fact that the majority of these cases would have remained unsuspected and undiagnosed were it not for routine x-ray study. In 86 of the 162 cases, neither careful history no physical examination gave a clue to the tuberculosis which was found on the chest film. This

TABLE 1

Incidence of pulmonary tuberculosis—The Mount Sinai Hospital Antenatal Clinic
(April 1, 1953-January 31, 1956)

A. Total Clinic admissions			4740
B. Patients with pulmonary tuberculosis			162 (3.4%)
Diagnosis by X-ray survey		161	
X-ray alone		86	
X-ray plus history		75	
Diagnosis by clinical examination		1	

TABLE 2

Analysis of patients with pulmonary tuberculosis, The Mount Sinai Hospital Antenatal Clinic 1953–1956

	Active Pulmonary Tuberculosis	Inactive Pulmonary Tuberculosis	Total
Diagnosis			
X-ray alone	28	58	86
X-ray plus history	12	63	75
Clinical examination	1	0	1
Racial origin			
Porto Rican	27	70	97
Negro	12	26	38
White	2	23	25
Oriental	0	2	2
Age			
15–20	9	12	21
21–35	28	96	124
36–50	4	13	17
Total	41	121	162

experience would suggest that any obstetrical program which does not include routine chest x-ray examination will overlook a significant number of cases having this important complication of pregnancy.

The value of routine x-ray study is emphasized by the observation that among cases of *active* tuberculosis, a larger proportion of cases were found by routine x-ray than among the inactive cases. This was, of course, to be expected since those patients with previously known disease would more likely fall into the inactive group, *active known* disease having been weeded out prior to possible registration at the Antenatal Clinic by sanatorium admission elsewhere, or by avoidance of pregnancy. Thus, of 121 patients with inactive disease, history could have led to a suspected diagnosis in 63. In contrast, of 41 patients with *active* tuberculosis, in 28 the diagnosis was unsuspected, and was made only by routine x-ray. This data is summarized in Table 2 which also compartmentalizes the group according to age and racial origin, the latter break-down suggesting that, in our patient population, white patients tended to present with inactive disease while Negro and Puerto Rican patients were more likely to have active

tuberculosis. Also, younger patients had a higher proportion of active disease, but no age group was immune.

PULMONARY TUBERCULOSIS IN PREGNANCY

Although those who, in the past, have advocated treatment of pulmonary tuberculosis in pregnancy without regard for the pregnancy but merely in its presence, had correct emphasis (1, 5) a number of nuances make it unwise to accept such recommendations without qualification, at this time. Such advice may have been valid when given, since for most of this period only rest and supportive measures were available. Later, medical or surgical collapse were utilized in some suitable cases. Nevertheless, with the present availability of much more effective treatment for tuberculosis in general, and with a multiplicity of techniques, therapy should be more selectively utilized in order to achieve its full potential.

ACTIVE PULMONARY TUBERCULOSIS

Initial evaluation of activity is primarily radiological. Of course, where the clinical status is one of toxicity, with weight loss, fever, malaise, etc., this would weigh heavily. But such a clinical picture, or even lesser degrees of it, were not seen in our clinic, and the problem was rather one of roentgenographic interpretation. When the initial radiological investigation, including special views and procedures as necessary, led to a tentative diagnosis of active tuberculosis, chemotherapy was begun immediately. Since most patients presented themselves during the second trimester of their pregnancy, this usually meant a three to five month antenatal period of chemotherapy and prolonged chemotherapy during the post-partum period. Duration of therapy depended upon the course under treatment. In the few cases in which serial films under therapy showed no change, and re-evaluation indicated a stable lesion, chemotherapy was discontinued in the post-partum period. Where the lesions continued to regress, chemotherapy was continuous and in some patients has been maintained for approximately two years. Experiences recounted below have confirmed the opinion that therapy must be prolonged to insure both maximum effect and stable regression.

With few exceptions, diagnosis of an active lesion was an indication for the use of combined chemotherapy. This consisted of isoniazid at a level of approximately 5–7 milligrams per kilogram of body weight, (7) P.A.S. at a level of 10–15 grams per day if this were tolerated, and dihydrostreptomycin (8) one gram daily for at least several weeks and then one gram twice weekly for a prolonged period. This chemotherapeutic regime was, of course, altered in those instances required by drug toxicity or intolerance. In a few cases, isoniazid alone was utilized in active disease. This usually was in those instances in which it had been begun as a prophylactic measure in what was presumed to be inactive disease. With radiological regression, indicating that the disease was really active, isoniazid alone was sometimes continued, provided no cavity was present.

All patients were treated as ambulatory clinic patients. The problem of ambu-

latory or non-institutional use of anti-tuberculous chemotherapy is still an incompletely resolved one at the present time and is discussed elsewhere (9). For our own part, we would simply observe that were it not for ambulatory, non-institutional, anti-tuberculous chemotherapy, the large majority of patients in our clinic would not have been treated. The patients with disease evaluated as inactive could not have been institutionalized and the majority of those with minimal but active disease would have refused hospitalization.

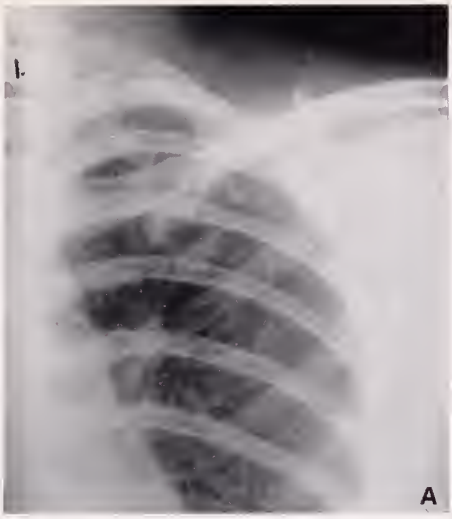
This is not to say that patients with active disease are not to be specially managed. They should be. Not only is there more extensive and intensive chemotherapy, but also special precautionary measures during and after delivery. When a patient with presumed active disease is admitted to hospital for confinement she is isolated with full isolation technique as practiced in tuberculosis. Actually, each patient with known active disease had negative sputum by the time she was admitted to the obstetrical wards for delivery. Nevertheless, since her disease was unstable, it was felt safer to err on the side of caution, since it is possible for reactivation to occur during delivery or in the immediate post-partum period.

Secondly, the new-born infant is isolated from its mother from the moment of birth, for the same reason. The infant remains separated from the mother until such time in the post-partum period, usually two months, that sputum negativity and lack of reactivation in the puerperium is confirmed. This usually necessitates placement of the infant in a special institution until the post-partum observation period has elapsed. This procedure is adopted even in those patients with active disease which show marked regression under chemotherapy in the antenatal period, since there is no guarantee that reactivation will not occur following delivery. Utilizing these precautions, all live infants have remained well so far in the experience in this clinic.

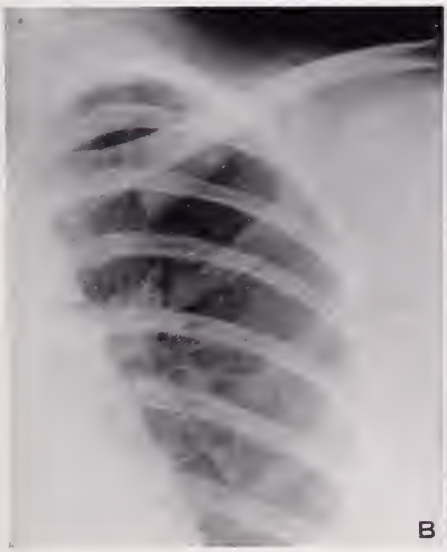
A typical illustration of the method utilized in this clinic in the management of active disease is illustrated by the following case.

H. R. Unit #1665. This 19 year old Porto Rican woman was seen in the Obstetrical Chest Clinic on Mar. 25, 1953 because of the finding on a routine prenatal film of caseous pneumonic tuberculosis in the left upper lobe (Figure 1a). Although she was asymptomatic apart from an admitted slight cough, the roentgenographic appearance, confirmed by the presence of a 2 cm. cavity on tomography, was clearly that of active tuberculosis. Accordingly, she was started on the day of admission on isoniazid 100 milligrams thrice daily, 12 Grams P.A.S. and daily dihydrostreptomycin. Her expected date of confinement was July 21, 1953. Guinea pig inoculation of gastric contents was reported positive for tubercle bacilli on May 26, 1953, two months later. By this time, however, numerous sputum smears, gastric cultures and guinea pig inoculations were taken, which later were reported negative.

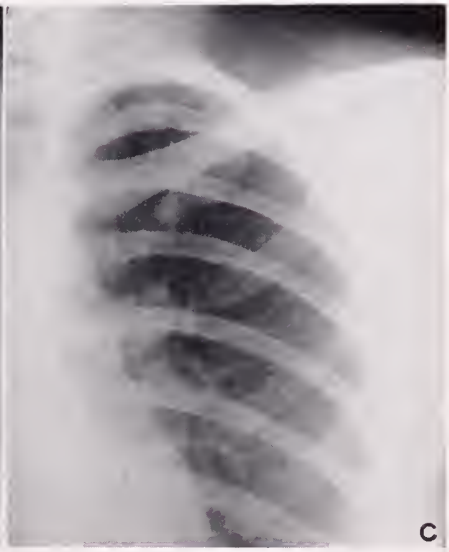
She remained well under combined chemotherapy during her entire antenatal course. In the months before her hospital admission for delivery on July 12, 1953, 10 bacteriological examinations failed to show tubercle bacilli. Moreover, an x-ray taken on April 15, 1953 showed early clearing and at this time, after three weeks of therapy, her cough had disappeared. There was rapid clearing on roentgenogram of her tuberculous infiltration and a film taken on April 28, 1953 showed fragmentation of the cavity wall and continued absorption of the exudate. By June 2, 1953 marked clearing had occurred with residual linear infiltrations.



H. R., March 17, 1953



H. R., October 20, 1953



H. R., December 27, 1955

FIG. 1. a) Routine prenatal survey film shows active caseous-pneumonic tuberculosis in left upper lobe. Cavity present. Sputum contained tubercle bacilli. b) Marked clearing on film seven months after institution of chemotherapy. Delivered three months before. Sputum negative since second month of therapy. c) Chemotherapy discontinued after two years. Film shows stable regression.

Despite her negative sputum and x-ray clearing she was isolated upon her admission to hospital. Following delivery on July 12, 1953, her baby was separated from her. Since guinea pig inoculation of sputum and gastric contents performed soon after delivery and six weeks thereafter were reported negative by October 20, 1953, her baby was returned to her. Serial films had also shown her regression to be stable (Figure 1b).

An audiogram done on April 14, 1954 showed some impairment of bone conduction of hearing and dihydrostreptomycin was then stopped. However, isoniazid and P.A.S. were continued for over two years. She has remained well since and an x-ray taken on Dec. 27, 1955 shows continued stability of the regression (Figure 1e).

INACTIVE PULMONARY TUBERCULOSIS

There are numerous reports of reactivation of inactive disease due to pregnancy. It is very difficult to evaluate these reports. Few would bear the scrutiny of modern investigational requirements. Moreover, as noted, the general fall in tuberculosis mortality and morbidity (6) would make even accurate data of two or three decades ago inapplicable today.

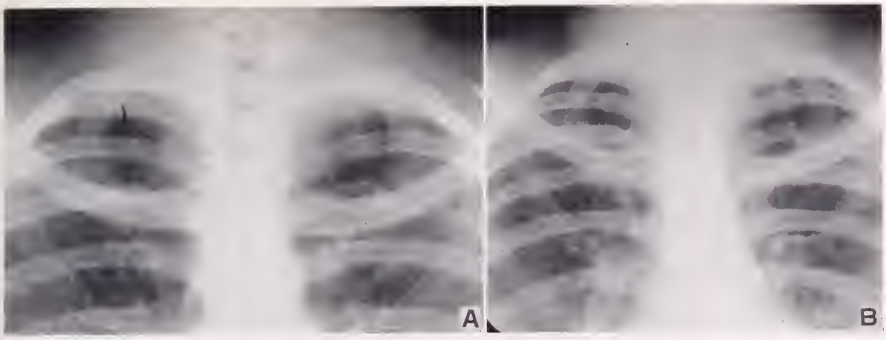
Therefore, especially since no two series in tuberculosis are strictly comparable, we cannot say with any degree of certainty how many instances of inactive disease seen in our clinic would have become active had they not been treated prophylactically. All we can say is that those patients treated with prophylactic chemotherapy went through their pregnancies and puerperiums with no reactivations.

As with patients evaluated having active disease, the provisional evaluation of inactive status was based principally upon roentgenographic interpretation. This decision was not made lightly, since it meant withholding anti-tuberculous chemotherapy until two months before the estimated date of confinement. This period has been an arbitrarily chosen one and should perhaps be the subject of study. In our group it has proven a manageable and effective one. The interval between the admission to the Obstetrical Chest Clinic and the start of chemotherapy was utilized in roentgenographic, clinical and bacteriological investigations. If, during this time, any evidence of activity would appear, immediate chemotherapy would be instituted. Thus, in one case in which roentgenographic interpretation was suggestive of inactive disease, previous films from another hospital were obtained during the weeks following admission to clinic and, since comparison showed extension of the infiltration over a two year period of time, the active nature of the disease was established and the patient was treated accordingly.

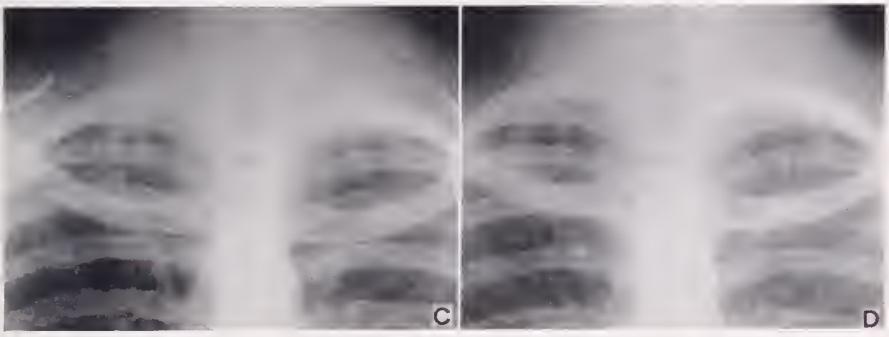
If, however, observation and especially serial roentgenograms did not alter the provisional evaluation of inactivity, anti-tuberculous chemotherapy was begun two months before the expected date of confinement. This, in almost each case, consisted of isoniazid. It was continued throughout the remainder of the antenatal period, during the hospital course following delivery, and for approximately 2–3 months post-partum. If serial films in the post-partum period confirmed the evaluation of inactivity, isoniazid was discontinued, but the patient remained under observation. While in the hospital, the patient was not isolated nor was the infant separated from its mother.

If, on the other hand, serial films during prophylactic isoniazid therapy showed regression of the disease evaluated as inactive, usually combined therapy with dihydrostreptomycin and P.A.S. added to the isoniazid was instituted.

This regimen has worked well in practice in the Obstetrical Chest Clinic. However, the arbitrary selection of 2 to 3 months of post-partum isoniazid



H. H., September 17, 1953 H. H., January 19, 1955



H. H., November 15, 1955 H. H., January 17, 1956

FIG. 2. a) Admission roentgenogram of H. H. showing residual of previous left upper lobe segmental resection and apparently inactive right apical infiltrate. b) Roentgenogram after second pregnancy, showing continued stability of right apex. c) When admitted to clinic for third pregnancy, apparently inactive infiltrate in right apex now shows reactivation. Therapy begun. d) Regression under therapy. Continued pregnancy and treatment.

therapy must be recognized as a practical manoeuver and not necessarily an ideal one. There is no evidence that regression may not occur after *more* than five months of isoniazid therapy. Other lesions may exist which will show reactivation after that period of time. Indeed, one case was seen in this clinic (Figures 2a–d) which did remain stable while under prophylactic chemotherapy and for several months thereafter yet showed x-ray reactivation eight months after isoniazid was halted.

OBSTETRICAL MANAGEMENT OF PREGNANCY COMPLICATED BY TUBERCULOSIS

Therapeutic Abortion. Since the establishment of the Abortion Committee in the fall of 1952, eighty therapeutic abortions have been performed up to March, 1956, on the combined ward and private services of the obstetric-gynecological department of the Mount Sinai Hospital. During the same period there were approximately 12,000 deliveries. The presence of pulmonary tuberculosis was a factor in only two of the artificial terminations of pregnancy and in neither the sole factor.

The first patient was a 38 year old woman who had had left lower lobe lobec-

tomy for tuberculosis. There had also been several admissions to the psychiatric ward for "an infantile personality with inability to assume any real responsibility or to tolerate any hardship or frustration." When the problem of therapeutic abortion was considered by the Committee in June 1953, x-ray revealed an inactive tuberculosis of the left upper lobe and an area of consolidation in the right middle lobe. Vital capacity was diminished. On combined psychiatric and medical grounds interruption of pregnancy with sterilization was recommended and performed.

The second patient had had a lobectomy, followed by a thoracoplasty, in 1951, four years after the birth of her last child. In January, 1956, when eight weeks pregnant, she complained of incapacitating dyspnoea on exertion. Pulmonary function studies in the cardio-pulmonary laboratory showed impairment of ventilatory function and hyperventilation at rest. To impose no further physical burden or risk upon the patient, interruption of pregnancy with sterilization was recommended and performed.

It is obvious, then, that active uncomplicated pulmonary tuberculosis has not necessitated therapeutic abortion in this institution in over 12,000 pregnancies.

Labor and Delivery. Labor is conducted in the ordinary fashion in the presence of either active or healed tuberculosis. The usual analgesic drugs as the barbiturates, demerol and scopolamine are not contraindicated and are given in accustomed dosages.

Delivery is by the vaginal route, unless there are obstetrical complications necessitating cesarean section. Attempt is made to prevent these patients from straining down forcibly in the second stage of labor by performing a low forceps delivery as soon as such a procedure is simple and safe for mother and child.

An active case of tuberculosis is cared for with rubber gloves, gown, and mask technique by all the professional and ancillary personnel who come in contact with her during the complete hospital stay. During labor she is kept alone in a first-stage room and when the birth is simple, she is delivered in her first-stage bed in the same room. When the room is vacated post-delivery, it is temporarily put out of service and thoroughly cleaned and washed before it may be reoccupied. If the patient requires an operative delivery, she is transferred to one of the delivery rooms which is also considered contaminated afterward until thoroughly scrubbed.

Some type of conduction anesthetic such as a low spinal (saddle block), caudal or pudendal nerve block is preferred to any variety of inhalation anesthetic for the actual delivery. Probably the best possible analgesic-anesthetic combination in such cases is an expertly managed, continuous caudal. It obviates the necessity for pain relieving (and cough suppressing) drugs, prevents the patient from bearing down in the second stage by obliterating the reflex through anesthetization of the area and provides excellent anesthesia for delivery. The drawback is that the method is technically difficult and very demanding on the professional personnel. If for some reason a general anesthetic is indicated, intravenous sodium pentothal is preferable to one of the inhalation gases.

Obstetric Surgery is not especially hazardous to the tuberculous woman whose pulmonary disease is chemotherapeutically controlled. Pulmonary tuberculosis

is rarely an indication for puerperal sterilization; nor does it offer a contraindication. If for reasons other than tuberculosis such a procedure is indicated, there is no need to delay its performance in the tuberculous woman who is responding adequately to drug treatment. A puerperal sterilization is usually done by ligating and severing the Fallopian tubes through a small infraumbilical incision within the first 12 post-partum hours. It may be performed under local anesthesia induced by infiltrating the abdominal wall, low spinal or intravenous sodium pentothal.

Puerperium. A patient with active tuberculosis is kept in a room by herself on the regular post-partum floor and placed under glove and gown precautions. If afebrile, she is allowed the same early ambulation as normal puerpera and discharged from the hospital to her home on the sixth or seventh day. Such a patient is completely separated from her newborn infant after its birth.

The freshly delivered woman with inactive tuberculosis is placed in the ordinary four-bed room with normal patients and no special precautions taken. She is allowed to nurse her baby if she desires.

Anemia. At delivery, the patient with active or healed tuberculosis is carefully watched for blood loss and if it is thought to exceed 500 cc., transfused. Furthermore, if the hemoglobin after delivery is found less than 9.0 grams, the patient is transfused before being discharged from the hospital.

RESULTS OF THERAPY

Of the 162 patients with pulmonary tuberculosis treated in the Obstetrical Chest Clinic, 138 have now been observed for a sufficient period of time to warrant evaluation of the results of such management. Duration of follow-up observation post-chemotherapy and post-partum is abstracted in Table 3.

TABLE 3

Follow-up observation of 138 patients with active and inactive tuberculosis in pregnancy.

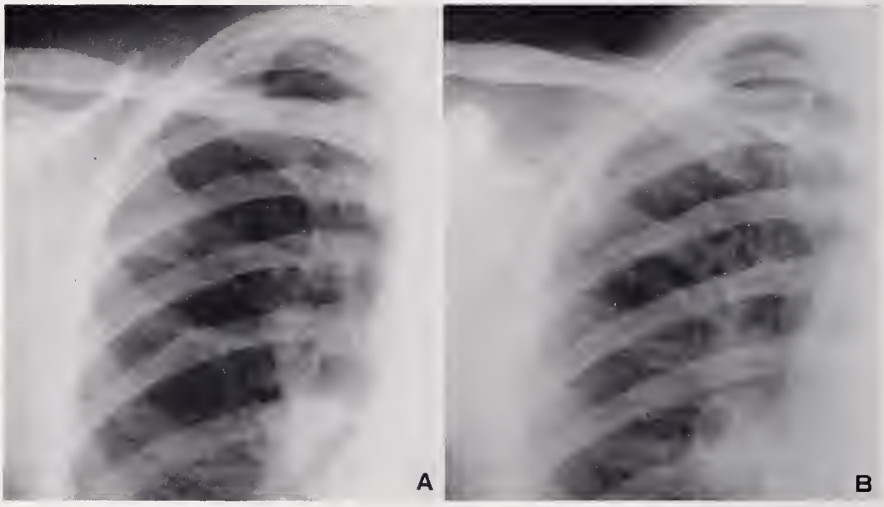
	Active	Inactive
A. Post onset of chemotherapy		
Less than 3 months	—	—
3–5 months	3	20
6–11 months	9	40
12–23 months	14	28
24–33 months	8	10
Average (months)	15.6	11.4
B. Post partum		
Less than 3 months	2	6
3–5 months	7	28
6–11 months	7	33
12–23 months	11	24
24–33 months	7	7
Average (months)	13.5	9.6

TABLE 4

Results of management of 33 patients with tuberculosis in pregnancy, evaluated as active

	Course Under Observation			
	No.	Stable	Regression	Progression
Chemotherapy	30	4	25	1*
No treatment	3	0	0	3

* Inadequate duration of therapy.



R. B., March 31, 1955 **R. B., January 23, 1956**

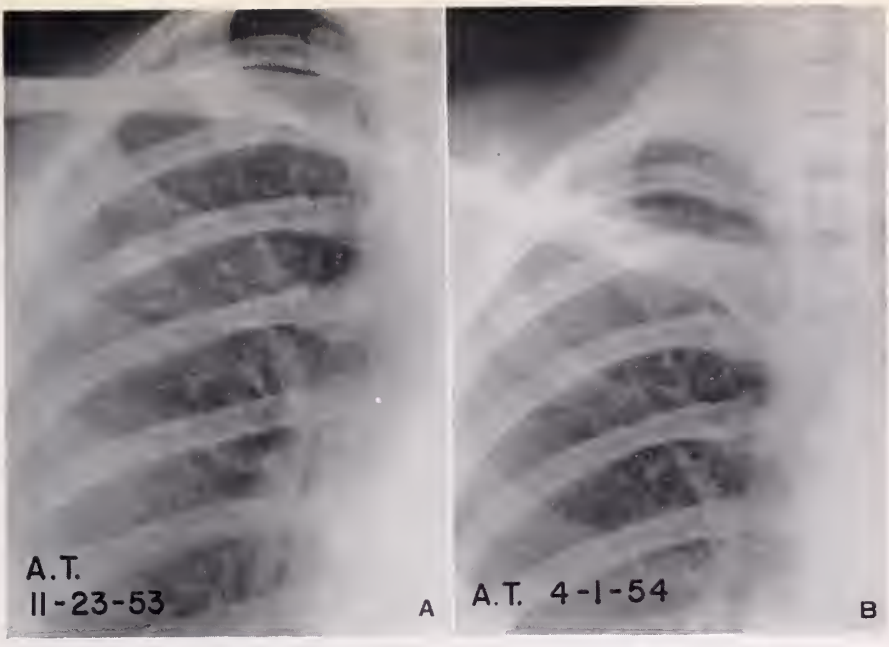
FIG. 3. a) Acute exudative disease found on routine prenatal survey film. b) Good response to combined chemotherapy characteristic of such disease.

34 patients were evaluated initially as having active disease and have had an adequate period of observation to date. One of these patients was transferred to another institution for reasons explained above. Of the remaining 33, three were not treated for various reasons while 30 had chemotherapy. Table 4 summarizes our experience with this group.

We have come to expect rapid regression under chemotherapy of active exudative disease during pregnancy. Figures 3a, b and 4a, b are typical illustrations of these results. Similarly, a number of examples of bilateral upper lobe possibly hematogenous disease without cavitation have responded well, as they do in the absence of pregnancy. Figures 5a, b and 6a, b are two such examples.

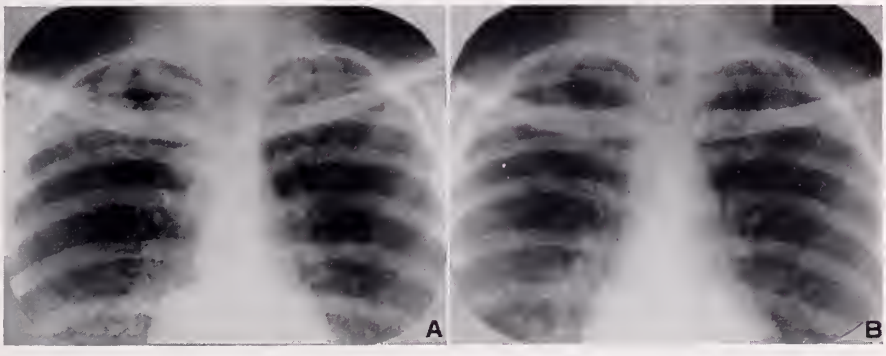
The unfortunate result of omission of chemotherapy in a patient with active disease, however, is detailed below.

E. G., Unit #38464. This 21 year old white woman was first seen in the Obstetrical Chest Clinic on May 3, 1955. At that time a nodular infiltrate was present in the second anterior intercostal space of the left upper lobe (Figure 7a). Although this had previously been present on a film of Dec. 27, 1954 (Figure 7b) obtained for comparison, it was felt that this



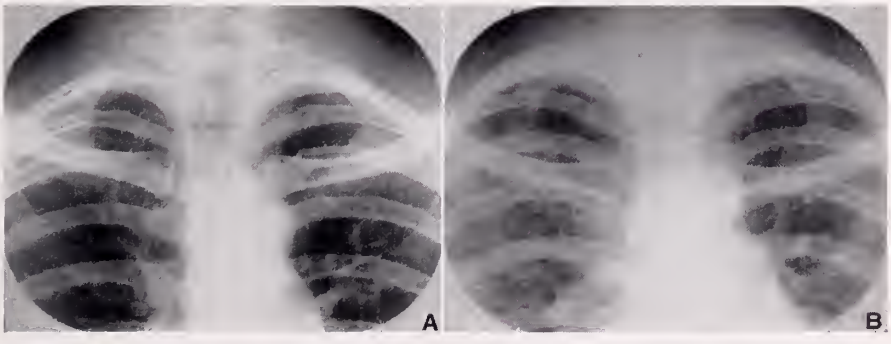
A. T., November 23, 1953 A. T. April 1, 1954

FIG. 4. a) Acute exudative disease found on routine prenatal survey film. b) Rapid therapeutic response to combined chemotherapy is well illustrated.



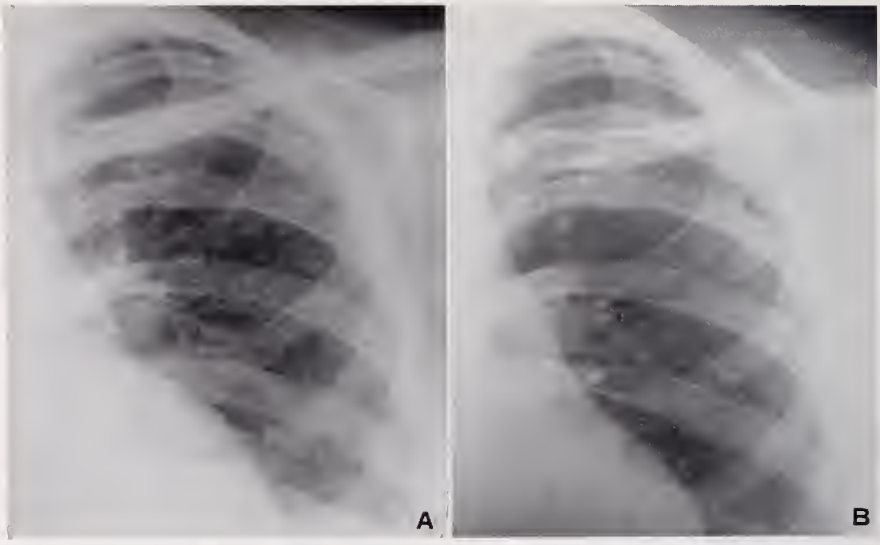
B. B., October 24, 1954 B. B., January 24, 1956

FIG. 5. a) Routine prenatal survey film shows bilateral upper lobe active disease. b) Good response to chemotherapy, which continues.



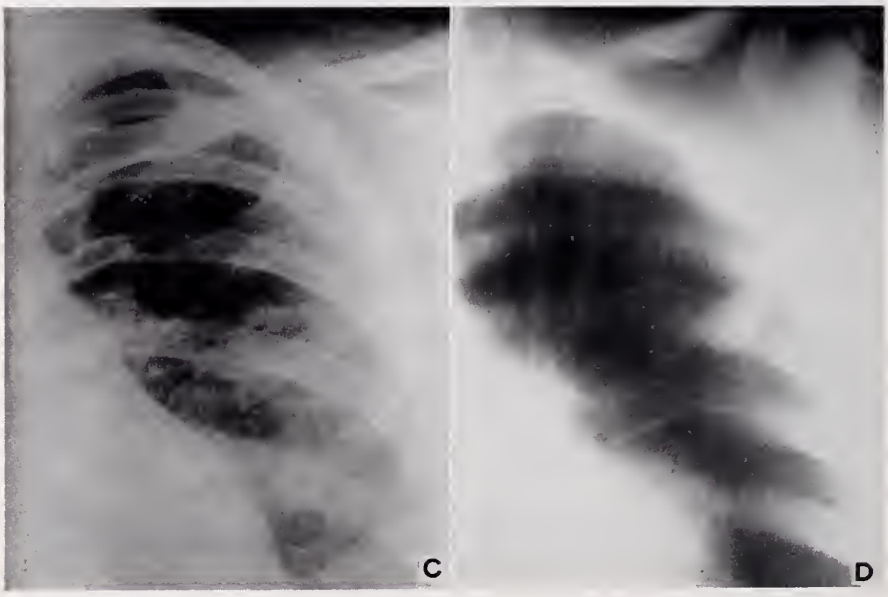
M. C., January 21, 1955 M. C., August 30, 1955

FIG. 6. a) Bilateral upper lobe active infiltrate found on routine survey film. b) Good response to chemotherapy, which continues.



E. G., May 24, 1955 E. G., December 27, 1954

FIG. 7. a) Routine prenatal survey film showing localized infiltrate in left upper lobe. b) This film, taken six months before, indicated that there had been no recent change. c) Unfortunately, there was no chemotherapy. Six months after delivery, coughing began and this film was taken, showing progression. d) Tomographic section at two inches A-P, showing localized infiltrate before delivery. e) Same tomographic level taken seven months later, demonstrating cavity formation in disease reactivated during pregnancy.



E. G., December 23, 1955 E. G., May 12, 1955
Tomograph; 2 inch section

E. G., January 3, 1956
Tomograph; 2 inch section
FIG. 7e

was a potentially active lesion because of its roentgenological appearance. It was regarded with especial dubiety because this young woman was an unstable diabetic. Accordingly immediate chemotherapy was advised.

No sooner had therapy been started when the patient was admitted to the hospital for elective section because of her diabetes. This was successfully performed on June 8, 1955 with the delivery of a live baby. On her discharge from the hospital on June 15, 1955, she was referred back to both the Diabetes and Obstetrical Chest Clinic but failed to attend the latter. She received no chemotherapy apart from three weeks in the antenatal period.

She remained clinically well until early in Dec. 1955 at which time she began to cough. Another chest film was then taken (Figure 7c) and this showed progression of the tuberculosis. Tomographic sections on January 3, 1956, as compared with those of May 12, 1955 (Figures 7d, e) confirmed the progression, with cavity formation at the site of the previous caseous nodule. The patient is now on combined chemotherapy and a film after one month of therapy shows regression but her ultimate outcome remains in doubt. Her infant has been separated from her and is being carefully observed.

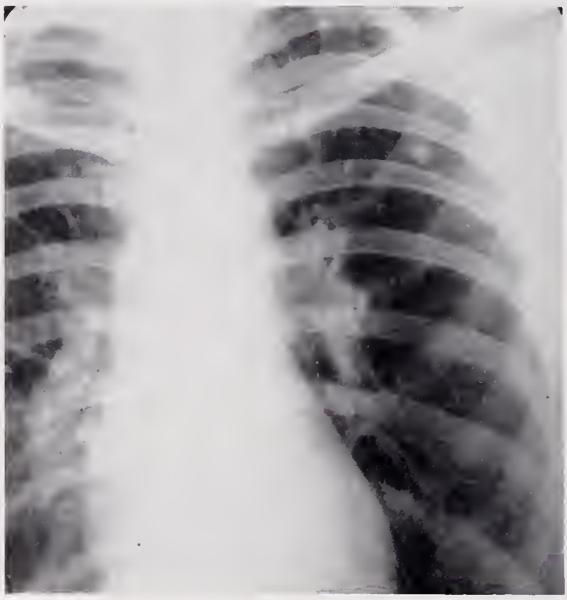
105 patients in the series who were evaluated as having inactive disease have now been observed in the Obstetrical Chest Clinic for a sufficient time to warrant analysis. Such analysis is contained in Table 5. This table indicates that seven patients deemed inactive showed regression of their infiltration on x-ray under what was planned to be prophylactic isoniazid therapy. Had this therapy not been instituted at least these patients with unstable disease would have remained unprotected during pregnancy. One patient, who received what turned out to be in retrospect inadequate therapy—although presumed adequate for prophylaxis of an inactive lesion—showed late reactivation. The patients who remained stable included 18 who had had previous thoracic surgery or collapse therapy (two patients with segmental resection, 5 with lobectomy, 1 pneumo-

TABLE 5

Results of management of 105 patients with tuberculosis in pregnancy, evaluated as inactive

	Course Under Observation			
	No.	Stable	Regression	Progression
Prophylactic chemotherapy	102	94	7	1*
No treatment	3	2	0	1

* Inadequate therapy.



L. P.

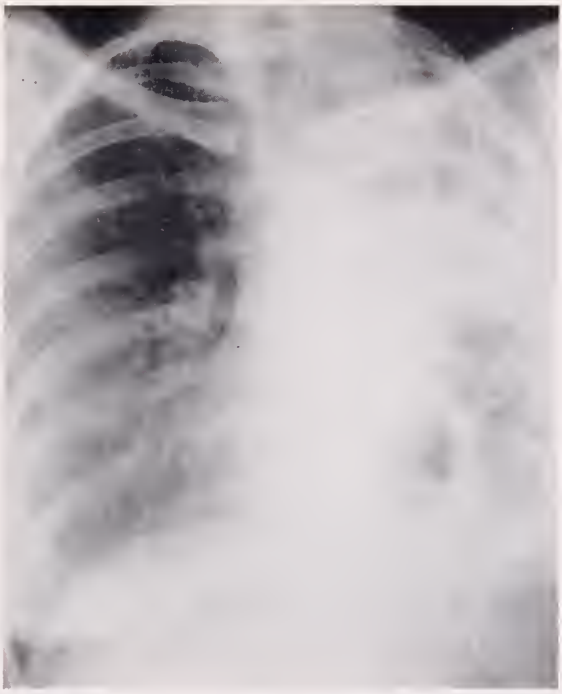
FIGS. 8–11. Characteristic examples of inactive disease treated prophylactically through pregnancy and the post-partum period.

nectomy, 1 thoracoplasty and 9 with pneumothorax or pneumoperitoneum). Figures 8 to 11 illustrate characteristic examples of inactive disease which remained stable under prophylactic chemotherapy through pregnancy and the post-partum period. However, of the three patients with disease judged inactive who received no prophylactic chemotherapy, the subsequent course of one showed progression.

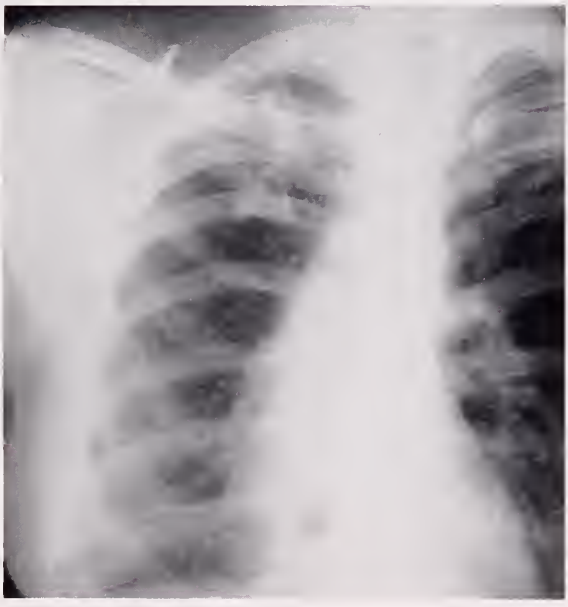
M. C., Unit 5984. This 18 year old Puerto Rican woman had known tuberculosis. She had had one pregnancy without any exaeerbation of her disease. She had been treated at another institution in 1950 with streptomyein. Subsequent observation in the Dept. of Health indieated that her left upper lobe tuberculosis was stable.

On admission to the Obstetrieal Chest Clinic on May 12, 1953 it was felt that her disease was inactive (Figure 12a), there being good agreement among the history, serial films and admission x-ray. It was planned, therefore, to start her on prophylactie ehemotherapy in mid—July 1953, since her expeeted date of confinement was Sept. 20, 1953.

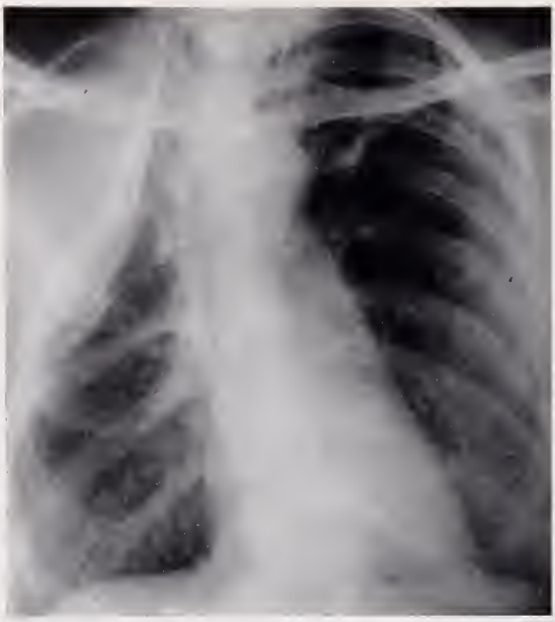
Unfortunately, she suffered a premature delivery on June 29, 1953 at another institution



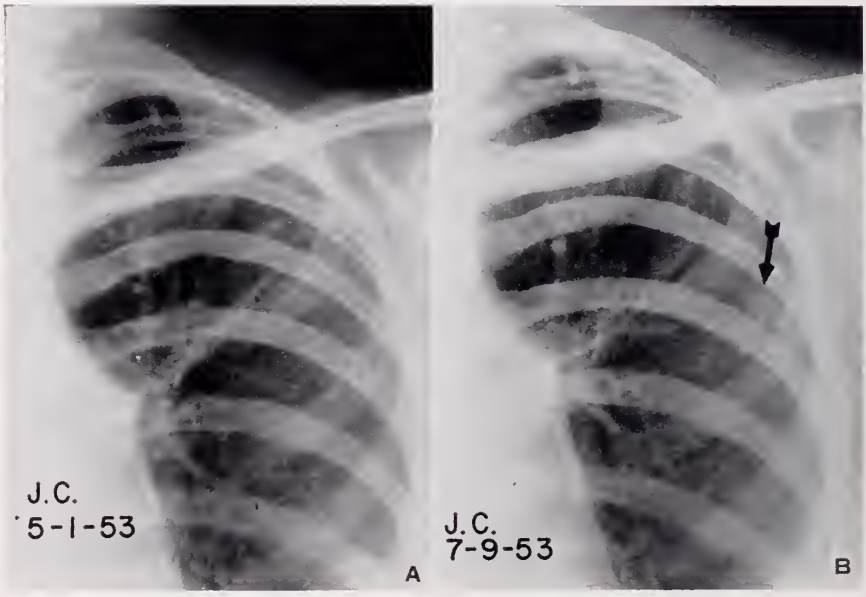
M. C.
FIG. 9



E. T.
FIG. 10



M. S.
FIG. 11



M. C., May 12, 1953 M. C., July 9, 1953

FIG. 12. a) Known disease in left upper lobe, considered stable on serial films for two years. b) Local spread of disease during pregnancy not treated prophylactically.

and then was brought to The Mount Sinai Hospital for post-natal hospitalization. A film on July 2, 1953 showed a new lesion in the 2nd left anterior intercostal space and this was confirmed on July 9, 1953 (Figure 12b). She was then discharged to a tuberculosis institution but subsequent inquiries revealed that she soon left this institution and cannot be traced.

During the above programs of chemotherapy of both active and inactive disease toxicity of chemotherapy has not proven a limiting factor. Of 147 patients treated with isoniazid there was one instance of peripheral neuropathy, which necessitated cessation of therapy, but which recovered rapidly on pyridoxine and Vit. B12 therapy. Of 18 patients treated with dihydrostreptomycin, therapy had to be stopped in four; 2 had tinnitus, one had a somewhat abnormal audiogram and a fourth suffered recurrent vomiting. In each of these instances the disease was well controlled at the time therapy was stopped. Of 20 patients given P.A.S. in four there was sufficient intolerance to warrant cessation. In no case was cessation of drug therapy because of toxicity responsible for reactivation of the disease.

SUMMARY AND CONCLUSIONS

1. From April 1, 1953 to January 31, 1956, 4740 patients were admitted to the Antenatal Clinic of the Mount Sinai Hospital. 162 (3.4 per cent) were found to have some evidence of pulmonary tuberculosis.

2. Routine antenatal chest x-ray was responsible for the discovery of the disease in most of these patients. It is suggested that such survey should be an essential part of an obstetrical program.

3. 41 of the patients were found to have active tuberculosis and 121 had inactive disease.

4. All cases of active tuberculosis require chemotherapy. The therapeutic regimen utilized at the Obstetrical Chest Clinic is described.

5. Prophylactic therapy for lesions regarded as inactive during pregnancy is a logical and desirable regimen.

6. The obstetrical management of patients with tuberculosis in pregnancy is described.

7. Of 34 patients with active disease treated with chemotherapy, 32 showed satisfactory response. Two had inadequate treatment, and did not improve. 3 other patients with active disease did not receive treatment. All showed progression of their disease.

8. 98 patients with inactive disease were treated prophylactically during pregnancy. 97 remained well, with no reactivation of their disease. One showed progression. Three received no therapy. One showed progression of disease.

9. These experiences suggest that all patients with tuberculosis in pregnancy should receive treatment. For patients with active disease, chemotherapy must be intensive and prolonged. With such a regimen, active tuberculosis responds well. If untreated, progression of disease is likely to occur. Inactive pulmonary tuberculosis will remain quiescent in almost all cases if treatment with prophylactic isoniazid is given.

Acknowledgement

We wish to express our thanks and appreciation to Miss Goldie Friedman and Mrs. Percenia Johnson, responsible for direction of the nursing care in the Prenatal Chest Clinic, and to Miss Josephine Leonardi and Miss Esther Wool of the Social Service Department. Without their invaluable assistance these studies would not have been possible.

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THE PROGNOSIS IN PATIENTS WITH ESOPHAGEAL VARICES DISCOVERED PRIOR TO BLEEDING

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In recent years, with the introduction of surgical techniques for relieving portal hypertension, greater attention has been directed to the natural course of esophageal varices (1–6).

Since the Ratnoff and Patek study in 1942 of the course of patients with massive gastrointestinal hemorrhage due to varices associated with Laennec's Cirrhosis (1), there seems to have been no particular change reported in the prognosis following the first bleeding episode. Their familiar figure of 40 per cent mortality during the course of the first hemorrhage and 70 per cent mortality within the one year compares closely with the data of Nachlas, et al., who reported 28 per cent survival after one year (8). Current reports range from 50 per cent mortality after one year (7) to 80 per cent mortality (9), depending on selection with regard to the extent of liver damage and the exact mode of exitus.

In the evaluation of any series, the mode of exitus assumes considerable importance. Obviously the patient who dies from exsanguination during the initial hemorrhage differs vastly from the patient who survives the hemorrhage to live many months before succumbing to intercurrent infection. The patient who survives the hemorrhage only to die of hemorrhage-induced hepatic coma or aspiration pneumonia should be included with the former group, whereas the patient overtaken by hepatic coma many months later should not. Many of the studies do not record these data.

In any large hospital group, a small number of patients will be found in whom the diagnosis of esophageal varices is made before the onset of hemorrhage. It would not appear to matter whether they are admitted for the therapy of liver disease or for some other extraneous cause, during the course of which both liver disease and esophageal varices are found. Needless to say, the vast majority of patients with varices present after their first hemorrhage and very few cases are found of so-called "virgin" varices. References in the literature to this group are meager, although Palmer et al. urge that the same surgical consideration be accorded this group as those who already have had significant bleeding (4). Since this group poses a perplexing problem, an attempt was made to locate and follow as many cases as possible of esophageal varices in which there has been no evidence of bleeding.

METHODS

The records of the Mount Sinai Hospital from 1934 to 1954 were reviewed. During that time 148 cases of esophageal varices were listed. Of these, 12 had no evidence of associated liver disease either by clinical evaluation or post-mortem follow up.

From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y

TABLE I

Basis of diagnosis of liver disease

	Hepatomegaly	Splenomegaly	Ascites	Jaundice	Abnormal Liver Chem.
	cm.	*cm.*			
1. A. S.	4	2	+	0	+
2. H. S.	16	10	+	+	+
3. C. M.	4	6	+	+	+
4. J. M.	2	8	0	0	+
5. M. S.	2	6	+	0	+
6. D. G.	2	6	+	0	+
7. H. L.	4	4	+	0	+
8. L. P.	8	6	0	+	+
9. H. E.	4	4	+	+	+
10. Y. S.	None	6	0	0	0

Fourteen cases were found in which esophageal varices were discovered before the onset of bleeding. Of these, four were discarded because they were not followed more than 1 month after the discovery of varices. Of the remaining ten cases (Table I), all except one occurred after 1944; a ratio of nine to one.

In the total series, 99 cases occurred after 1944 and 49 cases before; a ratio of about two to one for each ten year period. This disproportion may reflect differences in socio-economic circumstances and professional care during these time periods. There seemed to be a tendency in the decade prior to 1944 for patients to enter the hospital in desperate straits or almost preterminally.

The 10 cases were divided evenly between the sexes, but the females tended to be younger with four under 32 years of age. Ages ranged from 20 to 74 years with an average age of 44.2 years. The diagnosis of associated liver disease was made easily in all cases except one, Y. S., in which a diagnosis of splenic vein occlusion was suspected. The remaining patients had unequivocal hepatosplenomegaly and abnormal liver chemistries. Four had clinical jaundice and seven had ascites (Table I).

The following values of the liver function tests were considered abnormal: bilirubin, greater than 1.0 mgm; globulin, greater than 4.0 gms; cephalin flocculation, 3 plus or more; bromsulphthalein retention greater than 12 per cent in 45 min.; prothrombin time, 2 seconds higher than control; and alkaline phosphatase, greater than 12 King-Armstrong Units. Of the nine patients considered to have Laennec's cirrhosis, all had abnormal values for at least three of the above tests and in seven patients, every test value was abnormal. There seemed to be no constant relation of hemorrhage to bleeding tendency. The prothrombin time and platelet count were the only two studies done in every patient. The former was abnormal in six patients, the latter in four. The two patients who had the most marked abnormalities of both prothrombin time and platelets are, apparently coincidentally, the only two who have not yet hemorrhaged.

The diagnosis of esophageal varices was made on the basis of x-ray examination alone in six patients (Table II). In these cases, the picture of irregular

TABLE II

Basis of diagnosis of varices

	Unequivocal X-ray	Esophagoscopy	Post Mortem
1. A. S.	+		+
2. H. S.	+		
3. C. M.	0	+	
4. J. M.	+		
5. M. S.	+		
6. D. G.	+		+
7. H. L.	+	+	
8. L. P.	+		
9. H. E.	+		
10. Y. S.	+		

TABLE III

Name	Age	Liver Disease	Interval	No. of Bleeding Episodes	Result
1. A. S. (m)	59	+	4 mo.	1	Ceased 4 mo.
2. H. S. (f)	35	+	3 wks.	1	Not followed
3. C. M. (f)	29	+	8 mo.	1	Not followed
4. J. M. (m)	26	+	No bleeding		24 mo.
5. M. S. (f)	20	+	2 mo.	2	Not followed
6. D. G. (m)	69	+	1 mo.	2	Ceased 5 mo.
7. H. L. (m)	52	+	11 mo.	7	Ceased 6 yrs.
8. L. P. (m)	46	+	No bleeding		7 mo.
9. H. E. (f)	74	+	12 mo.	1	Ceased 13 mo.
10. Y. S. (f)	32	0	12 mo.	1	Not followed

filling defects at the lower end of the esophagus was unequivocal for classical varices. In one patient, barium swallow was normal and varices were found by esophagoscopy, and in another, esophagoscopy confirmed the x-ray picture (Table II). Two patients who came to post mortem examination revealed anatomical evidence of both gastric and esophageal varices. All patients were re-x-rayed after the acute bleeding had subsided, and no other site of bleeding in the gastrointestinal tract was found.

RESULTS

Results of the study are shown in Table III. It will be seen that not all cases could be followed through completely. However, for purposes of this study, it was considered sufficient for the patient to have been followed until the first bleeding episode. Of the ten cases, only two have not bled up to this point, one remaining well for seven months and the other for two years. Of the eight remaining cases, all had their first bleeding episode within one year after diagnosis. Four bled within four months; the mean "bleeding" time was five months following the diagnosis of esophageal varices.

Four cases could not be followed beyond the first bleeding episode, since their whereabouts is unknown. Two patients died within a month of the first hemorrhage, and another died during the second bleeding episode, three months later. One patient (H. L.) lived for six years and through seven bleeding episodes following the first, but this patient was treated with multiple sclerosing injections of the varices via esophagoscopy, in addition to open mediastinal packing.

Of the eight patients who bled, two died with the first hemorrhage.

DISCUSSION

There are immediately a number of criticisms that may be leveled at the foregoing material:

1) the number of cases does not constitute a large series,
2) not all cases were followed to their ultimate conclusion or for a sufficient period,
3) nine of ten cases had significantly and persistently abnormal liver chemistries and
4) esophageal varices easily identifiable by x-ray do not necessarily reflect the prognosis of those discoverable only by esophagoscopy.

Nevertheless, it was considered sufficient if the patients could be followed prior to the first bleeding episode. Once having bled, the cases fall into a group which has been studied thoroughly in the past and for which the poor prognosis is now well known. It is to be anticipated that more cases will rapidly become available in any large clinic with the present tendency to x-ray, and esophagoscope every case of liver disease. However, although the series is small, the overwhelming tendency to bleed during the course of one year is self evident and probably significant.

In all except one case, varices were found radiographically. It is still a moot point whether or not radiologically demonstrable varices are more likely to bleed because of their larger size than those found only by esophagoscopy. This question as yet cannot be answered, but may be influential in explaining the large morbidity revealed in this study.

In the future, we are likely to be presented with the cases of Laennec's cirrhosis who are admitted because of moderate evidence of liver decompensation and who show varices by routine esophagram. It is in these cases, that we must decide whether or not the mortality of a shunt operation is less than that of the first bleeding episode. Once a patient has bled there is no reason to suspect that he will be better off than before, or more likely to withstand an operation. Eighty per cent of this group of patients bled within 12 months, 37 per cent died within a month of the first bleeding episode. On this basis, there is no reason to suppose that the prognosis in these patients differs from that of the patient who comes to the attention of the physician after bleeding has started.

SUMMARY

One hundred forty eight cases of esophageal varices were reviewed and ten suitable cases found in which no bleeding occurred prior to the diagnosis of

varices. Most were associated with Laennec's cirrhosis: Eight of the ten patients suffered massive gastrointestinal hemorrhage within a year of the discovery and three died within a month of the first hemorrhage. There did not seem to be any significant difference, at least in this small series, between the prognosis in patients with varices that had bled before and in patients with varices that had not bled prior to their discovery.

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NEUROPHYSIOLOGICAL BACKGROUNDS OF CLINICAL NEUROLOGY*

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I. INTRODUCTION

When word came from Dr. Morris B. Bender, a former pupil of Dr. Wechsler, that I had been invited to give the first Israel S. Wechsler Lecture in Neurology, it pleased me much for I knew it would give me public opportunity to express appreciation for all that Dr. Wechsler has done to foster the advancement of neurology. I wanted also to thank him for the group of clinically trained men which he sent to my laboratory between 1932 and 1951 to do research in neurophysiology. Since many of them are well known to this audience, it would seem proper to mention their names on an occasion such as this. There were four from Montefiore Hospital as follows:

William Schick	1932–33
Irving Bieber	1933–34
Henry Wigderson	1936–37
Milton R. Sapirstein	1939–40

In addition to these there were five Abrahamson Fellows who came to us from this hospital:

Morris B. Bender	1936–37
Morris M. Kessler	1938–39
Edwin A. Weinstein	1939–40
Joseph A. Epstein	1948–49
Leonard I. Malis	1950–51

The men whom Dr. Wechsler has trained all proved to be excellent clinical observers. Having come from busy clinical services where they had scarcely known night from day, many had difficulty at first in becoming adjusted to the greater leisure of an experimental laboratory. When they arrived in the Laboratory, they were first shown the animals (cats, dogs, or monkeys) available for experimental work; they then saw the operating room, the animal quarters, and finally they met Mr. L. R. V. Kerby, my trusted English assistant, who was chiefly responsible for determining their destinies from then on. They were told that they could work on anything they liked, preferably some problem arising out of their clinical experience. Some were a little upset by this casual treatment, as was Morris Bender, but he ended by writing eleven important papers based on his work during his year in New Haven.

Since this is an inaugural lecture, I must first say a few words about the man

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whom it honors. Israel Wechsler was born in Rumania, a land which has given birth to many great neurologists. One thinks of such names as Marinesco, the Nicolescos, Dimitri Bagdazar, and Leon Ballif. Dr. Wechsler came to this country in 1900 when he was a lad of fourteen years. He later entered New York University and Bellevue Medical College. I don't know when he first became attracted to neurology, but I do know that he must have had very sound training as a physiologist at New York University, because every paper he has written reveals a knowledge of physiological principles and especially of neurophysiology—a grasp that is profound and, to physiologists, most inspiring. He belongs to a generation of neurologists which includes such men as Stanley Cobb and Henry R. Viets of Boston and Sir Francis Walshe, Foster Kennedy, Arnold Carmichael, and Macdonald Critchley of London who early came under the spell of Sherrington and of Rudolph Magnus and, like Viets and Walshe, Wechsler in his first studies began interpreting neurological phenomena in terms of physiology and the basic postural reflexes.

One of his original papers in this field, issued in 1922 (1), had to do with dystonia musculorum deformans and the occurrence of decerebrate rigidity phenomena. Two years later came a paper, "Involuntary movements: their unusual association and relation to the phenomena of decerebrate rigidity" (2). A year after that, another study appeared, entitled "Clinical application of tonic neck reflexes" (3), and finally in 1927 there was a most illuminating publication on "Loss of the righting reflex in man" (4). These contributions appeared at a time when the Magnus and de Kleyn reflexes (5) had not yet found their way into neurological textbooks, save for that of Israel Wechsler, the first edition of which was also published in 1927 (6)—a book which for nearly thirty years has had a profound influence on modern neurology and which I like to refer to as a text of "physiological neurology." It has the dynamic outlook which he has engendered in the men he has trained.

In 1952 Wechsler published a memorable discourse entitled "Neurology at the crossroads" (7). In this paper he took issue with those who believe that clinical neurology is a dying subject and he argued that it really should be regarded as the most scientific of medical specialties, especially when signs and symptoms are correlated with sound anatomy, physiology, and pathology. He holds his friends in psychiatry, neurosurgery, and psychosomatic medicine responsible for this ill-founded heresy. In his conclusion he mentions that studies on the pharmacological effects of drugs having selective affinity for various brain structures give indication of functional localization and he adds (7),

"There is no incompatibility between clinical and scientific investigation but the two complement each other. However, to be a scientist one must possess a disciplined mind and intellectual integrity, singleness of purpose, unquenchable curiosity, courage to express one's views in the face of opposition, and the capacity for objective criticism. It is comparatively easy to attain a fleeting reputation with superficial studies expressed in alluring language; it is considerably more difficult to acquire scientific knowledge. Words alone can be seductive and may succeed in giving merely the illusion of knowledge; but even beautiful language can conceal some very bad thinking. Advanced clinical

neurology has but just begun; its future, one may state with complete assurance, is full of promise."

The future, in which Dr. Wechsler sees much promise, has a solid foundation in the past and I have chosen an historical subject for this lecture because of Dr. Wechsler's abiding interest in the backgrounds of his special field. After studying the latest edition of his *Textbook of Clinical Neurology. With an Introduction to the History of Neurology* (8), I immediately realized, especially after rereading the historical section, that practically anything I could say about this aspect of *neurology* has already been said, clearly and with full authority. So it has seemed essential to limit my discourse to the more purely neurophysiological contributions of certain early writers which Dr. Wechsler mentions only in passing. I had not realized, for example, that Hippocrates had recorded so much sound neurophysiology in his descriptions of epilepsy, wounds of the head, and in his case histories. Galen's work in neurophysiology is better known, but I cannot resist bringing to your attention some of the particularly interesting passages in his works. And I can touch on the great neurophysiologists of the sixteenth, seventeenth, and eighteenth centuries without risk of repeating what Dr. Wechsler has already set down.

Prehistoric man was aware that a blow on the head was followed by loss of consciousness and that injuries sustained in other parts of the body, although they may have caused pain, did not affect man's awareness of his immediate surroundings. With this came the tacit recognition that the brain is concerned with the phenomena of consciousness [a theme on which Dr. Wechsler has just written (9)]. But who first proclaimed that the brain was associated with consciousness will probably never be known, for it was one of those elementary concepts which was no doubt recognized by many people in different parts of the world at various times and quite independently of one another. Scientific study of the brain and nervous system was likewise begun at different times and in many places.

II. THE ANCIENTS

We have it on the authority of Theophrastus (10) that Alcmeon, the Graeco-Roman physician of the fifth century B.C., taught that the brain was the organ of the mind and that he also recognized the existence of separate sensory and motor nerves. Indeed, Alcmeon may with justification be regarded as the first neurophysiologist of whom we have record, for he is also credited with having carried out experiments on animals that led him to think in terms of reflex action.

Clinical studies of abnormal neurological states are also to be found in the writings of both Hippocrates and Galen. Hippocrates, who was a contemporary of Alcmeon, left writings of two types: (i) his aphorisms and (ii) his case histories in which there is frequent mention of neurological signs and symptoms (11). Thus he says: "Unaccustomed attacks of numbness and anaesthesia are a sign of impending apoplexy." And again, "A wound on one temple produces a spasm in the opposite side of the body." Even more significant is the following:

"The most difficult fractures of the bones of the skull are those which occur along the sutures. Fractures are especially caused by heavy and rounded missiles and, in particular, by those which strike at right-angles, rather than from glancing blows. In order to determine whether there is a fracture present or not, give the patient a stalk of asphodel or fennel to chew with either jaw, and tell him to note whether he notices any bony crepitus; broken bones seem to make a noise."

In the first book of his *Epidemics*, Hippocrates gives the following case history (11):

A woman who lived on the sea-front was seized with a fever while in the third month of pregnancy. She was immediately seized with pains in the loins. On the third day, pain in the head, neck and round about the right clavicle. Very shortly the tongue became unable to articulate and the right arm was paralysed following a convulsion as happens in hemiplegia. Her speech was delirious. A restless night with insomnia; the bowels were disordered and the stools were small, bilious and unmixed.

Fourth day: speech was indistinct but she was no longer paralysed, convulsions. Pains continued as before and there was a painful swelling near the hypochondrium. She did not sleep and was completely delirious. Bowels disordered; urine thin and not of a good colour. . . .

On the eleventh day a relapse occurred with rigors and fever.

About the fourteenth day she vomited yellow bilious material rather frequently; sweating. Reached a crisis and the fever left her.

In another place in the first book of *Epidemics*, Hippocrates gives the classic description of mumps (12). In the early spring he records a form of mild fever which is never fatal:

. . . Many had swellings beside the ears . . . , either on one or both sides, in most cases without fever, and not necessitating confinement to bed; some, however, were a little heated. In all cases these swellings subsided without giving trouble, and none went on to suppuration as do those from other causes. In character they were flabby, large, diffuse, without inflammation or pain; in all cases they disappeared without a sign. These conditions occurred in youths, young men, and adults; mostly in such as took exercise in the wrestling schools and gymnasia; but they seldom attacked women. Many had dry coughs without expectoration; and hoarseness in speaking. Not long after, but in some cases a considerable time later, painful inflammation occurred in one or both testicles; fever in some cases, in others not. The condition was as a rule very troublesome. In other respects they had no illnesses requiring medical attention.

Such descriptions would stir the heart of any keen clinical observer!

The next prominent figure in the history of neurology was Galen, the Greek physician from Pergamum who flourished in the second century of the Christian era and who served as private physician to the Emperor Marcus Aurelius and his son, Commodius. Galen's neurophysiological writings are numerous. The French neurologist, A. Souques (13), has written an important paper on Galen's neurological knowledge, and his chief writings have been well translated by Daremberg (14). Let me cite three examples: the first is his description of the use of the hand in his *De usu partium* (15):

It appears to be the best constructed of all prehensile organs. Forasmuch as the hand can form a circle round a sphere, grasping it on every side, it also as securely and firmly holds the straight and the concave, which, if it be so, it can grasp all forms, for they are all formed from three figures—convex, concave, and straight. But, since many bodies are too bulky for one hand, nature has given a second, an auxiliary to the other, that each grasping opposite sides, should not hold it less securely than one very large hand. For this reason they are placed opposite each other (for they are formed for mutual use), and are in every respect equal, for they are the same organs and have similar duties. Consider the largest body a man can grasp with both hands, as a tree or a stone; and again, the smallest thing perceptible, as a grain, a hair, or a thorn; and then how great a number of bodies intervening between the largest and the smallest. You will find man grasping all these, as if the hand had been formed for each. Man seizes the least bodies with the tips of two fingers, the index and the thumb (which we Greeks call *megan*); and bodies a little larger with the thumb and the same finger, but not with the tips; for bodies still larger he employs three—viz., the fore, the middle, and the thumb; and if the body be still greater, he uses three fingers and the thumb, then all four with the thumb; afterwards he seizes with the whole hand; and finally, he seizes with both hands.

Even more striking are his observations on eye movements (15) which run as follows and which I am sure will be of great interest to Dr. Bender:

If, then, the eyes can be moved by our will, and if all movements of this kind are effected by muscles, it is evident that the Creator has surrounded the eye with muscles. But it is not sufficient for us to rest content with a knowledge of their utility, we must also investigate their number, taking special note of their size and situation. If, then, each eye has four movements—viz., inwards towards the nose; outwards towards the external canthus; upwards towards the eyebrows; downwards towards the cheeks—it is presumable that these movements are controlled by a precisely similar number of muscles. Thus there are two muscles at the sides (the internal and external recti), one in each canthus; two others the one above, the other below (the superior and inferior recti). The aponeuroses of all these muscles form a broad circle—a tendinous ring—which is continuous with the iris.

As it is necessary for the eye to have also a movement of rotation, nature has provided two other muscles each situated obliquely at the centre of an eyelid. These extend from above and below towards the outer canthus (superior and inferior obliques). Thus by means of these muscles the eye is turned in any desired direction. There also exists at their origin another broad muscle (suspensory or choanoid), which stretches and protects the attachment of the soft nerve (optic nerve). This muscle elevates the eye and causes it to rotate a little. Indeed, this soft nerve would easily be ruptured from its liability to suffer severe concussion by any injury to the head, were it not strengthened and protected on every side.

Galen's experimental studies on transection of the spinal cord have been widely quoted and have recently been well translated by Prendergast (16). I give this summary (15):

Moreover you have seen that transverse incisions of the whole cord deprive all parts of the body below of sensibility and of movement. . . . And you have seen in dissections that transverse incisions of the cord (from right to left or from left to right) which stop at its centre, do not paralyse all the inferior parts, but only the parts situated directly

below the incision—on the right when the right side of the cord has been cut; on the left when it is the other side.

III. NEUROLOGY PRIOR TO 1750

With the death of Galen, Graeco-Roman medicine ceased to flourish (17). Ancient texts were preserved in the monasteries of Byzantium and from there were transmitted by medieval scholars to the Arab world and later to the first medical school of modern times which was situated at Salerno, near Naples. The Arab caliphs between the tenth and twelfth centuries encouraged their scholars to render the written texts of classical antiquity into Arabic, this both in the Eastern Caliphate situated at Baghdad and the Western Caliphate at Cordova in Spain, whither many Arabic scholars travelled and settled. In this way the writings of Galen were saved for posterity, and with the invention of printing, Greek and Latin translations of the ancient poets, dramatists, and the medical writers such as Hippocrates and Galen began to appear. Through this circumstance Renaissance physicians, such as Vesalius, Paré, and that remarkable man, Jean Fernel (whom Sherrington, prior to his death, rescued from oblivion) came to know of Graeco-Roman neurology.

Jean Fernel. The first neurophysiologist who devoted full attention to the subject was Jean Fernel. His seven books, the *Natural part of medicine*, begun in 1538 and thus predating Vesalius, Charles Estienne, and his other contemporaries, dealt at length not only with problems such as muscular contraction, but also, and in considerable detail, with the brain-mind relationship. In discussing muscular movements it is noteworthy that he made a clear distinction between voluntary and involuntary movements, pointing out that some movements of the eyes and eyelids and of the head, and also of the hands during sleep (and our movements of breathing), do not proceed from intent or any other impulse of the mind, but lie outside the mind. Thus he distinguished a category of active muscular movements independent of the will or other intention—pure "motricity" acting of itself. Fernel does not elaborate this further but it was Descartes (18) a century later who put forward a similar idea:

> In treating of our muscular movements, and their relation to our thinking, Fernel makes in passing a notable remark, not met with in the customary handling of the subject. It is that some of our acts occur quite apart from 'appetition' and 'will.' Some movements of the eyes and eyelids, and of the head, and also of the hands during sleep, and again our movements of breathing, do not proceed, he says, from intent or any other impulse of the mind; they lie outside the mind. Thus he distinguishes a category of active muscular movement independent of will, or other intention—pure 'motricity' acting of itself. Fernel does not elaborate this further. But in the following century, whether unaware of Fernel's remark or not, Descartes returned to similar observations, and dealt with them in a manner which caught the abiding attention of the world.

Robert Whytt. After the time of Fernel there were many writers who touched upon the functions of the nervous system, René Descartes, Robert Boyle, Thomas Willis, Raymond Vieussens, and Stephen Hales, but there was no one who left such a great mark on the subject as the Edinburgh physician, Robert

Whytt, who in 1751 wrote a celebrated book entitled *An essay on the vital and other involuntary motions of animals*. Born in 1714 at Kirkcaldy, Whytt was educated at St. Andrew's and studied medicine at Edinburgh and Leyden, but he took his first medical degree at Rheims and a second one at St. Andrew's. While on the continent he had studied physiology under Boerhaave who occupied the chair of the "Institutes of Medicine," a term which Whytt took back to Scotland and which thereafter and until about 1900 was used in all Scottish schools for chairs of "physiology (19)". It is interesting in passing to recall that Osler's first academic post in Montreal was one of the "Institutes."

Whytt began his career as an experimentalist by investigating Mrs. Joanna Stephens' secret remedy for dissolving bladder stones, a malady which at that time was proving especially bothersome to members of Parliament—so bothersome that they had voted the huge subsidy of £5,000 to secure the formula (20, 21). Whytt found that the potion was made up of lime water mixed with ground egg and oyster shells. He published his finding in 1743 and shortly thereafter received indignant letters from the Right Honourable Sir Horace Walpole and the Bishop of Llandaffe who fancied that they had been benefitted by Mrs. Stephens' concoction. After this Whytt turned to physiological experimentation and he also developed a large clinical practice which led him to give his classic account of tuberculous meningitis, describing the three stages of the disease in such a lucid fashion that the account could be used even at the present day—as one will see if one consults Wechsler.

Descartes had envisaged the concept of reflex action without, however, offering experimental proof. Robert Boyle had observed that an insect when pricked may wiggle for some days after its head is cut off, and Stephen Hales proved in animals that such reflex action is abolished by the destruction of the spinal cord. Whytt found that preservation of a single segment of the frog's spinal cord suffices to maintain simple reflexes of the upper and lower limbs. But he is best known for having described the pupillary reflex to light and its pathway through the optic thalamus. He must also be credited with having formulated the broader concept of a *stimulus* and the reaction thereto. This is what he says (22):

> If therefore muscular motion were owing to any of the causes above mentioned, it might reasonably be expected that it would only follow upon the application of certain kinds of stimuli to the muscular fibres: but we know from experience, that instruments of different metals, provided their sharpness and figure be the same, have an equal power of bringing the muscles of animals into action:—that it makes no odds whether the stimulating substances be electrics per se, or non-electrics:—that acrid liquors of quite opposite natures have much the same effect, if their degree of pungency be equal:—that acids, alcalies, neutral salts, heat, pricking, tearing, and in short every kind of irritation, excite the muscles of animals into contraction; and that there is no difference in the motions they produce, except what arises from their acting as stronger or weaker stimuli, i.e. from irritating the part more or less.
>
> Further, no violent motion is produced by any bodies in nature, however active, unless the peculiar causes necessary to produce this be applied to them: but in order to the contraction of a muscle, it is not necessary that the stimulus should be applied to

its fibres; it is enough that the common membranes covering them are irritated, the same effect being hence produced as from wounding the very fibres of the muscle. This is evidently fact, in the case of the heart, stomach, guts, and bladder; nay, many times muscles are excited into action by a stimulus affecting a remote part with which they have no immediate connexion, or so much as even a communication by means of nerves, unless it be that general one subsisting between all the parts, as their nerves are derived from the same brain. Thus anything which affects the interior membrane of the stomach after a disagreeable manner, brings the diaphragm and abdominal muscles into convulsive contractions: the action of light, as a stimulus, upon the tender retina is followed by the contraction of the orbicular muscle of the uvea, and according to the various impressions made by sounds upon the auditory nerves, the muscles of the internal ear are contracted variously.

In a second publication entitled *Physiological essays* (23), which appeared in 1855, Whytt dealt in the first essay with the motion of fluids "in the very small vessles of animals," and he gives a most penetrating discussion of capillary hemodynamics. The second essay is entitled "Sensibility and irritability of the parts of men and other animals." This is a reply to the disputatious Albrecht von Haller who had chosen to criticize the reflex concepts which Whytt had promulgated in his earlier work. Here Whytt again distinguishes between direct and indirect stimulation. "This first kind of motion," he says, "seems to be owing to the soul or sentient principle" acting on the part moved, e.g. on skeletal muscle or the heart; the second, "to the soul as perceiving and acting in the brain: and of this kind is the motion of sneezing from an irritation of the nose, and the contraction of the diaphragm in vomiting." He adds that the brain is not necessary for the first kind of motion, but that the case is otherwise in the second "where the motion is produced as through the intervention of the brain and not by any stimulus applied to part moved."

Whytt's health had always been frail and he died in 1766, following a year's illness, with symptoms which suggest that he succumbed to diabetes. Dr. Wechsler in his account of the history of neurology tells of Whytt's followers, Prochaska and his *sensorium commune*, Bell and Magendie and the discovery of the separate functions of the spinal nerve roots, Marshall Hall and his celebrated paper on the reflex function of the medulla oblongata, the Webers and inhibition, Brown-Séquard and spinal pathways, David Ferrier and the excitability of the motor cortex and, finally, Sherrington's integrative action of the nervous system.

Great teachers achieve personal immortality through the students they inspire, and those who have had the good fortune to come under Israel Wechsler's influence have an abiding and dedicated loyalty that will carry his ideals and his teachings to future generations of men in medicine. Their zeal, indeed, reminds one of George Eliot's inspired lines:

> O may I join the choir invisible
> Of those immortal men who live again
> In minds made better by their presence; live
> In pulses stirred to generosity,

In deeds of daring rectitude, in scorn
For miserable aims that end with self,
In thoughts sublime that pierce the night like stars,
And with their mild persistence urge man's search
To vaster issues . . .

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APPENDIX A

Publications of Dr. Wechsler's Pupils Based on Work Done at Yale

Publications of Morris B. Bender

Fright and Drug Contractions in Denervated Facial and Ocular Muscles. Am. J. Physiol., 119: 270, 1937.

Abnormal Ocular and Pupillary Movements Following Oculomotor Paralysis. Report of a Case. Arch. Ophthal., N. Y., 18: 411, 1937. (With S. Alpert [2]).

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Regeneration of the Third Cranial Nerve in Monkeys. Am. J. Physiol., 123: 14, 1938.

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Factors in Functional Recovery Following Section of the Oculomotor Nerve in Monkeys. J. Neurol. Psychiat., 2(N.S.): 285, 1939. (With J. F. Fulton [2]).

Actions of Adrenaline and Acetylcholine on the Denervated Iris of Cat and Monkey. Am. J. Physiol., 130: 268, 1940. (With E. A. Weinstein [2]).

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The Relation of Forced Grasping and Groping to the Righting Reflexes. Am. J. Physiol., 105: 7, 1933. (With J. F. Fulton [2]).

Relation of the Cerebral Cortex to the Grasp Reflex and to Postural and Righting Reflexes. Arch. Neurol. Psychiat., Chicago, 39: 435, 1938. (With J. F. Fulton [2]).

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Respiratory and Vascular Responses in Monkeys from Temporal Pole, Insula, Orbital Surface and Cingulate Gyrus—a preliminary report. J. Neurophysiol., 12: 347, 1949. (With B. R. Kaada [1] and K. H. Pribram [2]).

Electroencephalographic Study of Experimental Cerebro-vascular Occlusion. EEG Clin. Neurophysiol., 1: 491, 1949. (With M. A. Lennox [2]).

Electrocorticographic Effects of Stimulation of Posterior Orbital, Temporal, and Cingulate Areas of *Macaca mulatta*. J. Neurophysiol., 13: 383, 1950. (With M. A. Lennox [1], R. H. Dunsmore [2] and K. H. Pribram [4]).

Publications of Morris M. Kessler

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Publication of Leonard I. Malis

Action Potentials in "Motor" Cortex Evoked by Peripheral Nerve Stimulation. J. Neurophysiol., 16: 161, 1953. (With K. H. Pribram [2] and L. Kruger [3]).

Publication of Milton R. Sapirstein

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Reflex Changes after Injury to the Pyramidal Tract in the Macaque, Gibbon and Chimpanzee. Arch. Neurol. Psychiat., Chicago, 30: 501, 1933.

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DURATION OF NITROGLYCERIN EFFECT AS MEASURED BY OBJECTIVE METHOD

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This paper reports a comparative study of the action of nitroglycerin by means of an objective method, and specifically investigates the duration of effect when the drug is given in different ways.

The nineteenth century saw the introduction of a group of potent vasodilating drugs, beginning with the introduction of amyl nitrite in 1867 (1) and proceeding through nitroglycerin, sodium nitrite, erythrol tetranitrate and mannitol tetranitrate. These drugs all act on the arterial system by causing relaxation or dilatation of the arteries and thereby facilitating the flow of blood. The action of these drugs, while very similar, shows interesting and useful variations. Amyl nitrite, for example, when inhaled as a vapor produces its effect in a few seconds and the duration of action is approximately ten minutes, while mannitol tetranitrate acts in about thirty minutes and the effect lasts about four hours. Nitroglycerin, which is absorbed through the mucous membrane of the mouth, acts in one or two minutes and the effect lasts for about one half hour. Because of its convenience and speed of action, nitroglycerin has become one of the most commonly used vasodilators since its introduction in 1879 (2).

The action of this group of drugs is easily demonstrated clinically and experimentally. They produce a fall in blood pressure, rapid bounding pulse, and a feeling of fullness in the head in varying degrees, depending on the specific drug and dosage administered. Meyer and Gottlieb (3) in their Pharmacology published in 1914, exhibit pulse tracings taken before and after the administration of amyl nitrite. The pulse wave after amyl nitrite shows increased height and sharpness of the main deflection, and also accentuation of the secondary or katacrotic wave which appears on the downstroke of the main wave. These characteristic features are useful for objective study of the drug effect.

This characteristic vasodilating effect was demonstrated by the author in 1937 (4) by means of a new and sensitive instrument now known as a capacigraph (5). This instrument, which operates electrically, and is known technically as an alternating current bridge, is sensitive to the slight volume change of a finger produced by the pulse wave. Two small electrodes are applied to a finger and connected to the capacigraph. When the circulation in the hand is stopped by inflating a sphygmomanometer cuff on the upper arm, the capacigraph records a straight line without evidence of any blood flow in the finger. As the pressure in the cuff is gradually reduced, the capacigraph records pulsation in the finger, first appearing at systolic pressure and gradually increasing in height, reaching a maximum at about diastolic pressure. This curve, very much like an oscillometer tracing is easily obtained, readily standardized, and shows characteristic alterations with various drugs, notably nitroglycerin.

Figure 1 shows a characteristic curve of the right index finger of a normal

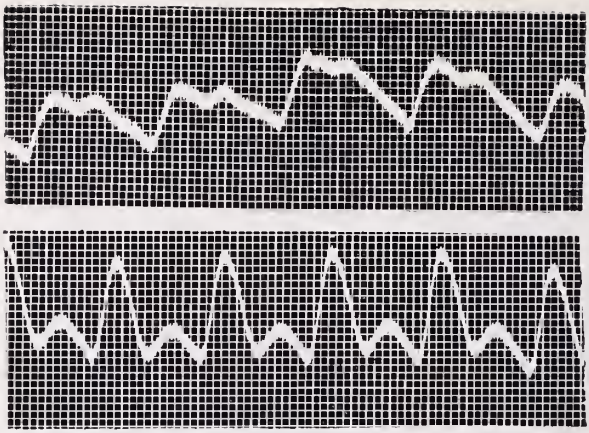

FIG. 1. The upper curve shows a normal pulse curve or capacigram of the right index finger before administration of nitroglycerin. The lower curve is from the same finger eight minutes after sublingual administration of $^1/_{100}$ grain of nitroglycerin. Note the sharp change in the main deflection and also in the secondary or katacrotic wave.

subject before and shortly after administration of $^1/_{100}$ grain of nitroglycerin. Not only is the main pulse wave higher and sharper, but the secondary or katacrotic wave is definitely increased by the drug. The constancy and measurability of this change in the secondary wave make it suitable for objective measurement of the effect of vasodilating drugs. It seems to be much less subject than is the main pulse wave to accidental factors such as emotion, fatigue, room temperature, ingestion of food, posture, etc. Therefore, attention has been concentrated on the changes in the katacrotic wave as a reliable index of the vasodilating effect.

This study concerns itself with the duration of action of the usual sublingual nitroglycerin tablet taken under the tongue as compared with a new form of nitroglycerin tablet which is absorbed slowly through the stomach and intestinal tract over a period of many hours. The short, sharp change in peripheral pulsation due to sublingual administration is readily shown, and the change due to slow prolonged absorption of nitroglyn* can be followed for many hours.

Figure 2 is similar to Figure 1 but in the former the characteristic changes of vasodilatation are recorded several hours after ingestion of the slowly released and continuously absorbed drug. These changes are not transitory as in the case of ordinary nitroglycerin but are found to persist for many hours.

Table I illustrates this difference by showing our findings with ordinary nitroglycerin in twelve individuals and with the slowly absorbed drug in eleven persons. These subjects consist of seven men and seven women varying in age from 16 to 72 years. The effect of sublingual nitroglycerin which becomes evident after two or three minutes is seen to persist for a period varying from 12 to 27 minutes with an average duration of about 18 minutes. The slowly absorbed

* Nitroglyn (sustained action nitroglycerin) manufactured by Key Corporation.

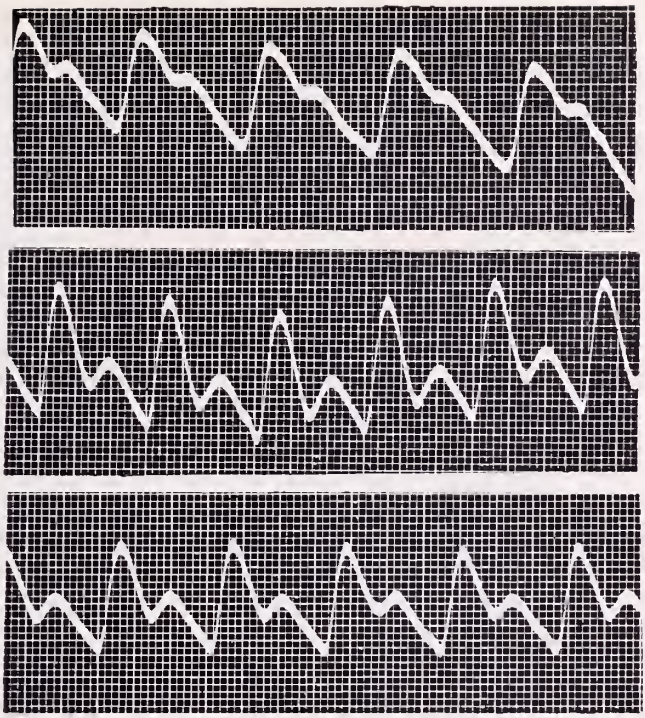

FIG. 2. The upper curve is a capacigram of the right index finger before administration of nitroglyn. The middle curve is from the same finger three hours after ingestion of $\frac{1}{5}$ grain of nitroglyn. The lowest curve is from the same finger four and one half hours after ingestion of $\frac{1}{5}$ grain of nitroglyn. Note that the characteristic alteration of the curve due to prolonged action nitroglycerin is still evident after four and one half hours.

TABLE I

Subject	Age	Sex	Duration of Effect with 1/100 Grain Nitroglycerin	Duration of Effect with 1/5 Grain Nitroglyn
1	16	M	not tested	over 300 minutes
2	25	F	27 minutes	300 minutes
3	26	F	over 20 minutes	over 510 minutes
4	28	F	18 minutes	480 minutes
5	29	M	16 minutes	not tested
6	29	F	18 minutes	300 minutes
7	31	F	12 minutes	not tested
8	45	F	25 minutes	over 300 minutes
9	49	M	12 minutes	not tested
10	50	F	15 minutes	not tested
11	63	M	20 minutes	390 minutes
12	70	M	19 minutes	over 420 minutes
13	72	M	not tested	over 326 minutes
14	77	M	20 minutes	over 420 minutes
Average duration			18 minutes	over 343 minutes

nitroglyn generally takes ten or more minutes to produce its initial effect but this persists for periods varying from 280 to more than 510 minutes with an average duration of about 340 minutes. These figures are approximate because the vasodilating effect disappears gradually and generally does not have a sharp end point. However the difference between the two forms of the drug is so marked that it can be stated with reasonable certainty that the nitroglyn or slow release drug has an effect approximately twenty times as long as the effect of the sublingual tablet.

The facility with which the vasodilating effect can be recorded by the method here employed suggests the feasibility of investigating various new drugs which recently have been advocated for this effect on the peripheral circulation. Both vasodilatation and vasoconstriction can be demonstrated and recorded readily.

SUMMARY

The capacigraph, a sensitive electrical instrument, which records finger pulsation, has been employed to investigate the circulatory effect of ordinary nitroglycerin tablets and of prolonged action nitroglycerin tablets known as nitroglyn.

Nitroglyn produces an effect which persists about twenty times as long as the effect of sublingual nitroglycerin.

The method employed depends on an objective curve and may be used to investigate peripheral vascular changes.

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THE SAGITTAL DIAMETER OF THE BONY CERVICAL SPINAL CANAL AND ITS SIGNIFICANCE IN CERVICAL SPONDYLOSIS

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The work of Elsberg and Dyke (1) demonstrated the usefulness in roentgen diagnosis of the interpedicular measurements made on antero-posterior projections of the spine. This is essentially a measurement of the maximum transverse diameter of the spinal canal. These measurements have been of greatest use in the thoracic and lumbar regions. In the cervical region, the pedicles, particularly in the upper portion, extend laterally as well as posteriorly and are difficult to delineate clearly. Moreover, in the cervical region, the maximum antero-posterior or sagittal diameter of the bony spinal canal is less than the maximum transverse diameter. It would seem, therefore, that in the cervical region a more critical measurement would be the sagittal rather than the transverse diameter.

Measurements of the sagittal diameter of the bony cervical spinal canal in a group of 200 normal individuals have been reported by Boijsen (2). On lateral films of the cervical spine in one hundred males and in one hundred females, the sagittal diameter was measured at each cervical level. The measurements were made from the posterior aspect of the body of the cervical vertebra to the closest point of the cortical line indicating the mid-line of the spinal canal posteriorly (Fig. 1). The cortical line is at the site of fusion of the laminae and the spinous process. This author pointed out that the sagittal diameters in the cervical region were one or two millimeters less in females than in males and that the AP diameters from C4 to C7 were essentially constant. The AP diameter of the first thoracic vertebra according to Boijsen (2) was also essentially the same as the AP diameter of the lower cervical vertebrae. In this series, target-film distances of both 1 and 1.5 meters were used. It was therefore considered desirable to repeat this work with a standard target-film distance of 72 inches. This long target-film distance routinely used for lateral views of the cervical spine is particularly useful when measurements are desired since the variations in correction factors due to magnification are decreased.

Lateral cervical spine films were taken using Bucky technique with the patient erect, usually sitting, and the head in a neutral position. The shoulder was in contact with the table-top. Table-top to film distance in the Bucky tray was 1.8 inches. The target to table-top distance was 72 inches. Measurements taken from the films were used directly without attempting to calculate actual values. The results without correction appeared to be sufficiently useful so that in general it appears unnecessary to include a mid-line opaque ruler to obtain actual values. The true measurements are therefore about 1.5 mm. less than those quoted in this report. Two hundred adult cases were examined, approximately an equal number of males and females. These cases were selected at random. However, an

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effort was made to exclude cases with known neurological disturbances or cases showing obvious bone or joint changes on the films. The range of ages was from the third to the sixth decades inclusive. In some individuals, there is a slight concavity of the posterior aspect of the cervical vertebrae which in general was neglected for measurement purposes. Incidentally, it should be noted that the cortical line or base of the spinous process used as the posterior border of the spinal canal should not be confused with a somewhat similar appearing vertical cortical line occasionally seen and due to the posterior aspect of the articular

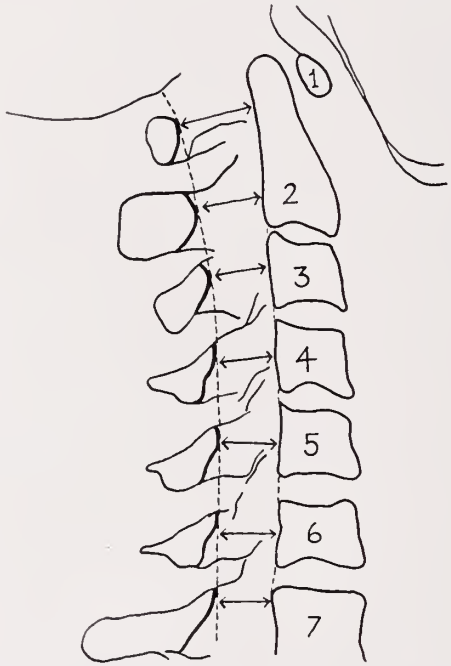

FIG. 1. Method of measurement of sagittal diameters of cervical bony spinal canal in normals. Imaginary lines along the posterior aspects of the bodies and through the most anterior points of the fused laminae and spinous process posteriorly outline the central vertebral channel. The AP diameters over the vertical distance of a single vertebral body, below C2, are essentially the same.

masses. Measurements at the level of the atlas were made utilizing the dens as equivalent to the body at this level.

The measurements obtained in this series of 200 cases are indicated in Table I. For C1, the atlas, the average AP diameter was 22 mm. For C2, the average was 20 mm. From C3 to C7 inclusive, the most frequent measurement was 17 mm. For these lower five cervical vertebrae, the range was from 12 to 22 mm. or 17 mm. plus or minus 5 mm. The value of 12 mm. was found four times in 1,000 measurements and the value of 22 mm. seven times in 1,000 measurements made at the levels of C3 to C7.

The application of these measurements to a particular case is frequently best done by examining the differences in the sagittal diameters of adjacent vertebrae

TABLE I

Values of the sagittal diameters of the cervical bony spinal canal from C1 to C7 inclusive in 200 adults

In the left hand column are the actual measurements, in millimeters. At each cervical level, indicated in the column headings, the number of cases with each measurement is given.

	C1	C2	C3	C4	C5	C6	C7
mm							
12	—	—	—	—	1	—	2
13	—	—	2	2	4	6	4
14	—	—	11	20	20	22	19
15	—	2	23	25	30	30	33
16	1	2	30	34	39	41	32
17	1	15	46	54	44	47	50
18	9	22	39	35	32	27	30
19	12	39	25	14	18	16	15
20	33	50	19	12	10	9	12
21	28	26	3	1	2	1	1
22	32	18	2	2	—	1	2
23	27	15	—	—	—	—	—
24	13	2	—	—	—	—	—
25	22	6	—	—	—	—	—
26	11	2	—	—	—	—	—
27	2	1	—	—	—	—	—
28	3	—	—	—	—	—	—
29	2	—	—	—	—	—	—
30	4	—	—	—	—	—	—
	200	200	200	200	200	200	200

or plotting the diameters on graph paper and comparing the shape of the curve so obtained with a standard curve. Figure 2 gives the differences observed between adjacent vertebrae in the form of bar graphs. Figure 3 indicates standard, somewhat idealized average, maximum and minimum curves. The values obtained in this study are essentially the same as reported by Boijsen (2) after making due allowance for differences in target-film distances.

The sagittal diameter at a particular level of the cervical spinal canal may be increased in cases of expanding intraspinal processes. Boijsen (2) reported that in seven of 13 cases of cervical intraspinal expanding processes, he was able to detect a local increase in the sagittal diameter. In the majority of these cases, however, the expanding lesion had developed before complete bony fusion of the laminae. In a limited experience to date in adults, local increases in the sagittal diameter have not been unequivocally observed independent of observable qualitative changes such as excavation or destruction of the posterior aspect of a vertebral body or thinning of a lamina.

One of the chief reasons for interest in the sagittal diameters in the cervical spine is the possibility of detecting significant decreases in this diameter associated with cervical spondylosis. To date, correlation between clinical findings and

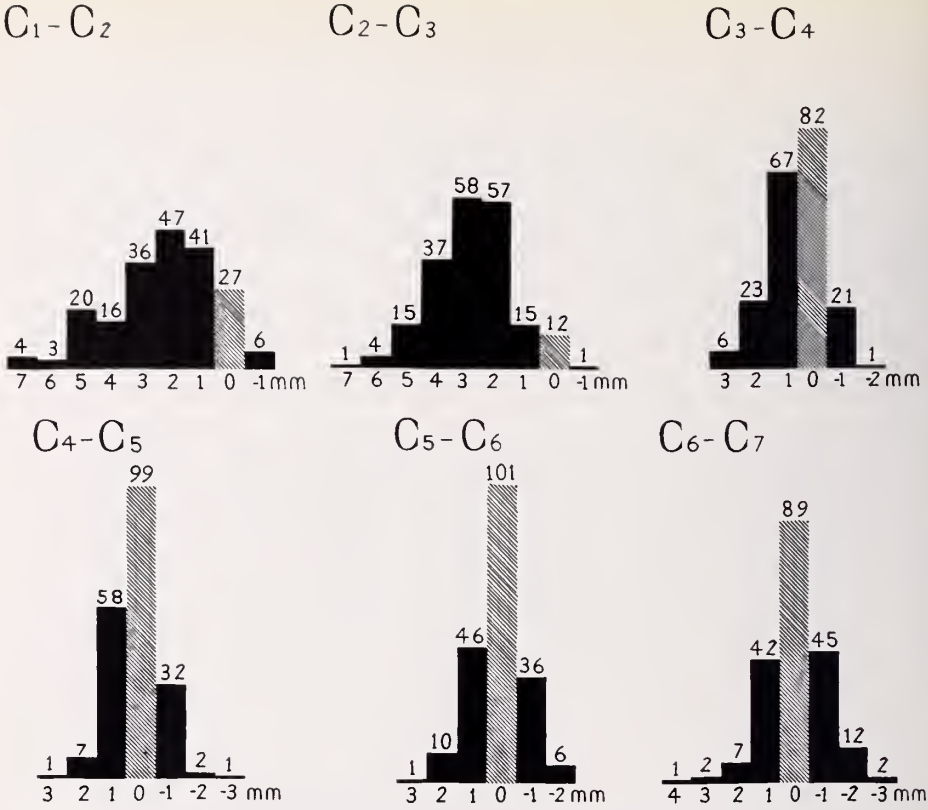

Fig. 2. Differences in millimeters between adjacent cervical segments. The sagittal measurement of the segment below is subtracted from the sagittal measurement of the segment immediately above and these differences are plotted in the form of bar graphs. A positive difference indicates that the larger measurement was found at the higher level. A negative difference indicates that the lower segment measurement was larger. The actual differences are indicated below each bar. The numbers above each bar indicate the number of cases with any given difference. The total number of cases measured was 200.

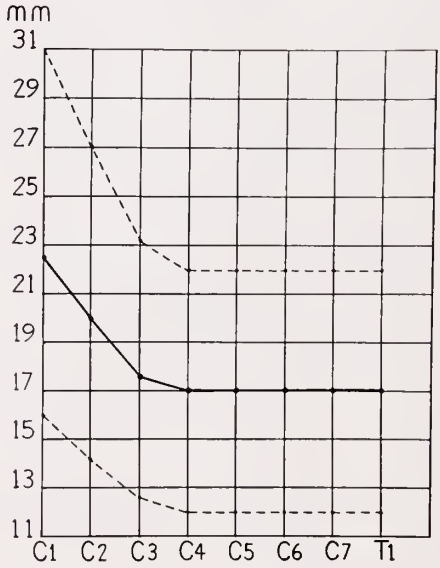

Fig. 3. Idealized "curves" for average, maximum and minimum sagittal measurements. It is assumed that the measurement of T1 is the same as C4 to C7. Plotted values are uncorrected measurements made from lateral films of the neck taken at 6 feet target-table top distance.

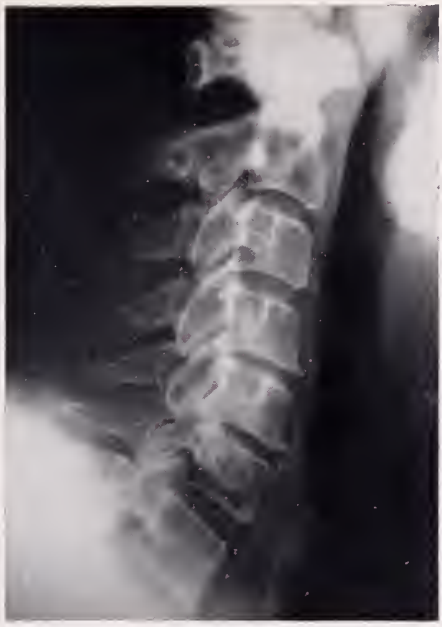

FIG. 4A

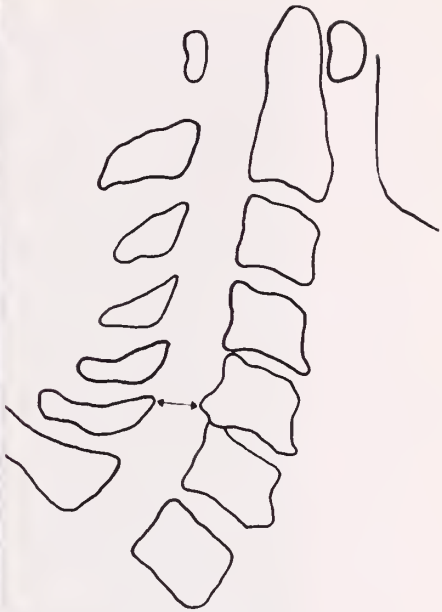

FIG. 4B

FIG. 4A. Male of 59 with typical ridge syndrome. Minimum sagittal diameter of spinal canal is between calcified projection at inferior margin of the body of C5 and the base of the spinous process of C6. In the neutral position of the head, this measurement was 11 mm.; in extension, 10 mm.; in flexion, 12 mm. The full extent of bony projections such as these might be difficult to delineate because of overlying obscuring bony shadows.

FIG. 4B. Diagrammatic drawing of Fig. 4A to indicate that the maximum sagittal diameter in spondylosis is usually between the bony projection on the posterior inferior aspect of one body and the base of the spinous process of the vertebra below. As a result, this diameter is less in extension (i.e., with the head and neck bent backward) than it is in flexion (i.e. with the head bent forward and chin approximated to the chest).

selected roentgen changes in cases of degenerative disease of the cervical spinal column has been poor. The simple presence of spurs or the narrowing of an intervertebral space or narrowing of intervertebral foramen are by no means good evidence that the patient is symptomatic. Pallis et al (3) suggested that perhaps the best indication of the presence of symptoms would be a diminished AP diameter of the bony cervical spinal canal at a specific level. This is particularly true in cases with symptoms or signs due to cord compression, that is, the so-called ridge syndrome. In this syndrome, associated with degeneration of the disc, a protrusion of the disc intraspinally may occur associated with bone formation on each side of the protruded disc. This condition has been differentiated from simple herniation or extrusion of nuclear disc material into the spinal canal as a result of traumatic tears of the annulus (4, 5). In this latter condition, calcification of the extruded material and secondary new bone formation of the articular margins of the vertebrae may also occur so that at operation it may be difficult to determine the pathogenesis in a specific case. Davidoff and Epstein (4) also emphasized the rôle of bony-hard osteophytes projecting posteriorly into the spinal canal. With the knowledge that, in asymptomatic adults, the antero-

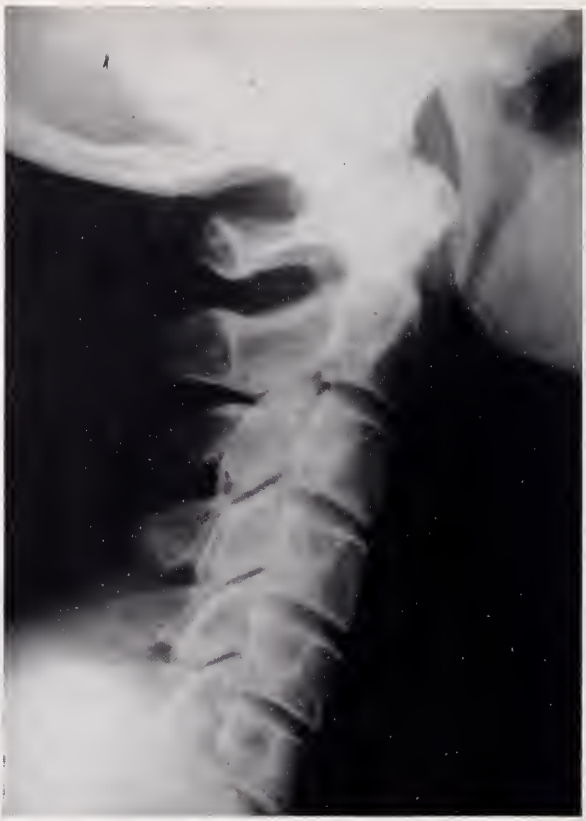

FIG. 5. Male of 50 with posterior bony projections of C4, C5 and C6. Minimum sagittal diameters at the C4–C5 level and at the C5–C6 level measured 10 millimeters. This patient had a ridge syndrome.

posterior diameter of the spinal canal should be at least 12 mm., it seemed reasonable that any diameter smaller than this due to intraspinal bony projection or new bone formation might cause cord compression. However, considerable difficulty arises in individual cases in ascertaining that the spurs seen in the lateral view of the neck actually protrude into the spinal canal. Moreover, intraspinal calcification associated with spurs and a ridge syndrome or herniation of nuclear material into the canal may be difficult to visualize in conventional films because of the large number of obscuring bony structures. It is also technically difficult to secure sharp mid-line laminagrams because of the long object to film distances involved. In individuals with osteophyte formation, it is of interest that the smallest antero-posterior measurement is usually between a spur on the inferior posterior aspect of a cervical vertebra and the base of the spinous process of the vertebra below. Since two vertebrae are involved in this measurement, this minimum diameter may be about 2 mm. less in full extension than it is in full flexion. In a small number of cases thus far investigated, the impression has been gained that cord compression may be predicted if the sagittal diameter at any level of the cervical canal is 10 mm. or less, with the head in a

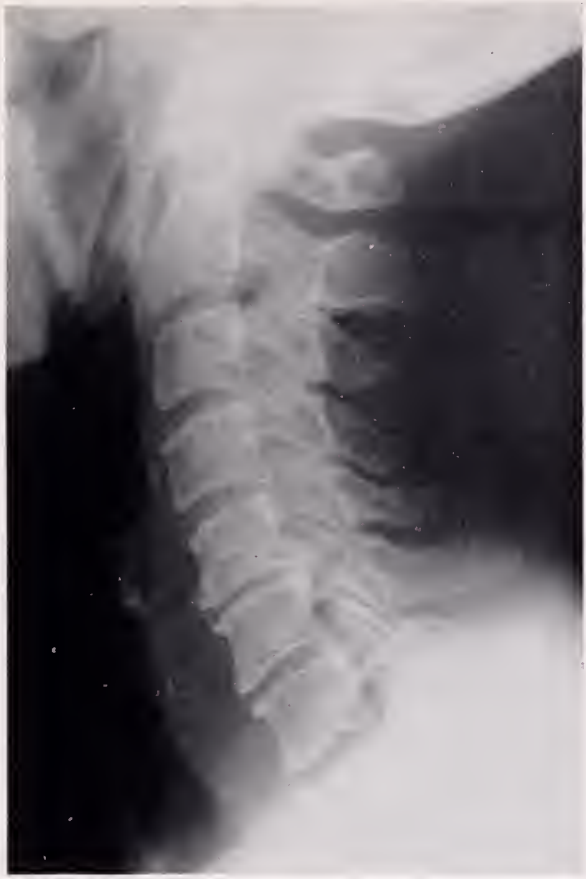

FIG. 6. Female of 62 with evidence of cervical "neuritis" but no long tract signs. Large posterior spurs between C5 and C6. The minimum sagittal diameter between the spurs and the base of the spinous process of C6 was 10 mm. The AP projection of the cervical spine showed that the C5-C6 spurs projected markedly laterally. On myelography, a unilateral defect obliterating the root pouch and a faint transverse ridge without any block were demonstrated. It is likely that the measured minimum sagittal diameter was not a true mid-line measurement.

neutral position (Figs. 4, 5). Exceptionally, with large spurs which project markedly laterally as well as posteriorly, only intraspinal root compression may be demonstrable on myelography despite an apparent sagittal diameter of 10 mm. or less (Fig. 6). When the minimum sagittal diameter is between 10 and 13 mm., cord compression may or may not be present. If the measurement is 13 mm. or greater, it is unlikely that simple spondylotic changes are the cause of cord compression (Fig. 7). The possibility of cord compression due to uncalcified or unvisualized extruded or protruding disc material is not thereby excluded. In such instances, however, if long tract signs are present, it is likely that the original sagittal diameters were on the small side of the normal range (Fig. 8) or that some spur formation is also present and contributes to the clinical picture. At any rate, in a patient with long tract signs and a suspicion of a non-traumatic

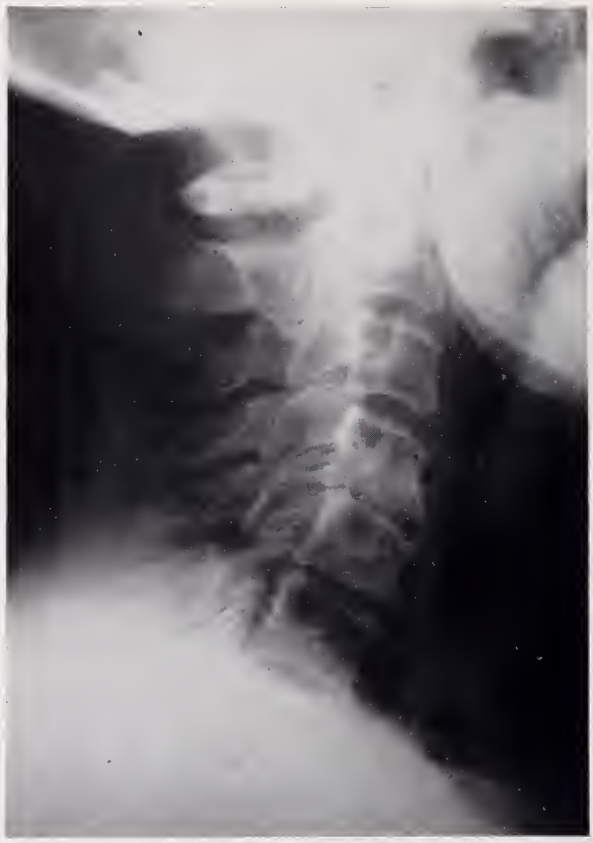

FIG. 7. Patient of 60 with large posterior spur on lower margin of C4. Minimum sagittal diameter at this level was 13 millimeters. Patient had no signs or symptoms of cord compression.

space-occuping lesion in the cervical spinal canal, the presence of adequate sagittal diameters suggests that the lesion is primarily related to the spinal cord or its meninges rather than to the spinal column or the discs.

The sagittal diameters of the cervical vertebrae do not appear to be closely correlated with the size of the vertebral bodies. Ratios—e.g. of the AP diameter of the cervical spinal canal to the AP diameter of the vertebral body—are therefore less useful than simple measurements. Measurements of the sagittal canal diameters in a small group of children indicate that the lower limit of the adult range may be reached as early as four or five years of age. The adult figure may be present as early as 12 years.

As noted above (Fig. 6) in the presence of postero-lateral spurs, the "minimum sagittal diameter" as measured on the lateral view may not be a true mid-line measurement. The application of the figure given above—i.e. 10 mm. or less as likely to be associated with cord compression,—must therefore be considered a correlated finding related to the mid-line value. On an empirical basis, one of the authors (L. M.) (6) has previously suggested the numerical value of 10 mm. as

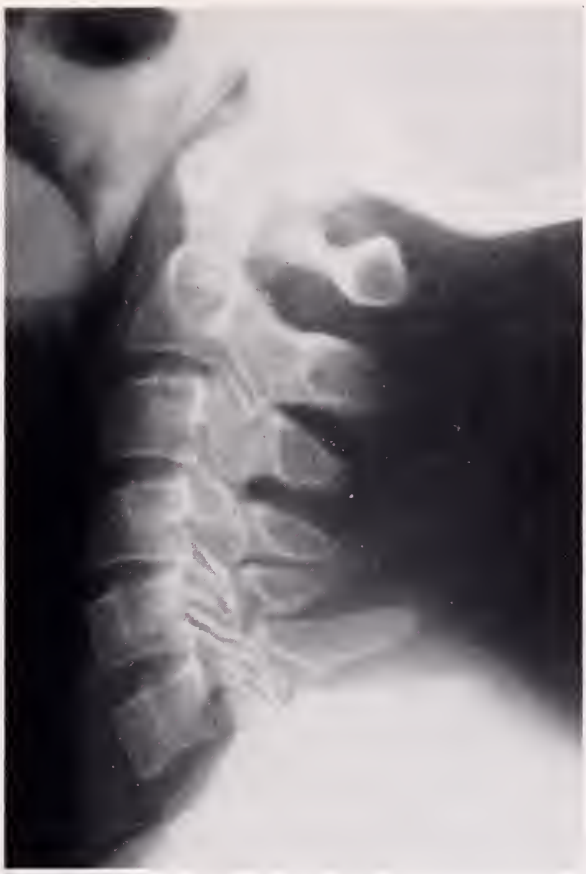

FIG. 8. Female patient, 51 years old, with moderately severe ridge syndrome. No remarkable posterior bony projections noted but the minimum sagittal diameter of spinal canal at level of C4 measured 11 millimeters. On myelography, a transverse ridge was found at the C4-C5 level with obstruction in extension.

a suitable figure below which cord compression is likely to be found. It would be desirable, in a particular case, to specify the exact point anteriorly used for the measurement of the "minimum sagittal diameter" but, in general, this is not possible without satisfactory laminagrams. As a result, the term minimum sagittal diameter may be a misnomer in specific cases and its use can be justified only on the basis of convenience in an effort to avoid more awkward terminology.

SUMMARY

1. Measurements of the sagittal diameters of the bony cervical spinal canal were made in 200 adults who showed no remarkable neurological findings or spondylotic changes. Idealized maximum, average and minimum values are given as well as the range of differences between successive cervical segments.

2. Increases in the sagittal diameters have been reported in expanding intraspinal lesions particularly in those which begin prior to complete fusion of the

laminae. In adults, local changes in the bony ring are likely to be as common as simple enlargement.

3. A sagittal diameter of 10 mm. or less due to posterior spurs is likely to be associated with cord compression. However, it is not always possible to be certain of the exact location of posteriorly projecting spurs in relation to the mid-line and intraspinal bone formation may be obscured by overlying bony structures.

4. A minimum sagittal diameter greater than 13 mm. suggests that cervical cord compression is not the result of simple spondylotic changes. An extruded "soft" disc cannot be excluded on this basis. However, in such instances, there is often a history of specific trauma and, if long tract signs are present, the sagittal diameter is likely to be small, with or without posterior spurs.

ACKNOWLEDGMENT

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ACUTE NONSPECIFIC PERICARDITIS: A SURVEY OF THE LITERATURE AND A STUDY OF 30 ADDITIONAL CASES

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Acute nonspecific pericarditis is the collective name for cases of acute pericarditis in which no systemic or local causal agent can be demonstrated, and is typically characterized by antecedent infection of the respiratory tract, chest pain, fever, tachycardia, pericardial friction rub, EKG changes, and a tendency to both pericardial and pleural effusion. However there are often many atypical findings.

It has been referred to as idiopathic, epidemic, primary, nonrheumatic, benign, relapsing, cryptic, fugitive, and recurring pericarditis. These names are all in some way descriptive of the disease.

The earliest description of this entity is probably in 1854, when Hodges, a Boston physician, wrote, "acute pericarditis is likely to occur from exposure to cold or when no exciting cause can be determined" (1). He reported the case of a 40 year old female patient with left anterior chest pain, chills, fever, weakness, nausea, and vomiting.

The disease however did not attract much attention until 1942 when Barnes and Burchell reported 14 cases of acute nonspecific pericarditis simulating acute myocardial infarction (2). Since 1942 an extensive literature has accumulated. This is probably due to the classification of acute nonspecific pericarditis as a specific entity rather than as part of some other disease.

Reeves analyzed 96 cases of all types of pericarditis in New York City and found rheumatic fever in 40%, purulent pericarditis in 20%, tuberculosis in 7%, uremia in 10%, neoplasm in 2%, and acute nonspecific pericarditis in 10% (3). Krook analyzed 64 cases of pericarditis; 33% were acute nonspecific pericarditis (4). He found the incidence of acute nonspecific pericarditis to be rising from 2 per year in 1942 to 8 per year in 1952.

Because of the increasing importance of this disease 30 cases diagnosed as acute nonspecific pericarditis at The Mount Sinai Hospital since 1942, have been reviewed. In thiss series 16 case were prior to 1950. A summary of the important findings of these cases is presented in Table I.

The diagnosis of pericarditis in 29 of the cases was made on the basis of chest pain and either typical electrocardiographic findings of pericarditis and/or a pericardial friction rub. In one case without chest pain the patient had the typical electrocardiographic changes and the pericardial rub. Other types of pericarditis were ruled out on the basis of associated signs and symptoms, laboratory tests, and the clinical course.

Age and Sex. The age range of the present series is 22 to 73 years with an average age of 48.5 years. There were 3 females giving a 10 : 1 incidence favoring males. Krook (4) reported an age range of 16 to 64 years with an average age

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TABLE I

Findings in 30 cases of acute nonspecific pericarditis

Average age	48.5
Ratio of males to females	10:1
Preceding upper respiratory infection	13 cases (43%)
Chest pain at onset	26 cases (87%)
Chest pain at some time during illness	29 cases (97%)
Radiation of pain (to one or both shoulders, back, or arm)	10 cases (30%)
Pain intensified by respiration, cough, swallowing or change in position	13 cases (43%)
Abdominal complaints during illness	2 cases (7%)
Dyspnea	11 cases (37%)
Pericardial Friction Rub	19 cases (63%)
Evidence of pericardial effusion by X-ray examination	11 cases (37%)
Coexistent pneumonitis or pleural effusion	19 cases (63%)
X-ray sign of atelectasis (Fleishner Line)	5 cases (17%)
Cough	12 cases (40%)
Fever	25 cases (83%)
Electrocardiographic changes	27 cases (90%)
ST segment elevations	15 cases (50%)
T wave changes	25 cases (83%)
Transitory Q3 waves	7 cases (23%)
Associated hypertension or history of hypertension	6 cases (20%)
Elevated sedimentation rate	20 cases (67%)
Leukocytosis	15 cases (50%)
Leukopenia	4 cases (13%)
Recurrences	11 cases (37%)

of 37. There were 3 females in his 24 cases or an 8:1 incidence favoring males. Another series from a Veteran's Hospital found an age range of 24 to 59 years with an average age of 38 (5). An army hospital reported an incidence of 3:1 favoring males and an age distribution of 18 to 63 years, with all except four, under 50 (6). Barnes and Burchell (2) reported an average age of 42 years in their series. Other reports (7–9) from civilian hospitals give an average age close to 35 years. Carmichael (10) reporting on 50 cases at the Massachusetts General Hospital stated that the disease can occur at any age and he especially stressed the "coronary age". The disease has also been reported in children (11, 12).

The average age of 48.5 years in the present series is definitely higher than that generally reported.

Preceding Upper Respiratory Infections. Comer (13) and Willius (14) were the first to stress the relation of acute nonspecific pericarditis to an antecedent upper respiratory infection, and Morrison (15) as early as 1906 reported a case of pericarditis in a child following an attack of acute follicular tonsillitis.

In the present series 13 patients (43%) had an upper respiratory infection from 3 to 30 days prior to admission. Most authors have found 50–80% of their patients with a history of preceding upper respiratory infection (2, 4–6). In some patients the infection was a simple upper respiratory infection and in others it was a severe respiratory infection usually atypical pneumonia.

In one series 29 of 50 patients had a preceding respiratory infection with a

7 to 14 day symptom free interval in one-half of these cases. In the 21 patients without preceding infections it was not infrequent for the disease to occur following unusual physical exertion or exposure to cold. In the present series 3 patients noted prior exposure to freezing lake waters.

Parker and Cooper (9) state that if electrocardiograms were taken on all patients with pneumonitis or upper respiratory infections many unsuspected cases of acute nonspecific pericarditis would be discovered.

Chest Pain. Chest pain is the dominating symptom of the disease, occurring in practically all patients (16). In the present series 26 patients (87%) presented with the chief complaint of chest pain. Three patients developed pain in the chest subsequent to their admission so that 29 of the cases (97%) had chest pain at some time during the course of their illness. In 22 patients (73%) the pain was a severe substernal and precordial pain. It usually developed abruptly.

The pain may be very difficult to distinguish from that of a myocardial infarction. Krook (4) in analyzing 54 cases of myocardial infarction in patients under 45 years found that 3 of the patients had in reality acute nonspecific pericarditis. There are however some differences in the pain of the two diseases. The pain in acute nonspecific pericarditis is usually not quite as severe as that of an infarction although at times it has been associated with shock (17, 18). The pain is usually not gripping in nature, nor is it associated with as much anxiety as the pain of infarction. Perhaps one of the most important distinguishing features is the accentuation of the pain in acute nonspecific pericarditis, by deep respiration, cough, motion, and swallowing. In one series this was found in 90% of the cases (6). This was present in 13 patients (43%) in the present series. The pain is thought to be referred from the left lateral portion of the parietal pericardium to the 5th and 6th intercostal nerves (19).

Radiation of the chest pain is usually to the left shoulder, arm, and hand, thus simulating the radiation seen in myocardial infarction. The neck, jaw, interscapular area, and epigastrium are less frequent sites of radiation. The pain to the neck and left shoulder is thought to be referred via the phrenic nerve.

In the present series 9 patients (30%) had radiation of their pain; 3 to the left shoulder, 2 to the back, 1 to the right shoulder, 1 to both shoulders, and 1 to the back and left shoulder. In addition 1 patient noted a tingling sensation which extended into the fingers of the left arm.

Abdominal Pain. Interesting and important are those patients who develop abdominal symptoms. Powers (20) reported that the frequent occurrence of abdominal pain with cramps, distention, tenderness, spasm, and vomiting may simulate a surgical emergency. He reports one case in which the abdomen was explored for possible ruptured appendix and another case explored for a possible perforated peptic ulcer. Of 13 patients in his series, 5 had significant abdominal pain. In 3 of the patients the pain subsequently migrated into the chest, neck, shoulders, and arms.

In the present series only 2 patients (7%) had abdominal symptoms. Both patients also had chest pain.

The abdominal pain is usually epigastric. It is abrupt and severe. It may last

several hours to several days, after which it is usually replaced by chest pain. The occurrence of such pain in acute nonspecific pericarditis stresses the value of routine preoperative electrocardiograms.

The abdominal pain is thought to be a peritoneal serositis which occurs as the local manifestation of a generalized polyserositis (4). The pain is referred by way of the lower intercostals.

Back Pain. One patient in the present series who entered with severe low back pain and no other localized pain, is presented below because such a complaint is quite unusual in acute nonspecific pericarditis.

Case 1. The patient, a 22 year old white male, was admitted to the neurology service of The Mount Sinai Hospital on 12/10/45, because of severe low back pain and a fever of 10 days duration. The patient stated that he awoke 10 days prior to admission with an annoying ache in his lower back. The pain gradually got more severe and began to radiate down both legs. Five days prior to admission a fever developed and persisted up to admission. There was no history of cough, dyspnea, or chest pain.

The patient had a history of osteomyelitis of the 4th lumbar vertebrae, treated at The Mount Sinai Hospital 12 years prior to the present admission. He was well in the interim.

Physical examination on admission was completely negative.

Laboratory data. Hemoglobin 13.0 gms. per cent. WBC 10,000 and later dropping to 7,000. Urine negative. BUN 12 mgm. per cent. Enteric agglutinins negative. Heterophile 1:8. Blood cultures did not grow out any organisms. Chest X-ray negative. X-rays of the lumbosaeral spine showed no demonstrable evidence of an osteomyelitis. ESR was 70 mm./hour. Patch test was negative. Two lumbar punctures were negative. Electrocardiograms showed elevation of the ST segment in all limb leads which returned to isoelectric within 5 days, at which time inversion of the T waves developed. The T wave inversions persisted until the time of the patient's discharge 17 days after admission.

The patient was suspected on the neurological service to have recurrence of his osteomyelitis. When this could not be demonstrated he was transferred to the medical service. Two days later a harsh systolic friction rub was heard for the first time. The rub lasted 4 days and then disappeared. The patient's fever did not respond to penicillin or sulfa drugs and persisted for 14 days. The low back pain subsided during the second hospital week and the patient was completely asymptomatic afterwards. He was discharged 17 days after admission.

Comment. This case is presented because it points out the unusual localization of pain in a patient with acute nonspecific pericarditis. No other case in which severe back pain was a presenting complaint could be found in the literature.

Dyspnea. Dyspnea is another common symptom. In the present series it was present in 11 patients (37%), and in one patient it was the chief complaint. Krook reported dyspnea in 41% of his patients (4). Although a pneumonia is frequently associated with this disease, many patients with dyspnea show no roentgen signs of pulmonary congestion. In these patients it is felt that the accentuation of pain on respiration causes splinting of the chest, which in turn causes dyspnea (5, 19). Mechanical compression of the lungs and bronchi is also thought to contribute to the dyspnea (19).

Pericardial Friction Rub. The widespread pericardial friction rub is the characteristic sign of acute nonspecific pericarditis. It was present in 19 patients (63%) in the present series. It is reported in from 70–95% of cases in the litera-

ture (4, 5, 6, 9, 21). The duration of the rub is usually one day to four weeks, and the mean duration is reported to be 9 days (21). In the present series 6 patients had the rub 7 days or longer and 9 patients had it 3 days or less. The rub appears early compared to that which develops following myocardial infarction, and lasts much longer. It is typically present in the first few hours and precedes the electrocardiographic changes. However, in one of the patients in the present series the rub developed after the first week of admission and in general a correlation between the onset of the rub and the electrocardiographic findings was not found. In two patients the rub reappeared for short intervals after having disappeared for a few days. The rubs are characteristically loud and heard over a large area of the precordium in contradistinction to the softer, localized rubs which develop after infarctions.

Enlargement of the Heart. Enlargement of the heart is a frequent finding in acute nonspecific pericarditis. It has been reported in from 33–68% of patients (4, 9, 10, 19). In the present series 15 patients (50%) had enlarged hearts by X-ray examinations. However, the size of the heart did not change during the illness in 4 patients, so that pericardial effusion probably was not the cause of the cardiac enlargement in these patients.

The enlargement is most commonly due to pericardial effusion, although some have postulated acute dilatation of the heart as an occasional cause (22). If an effusion is present and it is tapped, the fluid is most often sanguinous (23). In the present series there were no pericardial taps.

The cardiac enlargement may persist for a week up to two months (7). Wolff (22) states that in his 5 patients with cardiac enlargement there was return to normal size within one month. In the present series 11 patients had return to normal heart size in anywhere from 5 to 35 days with an average of 18 days.

Evidence of cardiac compression due to tamponade is not commonly reported, although venous distention and paradoxical pulse occasionally are noted (24). In the present series there was no evidence of tamponade although 2 patients showed transient rises in venous pressure.

Dressler (8) reports transient gallop rhythms and even congestive failure. In one case these subsided together with the manifestations of pericarditis and pleurisy, however in another the failure outlasted the pericarditis by several weeks. A transient gallop was observed in one patient in the present series.

Pulmonary Findings. Coexistent pneumonitis and pleuritis are often associated with acute nonspecific pericarditis (4, 9, 25, 26). The present series had 19 patients (63%) with pulmonary findings. The pleuritis may be dry and associated with pleural rubs, or wet and associated with effusions. Pleural effusion has been reported in 25% of cases in the literature (27). In the present series 12 patients (40%) had effusions. The effusions are usually left sided or bilateral. Unilateral right sided effusions are quite rare (8, 10). In the present series 2 patients had unilateral right sided effusions.

Four pleural taps were done and amber fluid aspirated in all cases. The fluid was high in protein content. Culture of the fluid for the tubercle bacillus was negative in all cases.

In the present series 5 patients (17%) had Fleishner lines in the left lung base on roentgen examination.

Cold agglutinins were negative in 16 out of 17 patients. Cases with significant titers have been reported (23). Streptococcus MG titers were negative in 6 patients.

There were 11 patients (30%) with significant cough in the present series.

Fever. Fever occurs in most patients with acute nonspecific pericarditis. In the present series 25 patients (83%) had fever. It lasted from 2 days to 3 months with an average length of 2 weeks. It is characteristically a more irregular and recurrent fever than seen after myocardial infarctions. In some cases the fever was as high as 105F.

Electrocardiographic Changes. The electrocardiogram shows abnormalities in over 80% of the patients with acute nonspecific pericarditis (4, 28). In Parker and Cooper's series (9) all 22 patients had cardiographic changes. However clear cut cases of acute nonspecific pericarditis without changes in the electrocardiogram have been reported (16, 21, 28). In the present series 27 patients (90%) had electrocardiographic changes.

ST segment elevations and T wave inversions, common to all types of pericarditis, were the most consistent changes in the present series. These are believed to be due to the pericarditis per se, the injury to the subepicardium and perhaps even myocardium, and to the amount of pericardial effusion (28–30). However, the subepicardial myocarditis probably causes most of the ST segment and T wave changes (27).

The ST segment is elevated with an upward concavity and this is present usually in all standard leads. These ST segment changes are very transient and may disappear in a day, usually within a week (4). In the present series 15 patients (50%) had ST segment elevations, and all except one returned to normal within 8 days. In one patient the ST elevation persisted for 6 weeks. A case is reported in which ST elevations persisted for 6 months (31). The ST elevation differs from that seen in myocardial infarction because it is present in two or more limb leads and there are no reciprocal ST depressions (32), except in one case reported by Barnes and Burchell (2).

The T waves are high and after one week decrease or become inverted (33). In the present series 25 patients (83%) had T wave changes. In 23 cases there was T wave inversion and in 2 cases a marked elevation of the T waves. In 15 of these cases the T waves returned to normal within a week to 3 months, the average being 3 weeks. In the remaining 10 patients T wave changes were still present at the time of discharge. T wave abnormalities persisting for months and even years have been reported (10, 27).

It has been reported that the T wave inversions seldom occur till after the ST segment returns to isoelectric. However, in many cases of the present series there were concomitant changes.

A low voltage QRS is seen in patients with significant pericardial effusions.

A very important diagnostic point is that permanent Q waves do not develop in acute nonspecific pericarditis. However, in the present series 7 patients

(23%) developed transitory small Q3 waves, and it is important to emphasize that small Q waves can be seen in this disease as a normal variant of an individual's tracing. It is conceivable that a patient with a past myocardial infarction may develop acute nonspecific pericarditis, and thus present an electrocardiogram with significant Q waves.

In the present series 6 of the patients were hypertensive, and in 3 cases the diagnosis of acute nonspecific pericarditis was made in patients with electrocardiographic changes suggesting left ventricular hypertrophy. One of these patients will be described in detail.

Case 2. The patient, a 62 year old white male, was readmitted to The Mount Sinai Hospital on 3/9/52 because of one week of nonproductive cough and three days of fever and chest pain. Three nights before admission the patient noted the onset of an elevated temperature to 102 F., and severe precordial pain. The fever persisted until admission although the pain became less intense.

Past history. The patient had multiple previous admissions for parotitis, otitis media, and prostatic hypertrophy. A diagnosis of Sjogren's syndrome was made on a previous admission. The patient had been hypertensive for 10 years. Slight cardiomegaly and a soft systolic murmur had been present on previous admission. There was no past history of chest pain or symptoms of cardiac failure.

On admission the patient appeared acutely ill. The blood pressure was 140/90 and the temperature 100 F. The patient had bilateral blepharitis, scarred tympanic membranes, and a perforated nasal septum. There was no neck vein distention. There were harsh breath sounds bilaterally and rales in both lung bases. The heart was enlarged to 2 cm. beyond the mid-clavicular line. A loud grating leathery rub, obscuring all heart sounds, was heard over the entire precordium. Except for an enlarged non-tender liver the remainder of the examination was negative.

Laboratory Data. Venous pressure 55 mm. rising to 75 mm. on right upper quadrant pressure. Circulation time was 18 sec. Urine negative. Wasserman negative. Hemoglobin 13.0 gms. per cent. WBC 11,000 dropping to 5700 at time of discharge. ESR 24 mm./hour rising to 58 mm./hour and falling to 19 mm./hour at discharge. BUN 18 mg. per cent. Cholesterol 321 mg. per cent. Blood culture failed to grow out any organism. Cold agglutinin and Streptococcus MG titers were negative. Chest X-rays showed increase in the transverse diameter of the heart and increased lung markings. Subsequent X-rays were without change.

An electrocardiogram taken in 1951, a year prior to admission, had shown ST segment depression and T wave inversions in leads I, AVL, V5 and V6, as well as small Q waves in I, II, V5, and V6. On admission (3/9/52) the EKG showed ST elevations in II, III and V1–V4 and was otherwise similar to the tracing in 1951. On 3/10/52 auricular fibrillation was present. On 3/13/52 RSR had returned and the ST elevations were beginning to return toward the isoelectric line. On 3/25/52 there were no longer any ST elevations although the ST depressions and Q waves previously noted had persisted unchanged. A follow-up tracing in 1953 was completely unchanged from the baseline tracing of 1951.

The patient ran a febile course in the hospital with spikes to 103 F. daily. The pericardial rub disappeared 2 days after admission and the systolic murmur heard in previous years was again audible. The patient was treated with aureomycin and chloromycetin without response. After 2 weeks, however, the temperature gradually returned to normal and the lungs cleared. Patient was discharged 3 weeks after admission.

Follow-up. The patient was again admitted on 12/3/53. This time because of massive hematemesis. This was controlled but the patient developed progressive ascites and died on 1/6/54. At post-mortem examination the patient was found to have Laennec's cirrhosis and esophageal varices. The heart showed a fibrinous pericarditis. There was no evidence of myocardial infarction. The coronary vessels showed arteriosclerotic changes but no evidence of occlusion. Microscopic sections revealed scattered fibrosis but no definite area of infarction.

Comment. This case is presented because it represents a case of acute nonspecific pericarditis occurring in a patient with hypertensive and arteriosclerotic heart disease. Electrocardiographic evidence of pericarditis was superimposed on an already abnormal electrocardiogram. It is the author's feeling that the diagnosis, although difficult, can be made.

The finding of a fibrinous pericarditis at autopsy without evidence of infarction suggests that the fibrinous reaction was related to the previous attack of acute nonspecific pericarditis. It has been reported that infections cause most cases of fibrinous pericarditis (34).

Vectorcardiography. In the present series three patients had vectorcardiographs. In two of the cases there was an open loop vector, directed inferiorly, anteriorly, and to the left. This was interpreted as consistent with the diagnosis of pericarditis. In the other case, a patient with a left bundle branch block, the vector was of no help.

No other cases could be found in the literature in which vectorcardiograms were taken. It is suggested that this is a valuable adjunct in the diagnosis of acute nonspecific pericarditis, and should be used in those institutions where it is available.

Cardiac Arrythmias. Cardiac arrythmias are generally infrequent although auricular fibrillation (4), paroxysmal auricular flutter (9), supraventricular tachycardia (5), and electrical alternans (35) have been reported.

In the present series 8 patients (27%) developed arrythmias. In 3 cases there was a transitory auricular fibrillation and in one case the fibrillation persisted through the time of discharge.

Sedimentation Rate. An elevated sedimentation rate is frequently present in acute nonspecific pericarditis. In the present series 20 patients (67%) had abnormal sedimentation rates. In 5 patients the sedimentation rate reached 100 mm./hour (Westergren).

White Blood Count. In most series of acute nonspecific pericarditis, leukocytosis has been a significant finding (4, 21). In the present series 15 patients (50%) developed a leukocytosis, commonly between 10,000–15,000 cells/cm. However, there were 4 patients (13%) in whom a leukopenia was noted.

Relapses. Acute nonspecific pericarditis is a disease characterized by relapses. It is not uncommon for the patient to be symptom free for a few days to a few months and then develop an acute exacerbation of pain, frequently with fever and sometimes with return of the rub. There were 33% recurrences in one month in Krook's series (4). Recurrences may occur even after years and a case is reported with 19 seizures of sudden severe substernal pain, accentuated by respiration (36). 11 patients (36%) of the present series either had previous or developed subsequent attacks of acute nonspecific pericarditis. In view of the fact that follow up was not adequate in most cases in the present series, the above percentage is probably much higher.

Recurrences usually were not preceded by antecedent respiratory infections. ST segment and T wave fluctuations usually were present during the recurrence.

Etiology. In 1909 Christian (37) stated, "these idiopathic pericardidites are probably true bacterial infections, but the organisms have either died out, or

are of a type not easily cultured". Through the present time we have still been unable to culture any organisms in this disease, either from the pericardial effusion or from the blood. It is now however generally felt that acute nonspecific pericarditis is a viral disease, although a specific virus has as yet not been identified. Viruses can cause pericarditis and a case of pericarditis in a patient with lymphogranuloma venereum is reported (38). Some feel that the Coxackie virus which causes Bornholm's disease may be implicated in acute nonspecific pericarditis, since both diseases run a benign course with recurrences, severe chest, abdominal, and shoulder pain. One case of Bornholm's disease complicated by acute nonspecific pericarditis has been reported (11). In one of the present cases the Coxackie virus was carefully searched for, but was not found.

A relation of acute nonspecific pericarditis to infectious mononucleosis has been reported (39), and a patient in the present series was thought to have concomitant infectious mononucleosis. However, he had an insignificant heterophile titer as did the 6 other patients tested.

The virus of atypical pneumonia has also been implicated and 3 cases of pericarditis in connection with viral atypical pneumonia have been described (26). However, in 11 patients tested for cold agglutinins Krook (4) only found one with a significant titer. In the 17 patients tested in the present series there was also one with a significant titer. It is theorized that perhaps a viral pneumonitis is a manifestation of a generalized disease affecting many organs and expressing itself in serositis. It has been postulated that the pericardium becomes involved by direct spread of the infecting organism from adjacent lungs and pleura.

The main evidence supporting the virus theory is the antecedent upper respiratory infection, the occasional occurrence of the disease in epidemics, and the benign course it usually runs. Against the viral etiology is the lag between the respiratory infection and the pericarditis and the leukocytosis.

Tuberculosis has also been postulated as an etiologic explanation for acute nonspecific pericarditis. Against it is the fact that pericarditis is usually painless in tuberculosis and does not usually run a benign course. Examinations of sputum, gastric washings, and effusion fluid have invariably failed to show the tubercle bacillus. Tuberculin tests are often negative (10). Of the 10 patients tested in the present series, 5 were tuberculin negative.

Toxins have been suggested as causing acute nonspecific pericarditis. This would make it similar to the pericarditis seen in uremia. No strong evidence supports this theory.

A hypersensitivity theory has been advanced, and to support it is the occurrence of the pericardium as a shock organ in some cases of serum sickness (40), and in other allergic conditions (41, 42). However, in these cases there is usually an eosinophilia and the patients respond to antihistaminics. No patients in the present series had significant eosinophilia.

Disseminated lupus erythematosis should always be considered in young patients with pericarditis. Lupus preparations were done on 6 patients in the present series and were negative in all.

Recently Dressler (8) has tried to make a strong case for the rheumatic

etiology of acute nonspecific pericarditis, by showing its similarity to the post-commissurotomy syndrome. Clinically both diseases are quite similar and according to Dressler the prognosis is good in both diseases, especially when treated with cortisone. Since the post-commissurotomy syndrome is believed to be rheumatic in etiology, it is reasoned that acute nonspecific pericarditis is also a rheumatic manifestation. Dressler feels that rheumatic pericarditis in adults is not nearly as serious as the rheumatic pancarditis which develops in children, and this would explain the benign course and good prognosis. The lack of serologic tests, such as the antistreptolysin titer, in this disease is considered unimportant because in the post-commissurotomy syndrome there is a conspicuous lack of positive serologic tests. Further evidence is offered by dramatic responses to salicylates reported in the foreign literature.

Against Dressler's arguments are the lack of any pathological evidence of rheumatic disease in cases of acute nonspecific pericarditis. It is also very rare for pericarditis to occur in rheumatic fever before joint manifestations (24, 43). It is probably true that some cases of acute nonspecific pericarditis, especially those with a past history of rheumatic fever, are rheumatic pericarditis. There is still, however, insufficient evidence to attribute all cases to rheumatic fever. In the present series none of the patients had a past history of rheumatic fever. Anti-streptolysin titers were negative in the 5 patients tested. Only one patient had joint complaints and these were all subjective. This patient concomitantly developed a rash and his joint pains were then attributed to a penicillin sensitivity reaction. None of the patients had any prolongation of the PR interval or changes in the QRS complex so often found in rheumatic carditis.

Treatment. The treatment is usually symptomatic. Patients are usually ambulated as soon as their symptoms allow, although activity is limited. The patients in the present series had an average hospital stay of 1 month.

There are reports in the literature of treatment with penicillin (44). Taubenhaus and Brams (45) reported improvement in 3 patients on aureomycin. Recently there have been reports of dramatic improvement with cortisone (12, 46). Most authors, however, report no response to antibiotics or steroids (6, 9).

In the present series 12 patients were treated with various antibiotics without any response. Penicillin, chloromycetin, streptomycin, aureomycin, and achromycin were tried. Salicylates were used without response in 3 patients. In one patient PAS and isoniazid were used prophylactically although there was no positive evidence of tuberculosis and all cultures were consistently negative.

One patient was treated with cortisone and a definite response was noted. The patient's fever immediately fell and there was diminution of symptomatology. It is suggested that further trials with steroids be cautiously attempted in this disease.

Prognosis. The prognosis is good in acute nonspecific pericarditis, although two fatal cases have been reported (47, 48). Both patients presumably died of cardiac tamponade. In one case the patient was treated for a myocardial infarction and put on anticoagulation therapy (47). He was found at autopsy to have a primary pericardial disease with hemorrhagic changes and an element of tam-

ponade. This case stresses the important differentiation between acute nonspecific pericarditis and myocardial infarction, especially when anticoagulation therapy is contemplated. Master (49) suggests withholding anticoagulants if there is any doubt in diagnosis. In the present series 2 patients were anticoagulated. In one patient it seemed that the pericardial friction rub began to increase in intensity with the start of the anticoagulant, so the drug was discontinued. In the other patient anticoagulation was continued throughout the patient's hospital stay. Fortunately no complications developed.

In a follow-up of 43 patients, 12 for over 9 years, Carmichael (10) found that the majority were in excellent health, with only 6 having electrocardiographic abnormalities. In one series no complications or permanent changes were found on follow-up (7). However, Godfrey (27) reported on three patients with myocardial damage, perhaps permanent, long after the initial attack of acute nonspecific pericarditis. The patients mainly complained of dyspnea and their tracings showed T wave inversions. In the present series 10 patients left the hospital with T wave inversions but long term follow-ups are not available. It has been suggested that perhaps some cases of Fiedler's myocarditis were originally acute non-specific pericarditis in whom permanent changes subsequently developed.

The overall prognosis in acute nonspecific pericarditis is very good although there have been reports of cases of chronic constrictive pericarditis developing in patients who give a history of a previous acute pericarditis (4, 50). The etiology of chronic constrictive pericarditis is obscure, although most cases are thought to follow tuberculous infections. In some of the obscure cases it is suggested that careful history will reveal an earlier attack of acute nonspecific pericarditis. However, the relationship, if any, between the two diseases has not been proven.

Summary. 30 cases of acute nonspecific pericarditis seen at The Mount Sinai Hospital since 1942 have been reviewed. The findings are compared with those of other authors.

In the present series a higher average age of 48.5 was found. It is stressed that the diagnosis of acute nonspecific pericarditis in patients who have evidence of hypertensive or arteriosclerotic heart disease, although difficult, can be made.

A case is presented in which the only complaint was severe low back pain. It is believed that this is the first such case in the literature.

In view of the dramatic responses to steroid therapy reported recently, and the apparent response of one patient in the present series, further study with these drugs should be attempted.

The suggested etiologies of this disease have also been reviewed.

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PULMONARY ROENTGEN FINDINGS IN FAMILIAL DYSAUTONOMIA

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In 1949 Riley, Day, Greeley and Langford (1) described a new syndrome in children which is characterized by numerous manifestations of autonomic dysfunction. The principal and almost constantly present features of this syndrome include: defective lacrimation, erythematous skin blotching, excessive perspiration, drooling, emotional instability, motor incoordination, hyporeflexia, and relative indifference to pain. Other features of the syndrome not always present in all patients but frequently the major presenting complaints include: hypertension, cyclic vomiting, frequent pulmonary infection, unexplained fever, breath holding spells, urinary frequency, mental retardation, convulsions and corneal ulcerations. In all of the cases reported to-date, the patients have been of Jewish extraction and study of the family histories of affected siblings strongly suggests that the condition may be transmitted as a mendelian recessive characteristic.

Although in 1949 Riley, Day, et al. (1) originally reported five cases, by 1952 Riley (2) was able to report a total of 33 patients with this syndrome collected from various sources. Moloshok and Reuben (3) have recently reported 16 additional cases.

The clinical aspects of familial dysautonomia have been previously reviewed (1–3) and it has been noted that the generally widespread nature of the neurogenic symptoms is sufficiently protean to create a difficult problem in differential diagnosis. The presenting symptoms may simulate other conditions of the pulmonary, circulatory, gastrointestinal or central nervous systems. A correct diagnosis may be particularly difficult in children under the age of two years before all of the features of the disease are apparent. When the prominent features of the disease become evident, however, the diagnosis can be made with assurance. In infants, there is frequently difficulty in sucking and swallowing with regurgitation or vomiting. Apneic or cyanotic spells may occur with hypothermia. These patients are usually weak, show diminished activity, excessive oral secretions and may have respiratory distress suggesting cerebral birth injury, atelectasis or pneumonia. High fever may occur with or without abnormal signs in the chest. The history of crying without tears or the observation of defective lacrimation in association with excessive perspiration, skin blotching, diminished reflexes and retardation of motor development are important diagnostic criteria. Moloshok and Reuben (3) have stressed the differential diagnostic aspects of the syndrome. The nature of the pulmonary roentgen findings encountered in a series of 20 children with this condition are the basis of this report.

Pulmonary manifestations, although not constant, are a prominent feature of the disease and occur to a significant degree in a majority of the patients.

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Riley found frequent pulmonary infection to occur in 74 per cent of his patients (2) and 13 of the 20 children in our series experienced noteworthy pulmonary difficulty. Recognition of the clinical and roentgenologic nature of the respiratory difficulties that occur in dysautonomia will often provide a clue to an early diagnosis of this congenital disorder of the central nervous system.

Pulmonary involvement is most frequently characterized by repeated episodes of pneumonia or bronchitis and is very often the reason for hospitalization. Respiratory symptoms most commonly begin during infancy and often suggest the presence of fibrocystic disease of the pancreas. A frequent finding and one which would suggest the possibility of dysautonomia is the sudden appearance of moist rales in the chest at the time of feeding. This is often mistaken for aspiration and in several of our patients led to esophagography for suspected tracheo-esophageal fistula. Moist rales may also appear suddenly following any type of emotional disturbance. In some cases, pulmonary disease may not be manifested clinically but may be discovered on roentgen examination made for investigation of unexplained fever.

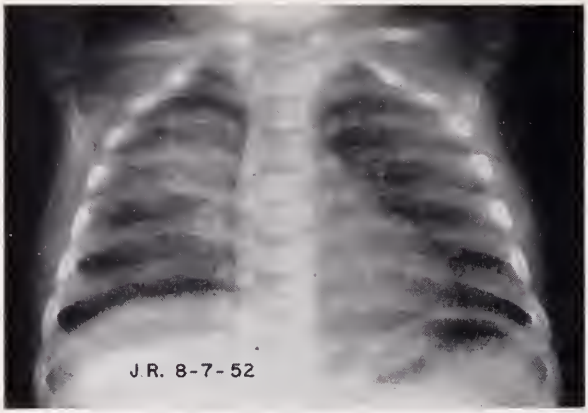
Episodes of respiratory difficulty are usually characterized by fever, cough and dyspnea. The physical signs are those associated with diffuse or localized bronchopneumonia or with asthmatic bronchitis.

Roentgen findings in the chest are not specific and vary during repeated episodes of pulmonary difficulty but are sufficiently suggestive to warrant investigation for autonomic dysfunction. They are represented by varying combinations of interstitial infiltration, emphysema and atelectasis. At different times, one or the other of these processes may dominate the appearance of the lungs. The interstitial infiltrations tend to be chronic, more or less diffuse, and usually but not always, involve both lungs. On occasion, there may be small nodulations of acinar involvement and patchy densities of lobular pneumonia or atelectasis may appear and disappear over relatively short periods of time. Over a period of prolonged observation, the distribution of the infiltrations may change rapidly or slowly but in the cases we have followed the lungs have not reverted to a completely normal appearance at any time during observation. An atelectatic pneumonitis of the right upper lobe is particularly frequent in infants and very young children and may be the only pulmonary roentgen manifestation of the disease for some time. When seen, it often persists for one or two months or longer.

Due to partial obstruction of the smaller bronchi, there is often an associated emphysema. In most cases this involves both lungs but it may be unilateral, lobar or even focal. While emphysematous changes may be outstanding at times in some cases, they may be notably absent or not demonstrable in others. On the basis of the cases we have studied we have the impression that emphysema may be more common in the earlier age groups.

While small focal areas of atelectasis may appear and disappear rapidly, larger areas of atelectasis, involving a lobe or lobar segment tend to persist over a period of months. In this series, gross atelectatic changes were noted in the right upper and middle lobes and in the left lower lobe.

The roentgen features of dysautonomia are well demonstrated in the following illustrative cases.



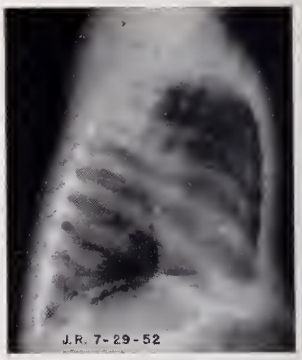


FIG. 1 FIG. 2

FIG. 1. Case 1: Pneumonitis of right upper lobe Infiltrations extending into right lower lung.

FIG. 2. Case 1: Lateral projection showing emphysematous chest with elevation of anterior chest wall.

CASE REPORTS

Case 1

J. R., was first admitted to the hospital on July 7, 1952 at the age of 6 months. Since the age of 2½ months he had had almost daily temperature elevations to 100–102°F., especially in the mornings.

Physical examination on admission revealed a temperature of 101.4°F., respiration of 40 and a heart rate of 200. The blood pressure was 120/84. On crying there was marked moistness of both conjunctival sacs but no tears as such were formed. The reflexes were hypoactive. Laboratory findings were not remarkable. The Wasserman and Mantoux tests were negative. Nose and throat cultures were negative on four occasions, and blood cultures were sterile. Stool trysin was normal. X-ray examinations of the chest made at intervals during the hospital stay showed an infiltration extending into the right upper and lower lung (Fig. 1). At times there was evidence of pulmonary emphysema involving both lungs (Fig. 2).

The patient was in the hospital for a total of 43 days. During that time the density in the right upper lobe persisted despite 600,000 units of penicillin per day for 4 weeks and 200,000 units of penicillin per day by aerosol for 13 days. His blood pressure varied from 70/40 to 140/90 and he showed a marked tendency to excessive perspiration and drooling. There was only one episode of skin blotching and that occurred symetrically on the chest on the day of discharge.

On September 16, 1954 he was again admitted to the hospital because of recurrent fevers. At this time he was eight months of age. With the use of penicillin and parenteral fluids he became afebrile after three days in the hospital and remained without fever during his stay. An erythematous blotching of the skin occurred during feedings and absence of tears was again noted. A Lipiodol esophagogram was negative. Bronchoscopy was performed and revealed no secretion in the right main bronchus or in the right upper lobe bronchus. The right upper lobe bronchus appeared slightly narrowed at its orifice. No intramural lesions were noted. The bronchus was flushed with sterile saline which was cultured. Enterococcus and aerobacter aerogenes grew out. X-ray examination of the chest on October 13, 1952 showed a triangular shaped density extending into the right upper lobe apparently representing an area of pulmonary infiltration and atelectasis. Involvement of the right upper lobe had persisted at least from the first examination made on July 11, 1952 and was still present when the patient was discharged on October 16, 1952 (Fig. 3).

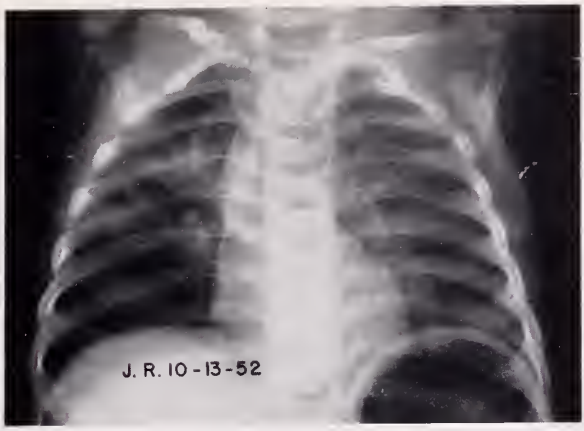


FIG. 3. Case 1: Persistent pneumonitis of right upper lobe

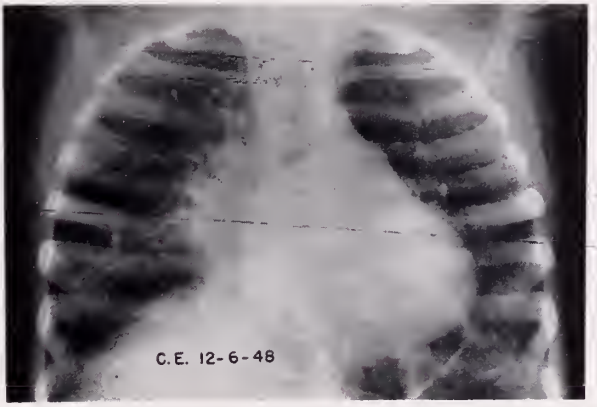
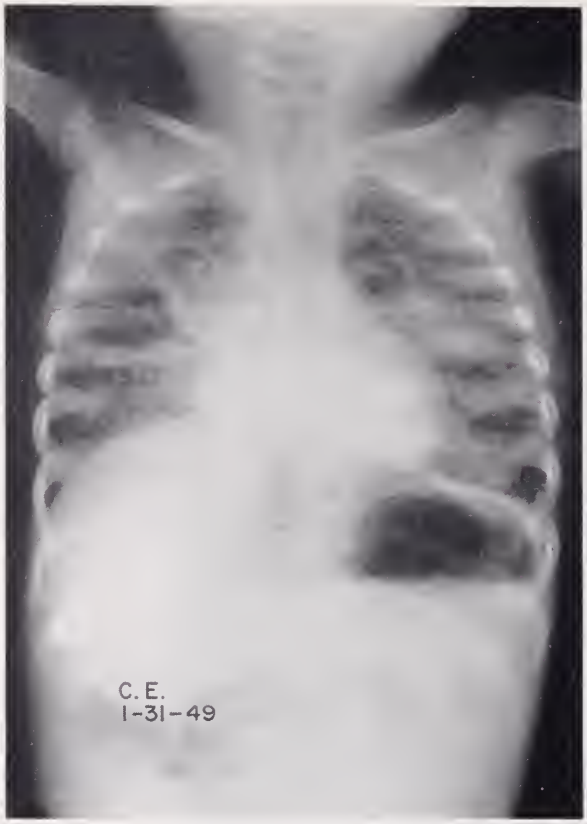


FIG. 4. Case 2: Pneumonitis at root of right lung extending into upper and lower lobes. Emphysematous right upper lobe protrudes into superior mediastinum. Both lungs are emphysematous.

Case 2

C. E., was an 18-month-old white female infant admitted to The Mount Sinai Hospital on November 29, 1948 with a history of frequent episodes of pneumonia since eleven days of age.

During a five months period of hospitalization there were recurrent periods of acute pulmonary crises characterized by marked dyspnea and cyanosis. On examination during these attacks, the temperature ranged from normal to 40.5°C. There was profuse diaphoresis and blotching of the skin. The chest was maintained in an emphysematous position and was hyperresonant on percussion. There were diffuse fine and medium moist rales bilaterally with asthmatic type expiratory wheezes. The blood pressure was normal. X-ray examination of the chest showed a homogeneous density at the root of the right lung extending into the right upper and lower lobes. There were also infiltrations extending into the left lower lobe. Both lungs were emphysematous. The diaphragms were depressed and the right lung was herniated into the upper mediastinum (Fig. 4). Subsequent examinations showed an atelectatic pneumonitis of the right upper lobe and development of patchy areas of pneumonia or atelectasis in lungs which contained interstitial infiltrations and showed emphysema (Figs. 5 and 6). After about three months there was incomplete resolution of the right



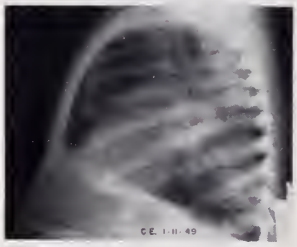


FIG. 5 FIG. 6

FIG. 5. Case 2: Atelectatic pneumonitis of right upper lobe. There are diffuse bilateral interstitial infiltrations with patchy areas of pneumonia or atelectasis.

FIG. 6. Case 2: Lateral projection showing elevation of upper anterior chest wall by emphysema and displacement of horizontal and long fissures by emphysematous right middle lobe. Infiltrations extend from lung root into upper and lower lobes.

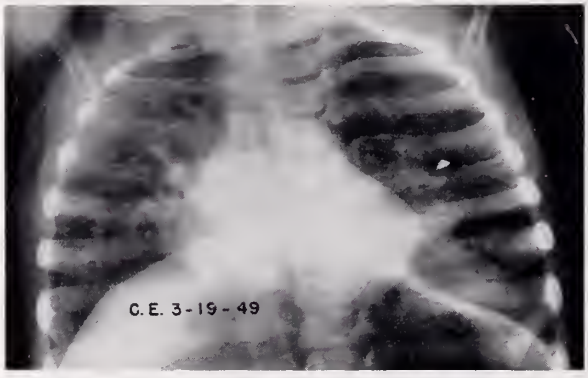


FIG. 7. Case 2: Incomplete resolution of right upper lobe lesion. Atelectasis of left lower lobe. The vascular markings are separated and distorted by emphysematous changes. The stomach is hugely dilated.

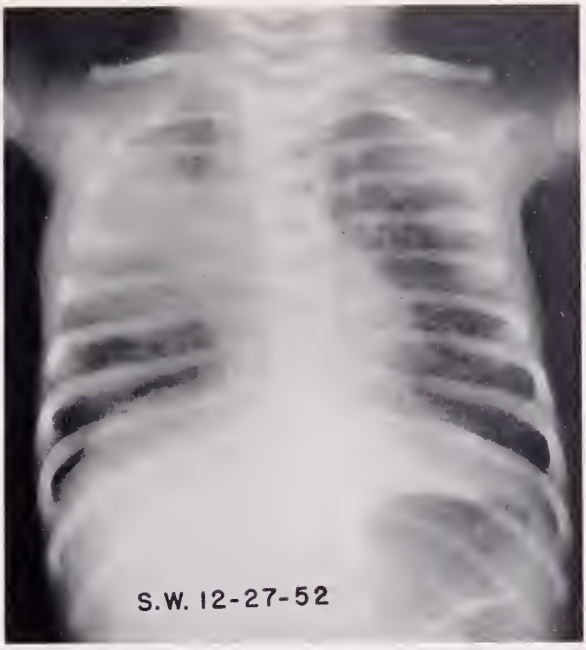


FIG. 8. Case 3: Atelectatic pneumonitis of right upper lobe with retraction of heart and mediastinum to the right. Diffuse interstitial infiltrations in both lungs.

upper lobe lesion but there was an atelectasis of the left lower lobe and emphysematous changes in both lungs (Fig. 7).

An oesophagogram was normal. Bronchoscopy revealed all bronchi to be patent; there were thick viseid secretions in the lower trachea and both main bronchi. Culture of these secretions revealed only monilia albicans.

The patient was treated during various periods with penicillin, sulfadiazine or aureomycin.

She was discharged during a period of relative improvement and was taken to Arizon- for climatotherapy. She fared poorly there and returned to New York where she was hospitalized elsewhere. She continued to have periods of respiratory distress associated with marked hyperpyrexia to 41.5°C. Elevated blood pressure was noted periodically and skin blotching was more prominent. Defective lacrimation was noted as well. The patient died at 2½ years of age following a prolonged period of hyperpyrexia.

Case 3

S. E., was seen shortly after birth because of a weak cry and marked retraction of the chest. A moderate degree of inspiratory stridor was present at times. Laryngoscopy and bronchoscopy revealed that the larynx and trachea appeared to collapse with inspiration. The respiratory pattern gradually improved but the infant took feedings poorly and failed to gain weight.

A roentgenogram of the chest was made at five weeks of age because of continued feeding difficulty and a low grade fever. This showed a lesion which was considered to be an aspiration pneumonia of the right upper lobe. At five months of age she began to run an irregular fever which was treated with penicillin, gantrisin, aureomycin and terramycin without success. Periodic fever ranging between 39-40°C has continued to be a problem since that time. Other manifestations of familial dysautonomia have become evident with time, in

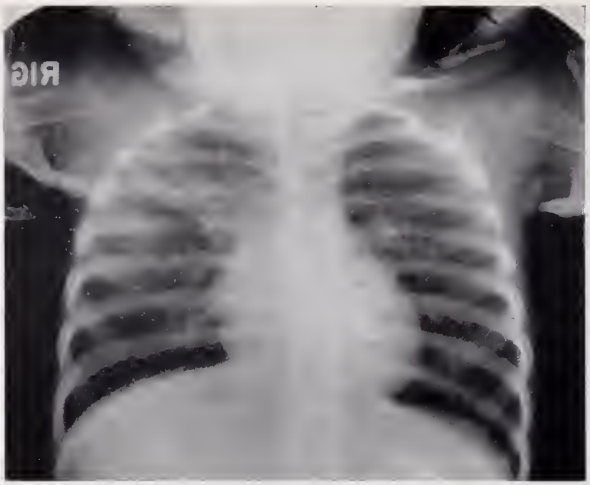


FIG. 9. Case 3: Pneumonitis of right upper lobe with bilateral interstitial infiltrations. The lungs appear emphysematous.

cluding absent tears, drooling, blotching of the skin, excessive diaphoresis and retarded motor development.

Numerous roentgenograms of the chest have shown, at various times, evidences of pneumonitis in the right lung, bilateral bronchopneumonia and varying areas of atelectasis usually of the right lung (Figs. 8 and 9). Occasionally moist rales have been audible bilaterally but physical signs have been meager as compared with the roentgen findings.

Case 4

D. K., a 2½-year-old white male, was first admitted to The Mount Sinai Hospital on August 3, 1950. There was a history of eight respiratory infections during the first two years with frequent "croup" and elevated temperatures ranging to 40°C. Three months before admission he awoke one night, screamed, had considerable difficulty in breathing, and became intensely cyanotic. He was admitted to another hospital where he was treated for croup, and improved. Roentgenogram of the chest revealed a persisting area of infiltration in the right upper lobe. A few days after discharge he was admitted to another hospital with a generalized convulsion and fever of 40.5°C. Diffuse signs were present in the chest and a roentgenogram revealed bilateral pulmonary infiltration and atelectasis of the right upper lobe. During the next ten weeks there was what was considered to be a "septic temperature" despite treatment with various combinations of penicillin, aureomycin, streptomycin, chloramphenicol and sulfadiazine. There were persistent signs in the chest and he was transferred to The Mount Sinai Hospital.

The child remained almost continuously in the hospital for the next ten months during which time he continued to exhibit irregular bouts of fever ranging from 39 to 41.5°C as well as periods of hypothermia with temperatures around 35°C. At intervals he became acutely and seriously ill during episodes of respiratory distress, with extreme dyspnea and cyanosis associated with moist wheezing respirations. Examination of the chest revealed diffuse medium and coarse moist rales and marked expiratory wheezing. At times there were localized areas of dullness and bronchial breath sounds. It was noted that he would develop moist rales in the chest when drinking fluids or when he was emotionally upset. On these occasions there was marked diaphoresis and blotching of the skin. He drooled excessively at all times.

X-ray examination of the chest made on admission showed a triangular shaped atelectatic

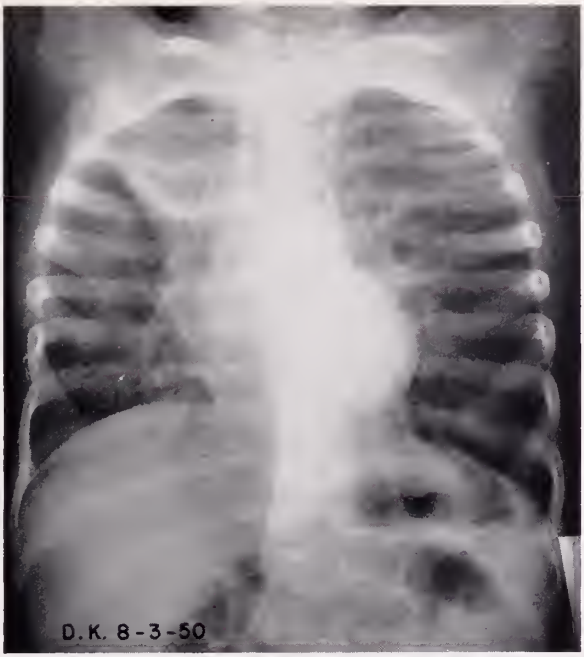


FIG. 10. Case 4: Atelectatic pneumonitis of right upper lobe associated with diffuse interstitial infiltrations extending into both lungs.

pneumonitis of the right upper lobe. Associated with this there were diffuse interstitial infiltrations extending into both lungs (Fig. 10). Numerous subsequent examinations showed slow resolution of the right upper lobe density but persistent interstitial infiltrations which varied slightly in distribution but remained more or less diffusely bilateral. In 1951 areas of atelectasis appeared in the posterior segment of the right upper lobe and in the middle lobe. Recent roentgenograms made of the patient who is now seven years of age continue to show diffuse bilateral chronic interstitial pneumonia (Figs. 11, 12 and 13).

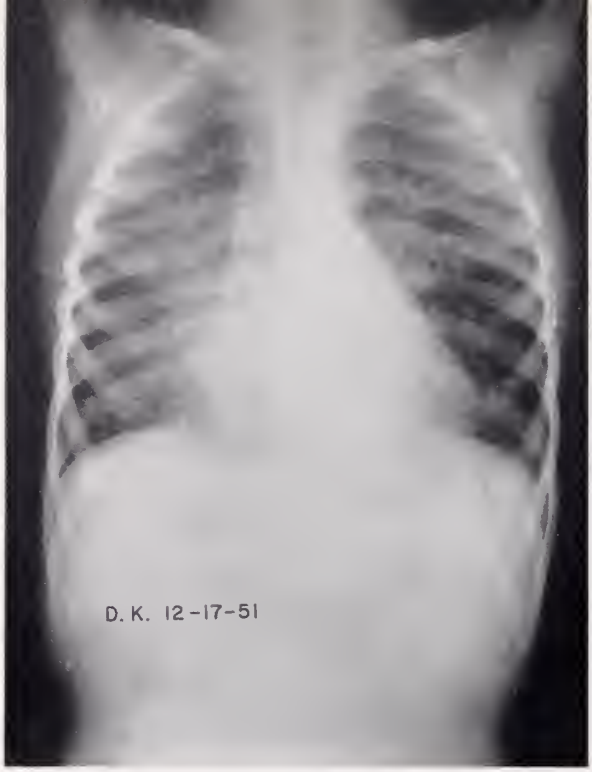
Bronchoscopy was performed soon after admission and revealed edema of the mucous membranes of the right bronchus and its branches. Because roentgenograms gave evidence of right upper and middle lobe atelectasis, bronchoscopic aspiration was performed repeatedly and varying quantities of white viscid secretions were removed, but no improvement occurred. Cultures of the bronchial secretions were either sterile or yielded Pseudomonas aeruginosa or monilia albicans.

Other features of familial autonomic dysfunction were recognized after this diagnosis was established. Stress hypertension was quite marked. Although the patient's eyes appeared normally moist he cried without tears. There was moderate motor incoordination and he walked with a broad-based gait. Deep tendon reflexes were inconstantly present. An electroencephalogram was normal.

The patient is now seven years of age and he still requires frequent admission to the hospital for hyperpyrexia and respiratory symptoms. He appears to adjust to hospitalization more rapidly during the past year so that the duration of his stay in the hospital has been shortened.

Case 5

P. M., appeared lethargic at birth and sucked poorly. Nipple feeding was poorly taken and there was cough on attempted swallowing; for this reason he was tube fed. X-ray exam-



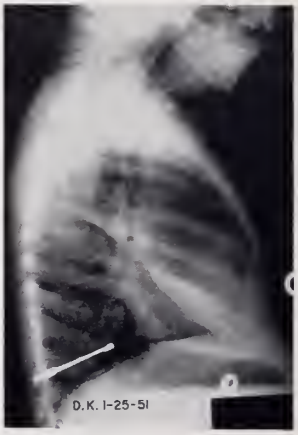


FIG. 11 FIG. 12

FIG. 11. Case 4: Resolution of triangular density in right upper lobe. Bilateral interstitial infiltrations.

FIG. 12. Case 4: Lateral projection showing area of atelectasis in posterior segment of right upper lobe and in right middle lobe.

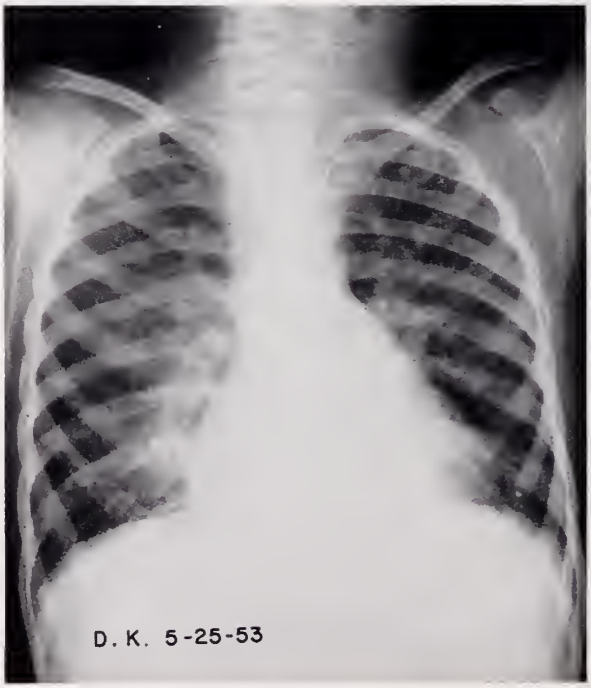


FIG. 13. Case 4: Chronic bilateral interstitial infiltrations

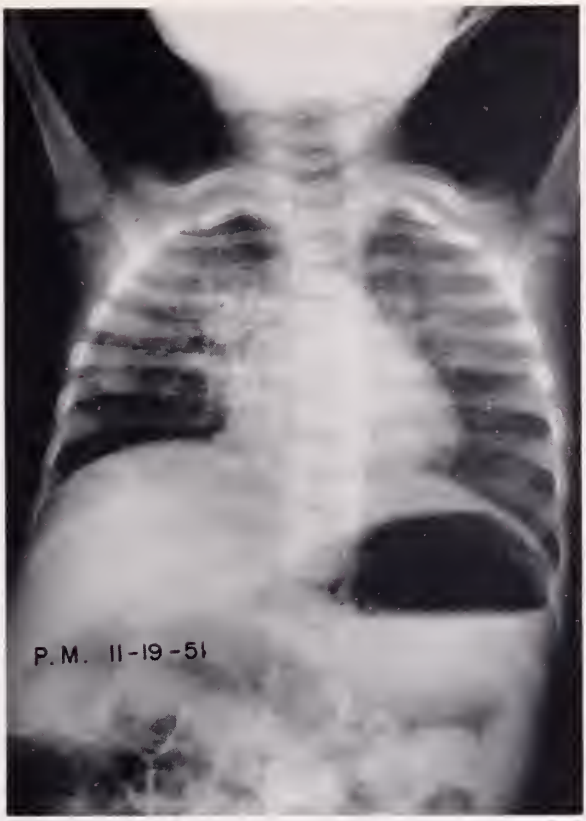


FIG. 14. Case 5: Pneumonitis of right upper lobe partially obscured by residual Lipiodol from previous bronchogram. Infiltrations extending into left upper lobe.

ination of chest showed an infiltration extending into the right upper lobe. Esophagogram and tracheogram were normal. Subdural taps were negative. At two months of age he was transferred to another hospital for supportive care. There bronchography was reported as negative. Because of the continued feeding problem he was readmitted to The Mount Sinai Hospital at the age of seven months. At this time he appeared weak and hypotonic. He seemed insensitive to pain caused by needle prick. There was excessive sweating unrelated to temperature or time of day. On excitement a diffuse blotchy erythematous rash would appear and the blood pressure would rise to systolic levels of 150 to 200 mm. Hg. There were wide swings of body temperature from 98.8° to 105°F., apparently unrelated to episodes of pulmonary difficulty. X-ray examination of the chest at this time showed the infiltration in the right upper lobe. Some contrast substance was present in the right upper lobe residual from the bronchography performed at another hospital (Fig. 14). Since no progress was made in correcting the feeding difficulty the patient was again transferred for supportive care. He subsequently died following an attack of apnea and cyanosis, never having spent a day out of a hospital.

DISCUSSION

The pulmonary manifestations in the syndrome of familial dysautonomia are due primarily to varying degrees of bronchial obstruction with or without second-

ary infection. It is our impression that while secondary infection may supervene, it does not play a primary role in the pulmonary changes. On numerous occasions, pneumonia or other pulmonary infection was suspected, particularly when fever and respiratory symptoms co-existed but pathogenic organisms were isolated in only a few instances and response to antibiotic and chemotherapy was unsatisfactory. Cultures of bronchial secretions obtained bronchoscopically during periods of pulmonary involvement and during febrile periods were either sterile or yielded organisms such as Pseudomonas aeruginosa or aerobacter aerogenes after the patient had been on prolonged antibiotic and chemotherapy. When bronchoscopy was performed, it revealed clear mucoid secretions in the bronchi. While attacks of respiratory difficulty are usually associated with fever, fever may be present in the absence of any clinical or roentgen manifestations of pulmonary involvement. It may also accompany manifestations of dysautonomia in other systems in the absence of pulmonary findings. It is therefore assumed that fever is more often a manifestation of autonomic dysfunction than a result of pulmonary infection.

Because infants with this syndrome usually have excessive salivation and difficulty in sucking and swallowing, aspiration has been considered a possible causative factor. The rapidity, however, with which moist rales and wheezes occur in the chests of some patients when emotionally upset and during feedings is particularly striking. Such changes may occur in the patient upon sight of the food and before any part of it has been ingested. In several esophagographic studies made with Lipiodol to exclude tracheo-esophageal fistula, no roentgen evidence of aspiration could be demonstrated. It is possible that aspiration does occur at times in some cases, however.

The pulmonary roentgen findings are very much like those occurring in fibrocystic disease of the pancreas. Varying degrees of obstruction probably due to thick bronchial secretions, lead to interstitial infiltration, atelectasis and emphysema. Di Sant'Agnese (5) has recently emphasized the primary role played by bronchial obstruction in fibrocystic disease due to the difficulty in removing viscid secretions. A similar mechanism may be involved in dysautonomia. Atelectasis of the right upper lobe has also been stressed by Di Sant'Agnese as a characteristic finding in pancreatic fibrosis. Involvement of the right upper lobe is also very frequent in infants with dysautonomia. Emphysema may be less common in dysautonomia or may be more temporary than in fibrocytsic disease in which it is apt to be a more or less constant feature. The changes in dysautonomia may also resemble those described in agammaglobulinemia and in some phases of idiopathic pulmonary hemosiderosis. The clinical and laboratory features of these diseases, however, serve to distinguish them from dysautonomia. It would be difficult, however, purely on the basis of the roentgen findings to distinguish dysautonomia from aspiration pneumonia or chronic interstitial pneumonia due to other causes.

Recognition of the nature of the respiratory difficulties that patients with dysautonomia present or of the roentgen appearance of the chest may provide a clue to an early correct diagnosis. Suggestive findings lead to a search for other diagnostic criteria of the syndrome.

SUMMARY

1. Familial dysautonomia is a syndrome characterized by numerous manifestations of autonomic dysfunction in the circulatory, gastrointestinal, pulmonary and central nervous systems. All of the cases reported to-date have been in patients of Jewish extraction and the condition appears to be transmitted as a recessive characteristic.

2. Pulmonary manifestations occur to a significant degree in a majority of the patients and are represented by varying combinations of interstitial infiltration, atelectasis and emphysema. The changes may resemble those occurring in fibrocystic disease of the pancreas, agammaglobulinemia or phases of idiopathic pulmonary hemosiderosis.

3. Pulmonary changes are the result of varying degrees of bronchial obstruction with or without secondary infection and are considered to be due to bronchial hypersecretion. The possible causative role of aspiration is briefly discussed.

4. Recognition of the clinical and roentgenological nature of the respiratory difficulties that occur in dysautonomia will often provide a clue to an early diagnosis of the condition.

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Radiological Notes

USE OF 0.3 MM. FOCUS FOR SPOT RADIOGRAPHY

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New York, N. Y.

"Spot" or "aimed" radiography refers to radiographic exposures made during the course of fluoroscopy. With this technique, it is possible to obtain films in the optimum projection, at selected phases of respiration or filling of a viscus with barium and with various degrees of compression. A disadvantage of this method is the fact that the films so obtained are of poorer quality than conventional radiographic exposures. One reason for this is the increased "geometrical

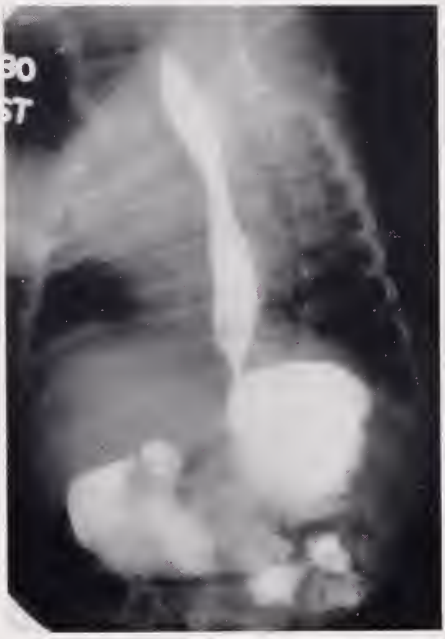

FIG. 1. "Spot" radiograph of esophagus and stomach of infant taken during fluoroscopy. This was taken with the 0.3 mm. focus at 15 milliamperes and 90 kilovolts peak (photo-timed).

blurring" due to a relatively short target-film distance. With the availability of smaller focal spot sizes for fluoroscopic-radiographic tubes, specifically the 0.3 mm. focus, geometrical blurring can be decreased. The improvement in image sharpness on the fluoroscopic screen is particularly evident during chest and gastrointestinal fluoroscopy when the screen is at a distance from the part under observation. Spot radiography with 0.3 mm. focus tubes available at present can be done only at 15 to 20 milliamperes so that exposure times are about 10 times larger than with more conventional set-ups. In thin or motionless parts,

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Fig. 2.

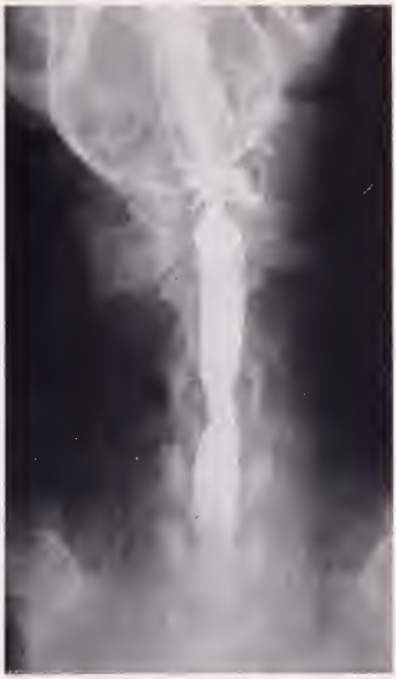

Fig. 3.

Fig. 2. "Spot" radiograph of chest in adult taken during fluoroscopy with the 0.3 mm. focus.

Fig. 3. "Spot" radiograph of trachea of dog taken during fluoroscopy with the 0.3 mm. focus. Local narrowing in trachea was operative.

the increased time does not create a problem. As a result, spot radiography with the 0.3 mm. focus has been feasible and useful in gastrointestinal and chest investigations of infants and children (Fig. 1), in the chest in adults (Fig. 2) and in investigative work in animals (Fig. 3). It is likely that improvements in tube design, the utilization of voltages above 100 kilovolts, the use of wave-smoothing devices and faster screens and emulsions will extend the range of usefulness of the 0.3 mm. focus in the future.

ROENTGEN FINDINGS IN THE COLON IN A HEMOPHILIAC WITH MELENA

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New York, N. Y.

The bleeding diathesis in hemophilia may manifest itself by hemorrhage from the gastrointestinal tract. It is not usual, however, to discover roentgen changes

in such a case. Recently, the opportunity of studying such a patient was presented.

CASE REPORT

The patient, J. S., was a 12 year old white boy who was admitted to The Mount Sinai Hospital on July 19, 1955. He was a known, well documented hemophiliac on the basis of an anti-hemophiliac globulin deficiency. His first episode of bleeding occurred during the course of circumcision several days after birth. He experienced multiple episodes of hemarthrosis and gingival bleeding and on one occasion extensive hemorrhage from a lacerated lingular frenulum. The patient was frequently constipated and often required cathartics. On the evening prior to admission, straining at stool resulted in the passage of a large quantity of dark and bright red blood per rectum. There was no history of trauma to the abdomen. On admission eight hours after the appearance of blood in the stool, the patient appeared markedly pale but was not in shock. The temperature was normal, pulse 152 per minute, blood pressure was 95/60 mm. Hg. There was some swelling and diminished range of motion of the right elbow and both knee joints. Rectal examination revealed a small amount of dark red blood. Laboratory examination showed a hemoglobin of 6.8 gm., hematocrit of 21 per cent, a white blood count of 6800 per $mm.^3$ with normal differential. Blood clotting time was longer than one hour.

The patient was treated symptomatically with whole blood as well as fresh frozen plasma transfusions. Four days following admission, the hemoglobin was 11 gm. Barium enema was done at this time. There was no bleeding per rectum during the hospital stay of the patient.

The barium enema was done without discomfort to the patient. The barium flowed without delay through the entire colon. A segment about 9 cm. long in the distal transverse colon showed a constant lack of complete distensibility (Fig. 1A). The contours of this segment were irregular and somewhat jagged with longer involvement of the superior than the in-

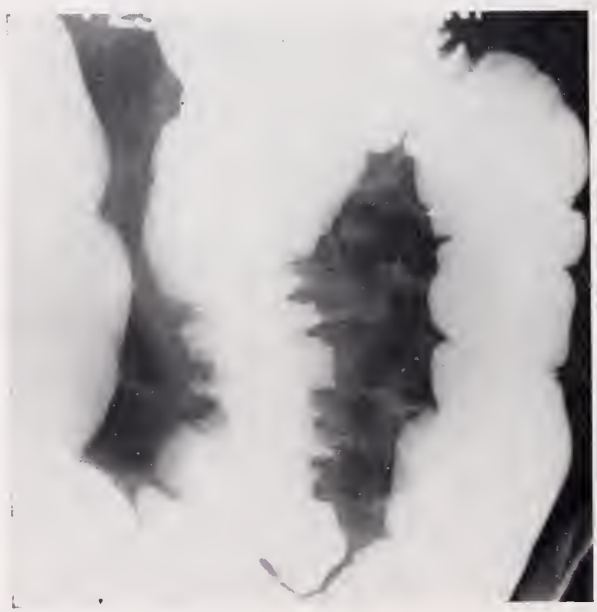

FIG. 1A. Barium enema examination: A segment about 9 cm. long in the distal transverse colon shows limited distensibility without any rigidity. Contours of involved segment are coarsely serrated; superiorly, a double contour is seen in many places.

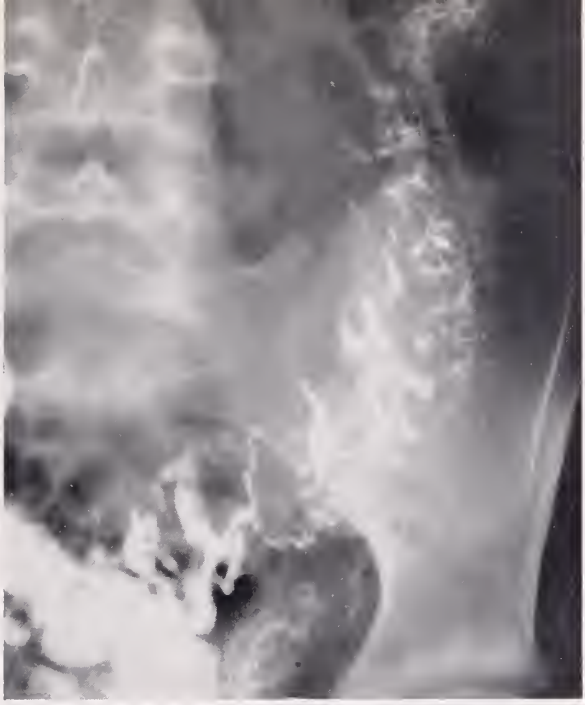

FIG. 1B. Evacuation film from same examination as Fig. 1A shows failure of involved segment to contract completely despite good evacuation. The fold pattern is markedly thickened.

FIG. 2. Barium enema re-examination 13 days after Fig. 1: Residual changes are seen especially along inferior or left border. Distensibility has improved and involved segment appears shorter.

FIG. 3. Barium enema re-examination two months after Fig. 2 shows no abnormality

ferior border. There was no discrete filling defect within the lumen of the bowel and no rigidity of the bowel wall. Gas-containing loops of small bowel were noted adjacent to this portion of the colon indicating that no sizeable extra-colonic mass was present. After evacuation of the barium, the involved segment did not contract as well as the remainder of the colon and the mucosal folds within this segment appeared to be fewer in number and thicker than elsewhere (Fig. 1B). Barium meal examination was also done on this patient five days after the barium enema examination and revealed no abnormality in the esophagus, stomach or duodenum or small bowel.

Barium enema was repeated 13 days after the first enema examination. On the second examination, changes similar to those previously described were present in the same region along the inferior border but the superior border in this region showed a normal haustral pattern and normal distensibility (Fig. 2). A third examination performed two months later showed a completely normal colon (Fig. 3).

DISCUSSION

The pathogenesis of gastrointestinal bleeding in hemophiliacs has been described as due to hemorrhage with subsequent rupture into the lumen of the gut (1–4). Rupture may also occur into the peritoneal cavity (5). Intestinal obstruction presumably also the result of intramural bleeding has also been described (6). The findings described above in the patient reported are most consistent with intramural thickening of temporary character and the assumption that this was the result of bleeding into the wall of the colon is confirmed by the presence of both dark and red blood in the stool. It is possible that some of the roentgen findings may have been the result of functional disturbances associated with intramural bleeding.

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CASE REPORT: DYSPHAGIA FOR LARGE TABLETS LEADING TO DISCOVERY OF BENIGN ESOPHAGEAL STRICTURE

HERMAN C. ZUCKERMAN, M.D. and MAX L. SOM, M.D.

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A. A., a 39 year old female presented herself with the complaint that, on swallowing a coricidin pill, it stuck somewhere in her chest on three different occasions. She experienced this difficulty for the first time three weeks before when a similar pill was swallowed with difficulty. The patient had no other complaints. A routine fluoroscopic examination of the esophagus was not considered remarkable. There was no delay to the passage of either thin or thick barium through the esophagus. The patient, however, volunteered to take a coricidin pill and demonstrate the difficulty under fluoroscopy. The pill was administered with thin barium and it was obvious that it became trapped in the esophagus at the thoracic inlet (Fig. 1). It remained trapped in this position for about five minutes. After this time, the patient's distress was marked and she made rather violent efforts to regurgitate the pill during which the pill passed distally beyond the site of obstruction. This sequence of events was repeated on three different occasions on two examinations performed 10 days apart. Films of the esophagus with thin barium showed a minimal lack of distensibility over a segment of the esophagus at the thoracic inlet about 4 to 5 cm. in length (Fig. 2). There was no evidence of any filling defect. It was striking that the contours of the esophagus at this level showed a finely scalloped appearance which was exactly reproducible and superimposable on films taken several days apart. Esophagoscopy was performed and demonstrated slight but definite narrowing about 22 cm. from the upper incisor teeth. The narrowing was overcome with little difficulty by pressure on the esophagoscope. Over a distance of about 5 cm., the mucosa of the narrowed segment was redundant and thrown into folds. The appearance of this mucosa was distinctly different from the mucous membrane proximal to it and from the normal esophageal mucosa distal to it. A biopsy of this abnormal mucosa was taken. Microscopic examination was reported as esophageal tissue showing transitional cell metaplasia (Fig. 3). Over most of the biopsy specimen,

the epithelium was transitional. In other places, only the basal layer was transitional and the more superficial layers appeared to be squamous. Within the epithelial layer, there were scattered eosinophiles. There was a suggestion that there might also be some increase in submucosal fibrous tissue and small vessels.

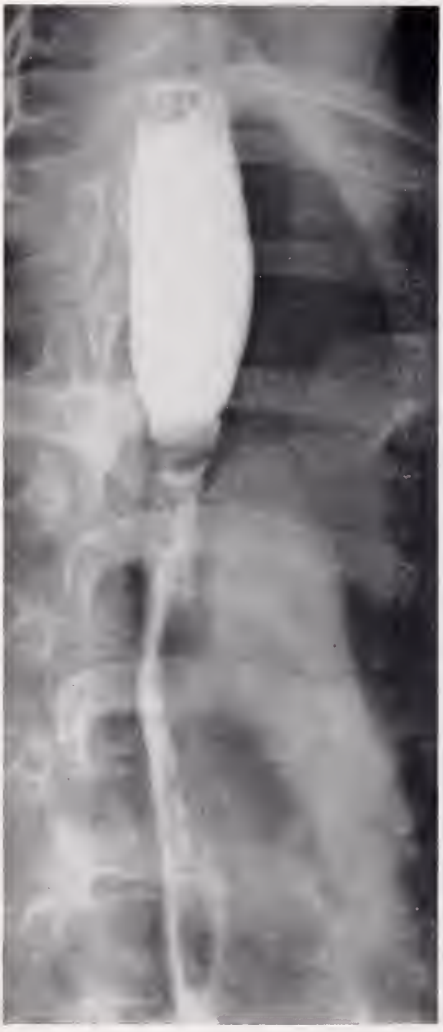

FIG. 1.

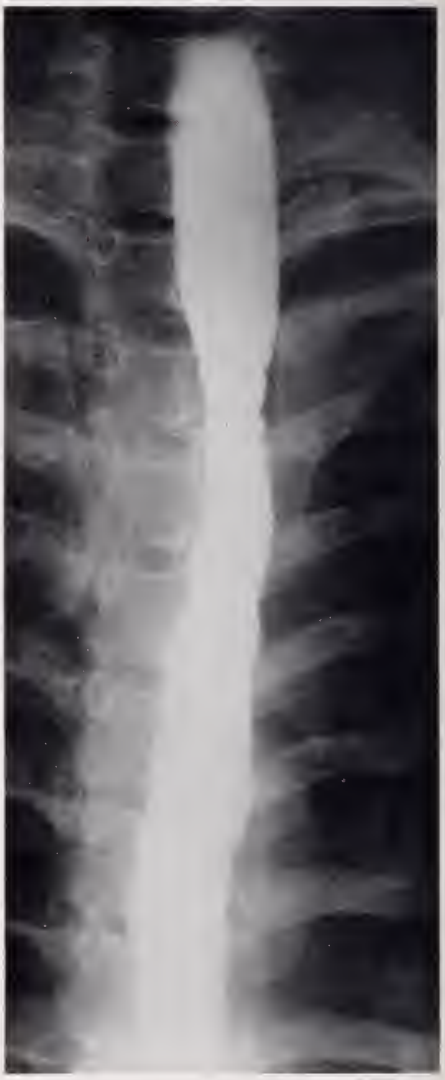

FIG. 2.

FIG. 1. Coricidin tablet trapped in esophagus at thoracic inlet. Shallow contraction band around proximal margin of tablet. The tablet remained in this position for about five minutes before retching efforts of the patient resulted in its distal passage. This sequence of events was repeated three times on two different days.

FIG. 2. Esophagus filled with thin barium shows short segment of limited distensibility at thoracic inlet with scalloped contours. Re-examination 10 days later gave *exactly* the same appearance.

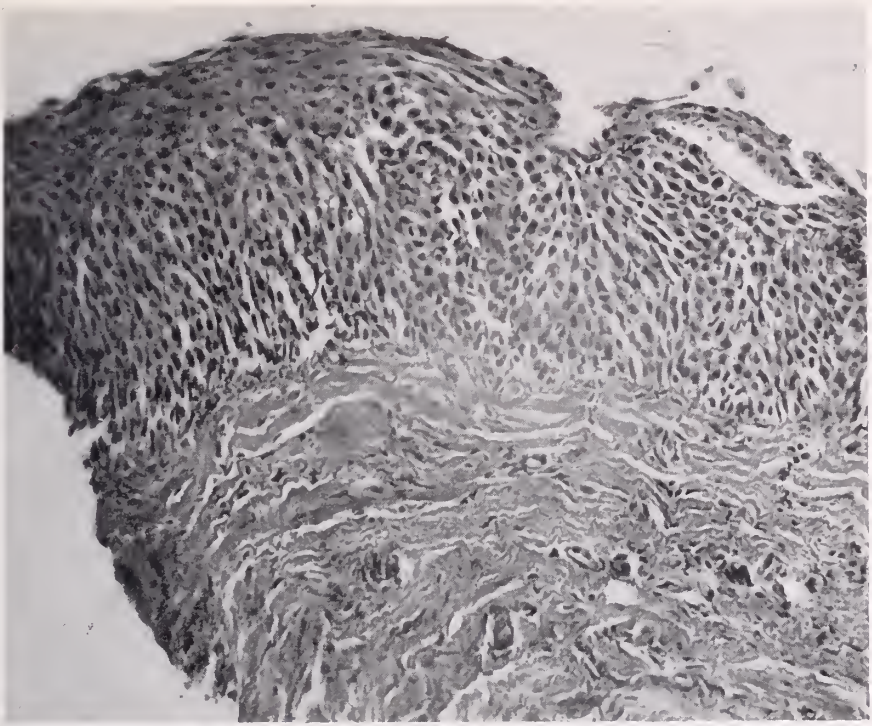

FIG. 3. Esophageal biopsy of abnormal mucosa 22 cm. from incisor teeth shows transitional cell metaplasia and increase in subepithelial fibrous tissue.

The pathologist was not willing to state whether the changes were inflammatory or congenital in nature.

On questioning the patient in greater detail, she denied swallowing any caustic material and there was no history of any episode of unconsciousness or of intubation of the esophagus. She, however, did state that, for about one year, she had been eating more slowly than usually and was considered to be a "slow eater" by her friends. She also admitted that occasionally she was conscious of some difficulty in swallowing certain foods.

The case was of considerable interest radiologically because of the fact that the slight narrowing in the uppermost portion of the esophagus could easily be missed by routine fluoroscopic and radiographic examination of the esophagus. The maximum diameter of a coricidin pill is about 12 mm. The observation of obstruction to a rigid tablet in this case suggested the possibility that similar objects might be used for a test for normal patency of the esophagus. Schatzki and Gray (1) used large gelatin capsules to demonstrate obstruction resulting from a "lower esophageal ring (1)." Domner and Teschendorf have described several sizes of gelatin capsules used to test the calibre of the lumen of the esophagus (2). The largest size used by these authors was 12 mm. by 20 mm. The nature of the stricture in the present case and the significance of the transitional cell metaplastic changes are not clear.

Acknowledgement to Dr. Irving A. Glass for referring this patient for examination.

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THE JOSEPH H. GLOBUS MEMORIAL PRIZE

The Joseph H. Globus Award is named for Dr. Joseph H. Globus, who founded and for twenty years zealously served as editor of the Journal of The Mount Sinai Hospital. The prize is offered annually to members of the staff up to and including Assistant Attending level. Its purpose is to stimulate the interest of the younger members of the Hospital staff in the Journal of The Mount Sinai Hospital.

Joseph H. Globus

The second annual award of the Joseph H. Globus Memorial Prize has been presented to Dr. Howard L. Moscovitz for his paper entitled, "Generalized Herpes Zoster Initiating a Minor Epidemic of Chicken Pox", which appeared in the July-August 1955 issue of the Journal (Vol. xxii No. 2). The Prize committee, Dr. Paul Klemperer, Chairman; Dr. Eli Moschcowitz and Dr. John H. Garlock, selected it as the best of those papers in Volume XXII qualified for consideration.

In the July–August issue:

Symposium on

The Management of Tuberculosis

The medical picture of tuberculosis has changed radically since the advent of modern chemotherapy. The dramatic alternatives within the past four years are pointed up in articles on tuberculosis of the lungs and pleura, meninges, bone, genito-urinary system, skin, gastrointestinal tract and lymphatic system. In addition there will be discussions of physiology, rehabilitation and many other clinical facets of the disease.

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Because of the considerable production costs of this issue of The Journal of The Mount Sinai Hospital, it is necessary that the price of single copies be increased accordingly. Single issues of this symposium may be obtained by writing to

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Symposium on the MANAGEMENT OF TUBERCULOSIS

Guest Editor, IRVING J. SELIKOFF, M.D.

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SYMPOSIUM
ON
THE MANAGEMENT OF TUBERCULOSIS

Guest Editor

IRVING J. SELIKOFF, M.D.

Editor's Note

The last few years have seen no field in medicine change more radically than has the management of tuberculosis. The pathology, course, medical management, surgical therapy, hospitalization, prognosis, all must be re-evaluated because of the impact made by the introduction of the isoniazid drugs.

Dr. Irving J. Selikoff pioneered and spearheaded this advance. For this achievement, he has received the Lasker Award of the American Public Health Association in 1955 and other recognition of the importance of his contributions. The Journal of The Mount Sinai Hospital is fortunate to have him serve as guest editor in this symposium on the management of tuberculosis.

INTRODUCTION

The introduction of effective chemotherapy for the treatment of tuberculosis in the past decade is rapidly changing many basic concepts of the management of this disease. So widespread and fundamental are these alterations, that this period has been aptly designated the "Antimicrobial Era" in the history of human tuberculosis.*

The happiest change has been in prognosis. Throughout the world, the tuberculosis death-rate has fallen, during these past ten years, by approximately 70 per cent. With full utilization of our therapeutic resources, it may be hoped that this will decline still further.

This symposium, in perspective, then, is aptly devoted to the therapeutic management of tuberculosis, recording the current (and still changing) concepts of such management at The Mount Sinai Hospital. The contributions to the symposium emphasize the therapeutic advances in almost every major phase of tuberculosis and the problems in their application.

It is altogether proper that this symposium be derived from a general hospital. Tuberculosis is rapidly being brought back—literally and figuratively—into general medicine and its treatment is no longer largely confined to isolated, outlying sanatoria. Thoracic surgery, with its requirements of highly skilled surgeons, anaesthesia, blood banks, specialized techniques and equipment, started this process, and the chemotherapy of the "Antimicrobial Era" has hastened it.

The annual number of new cases of tuberculosis continues at a high level, and has so far declined much less than the death rate. Since most of these new cases will first present themselves to general hospitals or their staffs, this trend is an important one. This is not to say that specialized tuberculosis institutions will not be required for some cases, especially those needing long-term care, but the development of ambulatory therapy suitable for many patients makes urgent the assimilation of techniques of tuberculosis treatment into general hospitals.

The Mount Sinai Hospital
New York City, May 1, 1956

Irving J. Selikoff, M.D.
Guest Editor

* Drolet, G. J., and Lowell, A. M.: Whereto Tuberculosis? The First Seven Years of the Antimicrobial Era. 1947–1953. Amer. Rev. Tubere., 72: 419, 1955.

THE CHEMOTHERAPY OF TUBERCULOSIS

IRVING J. SELIKOFF, M.D.

Paterson, N. J.

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INTRODUCTION

Chemotherapy has, in one brief decade, completely changed the management of tuberculosis. However, in historical perspective, this has been the culmination of an evolving treatment of tuberculosis which began 100 years ago and which has been constantly changing with ever increasing momentum.

The beginning of systematic therapy for tuberculosis had to wait upon the establishment of the infectious nature of the disease by Villemin (1) and its

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etiology by Koch (2). Prior to this, there had been some halting steps in the advocacy of rest on an empirical basis (3), in place of the myriad of potions, leeches, emetics, demulcents, etc. But, until the monumental contributions of Villemin and Koch, the "open life" and rest regimens were usually haphazard and misdirected, being considered as useful for the "heart weakness" and "anemia" thought (4) to underly the deterioration of the tuberculous patient. It was Trudeau, in the United States, who developed the rest regimens into a systematized and purposeful program (5). Thus, by the end of the 19th century, rest programs became the established method of treatment for pulmonary tuberculosis (6).

Almost simultaneously with the introduction of general body rest as a supportive measure, came the concept of local rest for the diseased organ. Forlanini, in 1894, in a brilliant example of clinical reasoning and experiment, introduced pneumothorax as a controlled technique into the treatment of tuberculosis (7). This procedure spread rapidly to northern Europe and Scandinavia, thence to Great Britain and was introduced into the United States early in the twentieth century, although indigenous independent attempts at pneumothorax had been made here before the turn of the century (8). The concept of local rest was soon strengthened by the addition of surgical collapse measures, particularly thoracoplasty (9).

These procedures, with numerous variations and modifications, remained the mainstay of the treatment of tuberculosis until the last 15 years, when resectional surgery rapidly achieved an important place in the therapeutic program, in many cases providing an effective method of treating the local lesion. However, the full impact and importance of resectional surgery was incompletely appreciated because of the simultaneous development of chemotherapy for tuberculosis.

EVOLUTION OF CHEMOTHERAPY FOR TUBERCULOSIS

Attempts at chemotherapy of tuberculosis began almost immediately following the discovery of its bacterial etiology. Koch noted that potassium aurocyanate had a strong in vitro antituberculosis effect (10). Others utilized various metals and salts in crude experimental studies. Trudeau, for example, tells of attempts to cure experimental tuberculosis in rabbits with creosote injections, carbolic acid, etc., but noted that, unfortunately, ". . . the tubercle bacillus bore cheerfully a degree of medication which proved fatal to the host!" (11).

Interest in antimicrobial substances was revived after Ehrlich's fundamental discovery that chemical cure by antimicrobial compounds was possible and his development of necessary theoretical and methodological principles. Gold remained the only chemotherapeutic agent used to any significant extent, however, during the first decades of this century. Copper compounds were also investigated but as with gold, only a non-specific activity was observed, with stimulation of connective tissue repair but without direct antibacterial action. Experimentally, these compounds often were shown to have in vitro antibac-

terial activity but none seemed to have chemotherapeutic effect in experimental tuberculosis of animals (12, 13).

Following Ehrlich's studies of dyestuffs in trypanosomiasis, in 1907, attention was directed to these compounds for bacterial infections, including tuberculosis. However, although numerous attempts were made, and a number of azin dyestuffs found to have in vitro antituberculous effect (14, 15), these studies did not prove fruitful. Many other dyestuffs, including acriflavine, were also investigated without significant results.

Although dyestuff research in the chemotherapy of bacterial infections approximately delimited by the years 1910 to 1930 failed to produce effective antibacterial compounds, this early work was exceedingly useful in developing a number of basic principles. Most important, it was established that chemical agents were able to interfere with the pathogenic properties not only of protozoan infections but also of bacterial, and were able to suppress bacterial growth without interfering with the well-being of the host. Incidentally, the knowledge and properties of bacterial drug resistance were also developed at this time (16). Not developed, however, were antibacterial agents of high systemic activity and low toxicity.

The spectacular development of antimicrobial substances in the next two decades supplied these desired compounds. The first important advance was Domagk's discovery, while engaged in the continuing investigation of the antibacterial properties of dyestuffs, of the anti-streptococcal activity of a simple azo-dyestuff, Prontosil (4′-sulfamyl-2,4-diaminobenzene HCl) (17a). A further impetus was given by the observation of Tréfouël, Tréfouël, Nitti, and Bovet that the dyestuff portion of the compound was not necessary for the antibacterial action, which was dependent rather upon its simple sulfonamide moiety (17b). From this valuable observation, through chemical variation, have resulted all the therapeutically valuable sulfonamides now in use.

Related to the sulfonamides in many respects, are the sulfones. The parent sulfone, bis (P,P¹-aminobenzene) sulfone (18a) was developed in investigations seeking to find compounds more effective than the sulfonamides, and was indeed found to have higher activity in coccal infections than sulfanilamide. However, it was too toxic for extensive human use. Less toxic derivatives were then prepared, including the glucose derivative Promin and the rongalite derivative Diasone (18b, c). These substances were found to have significant antibacterial activity in coccal infections. Prompted by the knowledge that a number of sulfonamides had some slight in vitro antituberculous activity, the sulfones were so tested and they were found to have activity in experimental tuberculosis of animals (19). With this demonstration, in vivo, that tuberculosis was susceptible to antibacterial action of chemical compounds, antituberculous chemotherapy is connected by the thread of experimental continuity to the earliest days of antimicrobial chemotherapy research.

A totally different direction provided the next major advance. In 1944, Schatz, Bugie, and Waksman (20) introduced streptomycin and its effectiveness in experimental tuberculosis of animals (21) and its clinical usefulness in

human tuberculosis were soon demonstrated (22). Interesting comments on the early development of this important antibiotic have been recorded recently (23–25). Dihydrostreptomycin was also introduced, differing from streptomycin only in having a hydroxyl instead of a carbonyl group in the streptobiosiamine portion of the molecule, and produced by the catalytic hydrogenation of streptomycin. Streptomycin remains one of the mainstays of antituberculous chemotherapy at the present time.

During the past ten years the search for additional chemicals and antibiotics with antituberculous chemotherapeutic activity has been intensified and diversified. Partly, this is due to the realization that, with our present knowledge, the discovery of new compounds must still remain empirical. Biological analysis and study fail to reveal, so far, sufficient rationale to explain chemotherapeutic action: they certainly do not provide sufficient data to be able to predict profitable lines of investigation or probable activity of derivatives within a series of compounds. As Schnitzer puts it ". . . notwithstanding the progress of the chemotherapy of bacterial infections in the last 20 years, our knowledge of the fundamentals of our efforts is still very small; and honesty compels us to confess that, although we can find new drugs, we cannot create them" (26). The results of this empiric approach invalidated some of the assumptions thought to be limiting factors to successful antituberculous chemotherapy. For example, the waxy outer layer of the tubercle bacillus, assumed to be a highly important limitation, is no longer so regarded and the in vitro antitubercular activity of any substance is not necessarily correlated to its lipoid solubility (27). Similarly, the necrotic caseous center of many tuberculous lesions can be well penetrated by many substances (28).

Just as the observation that several sulfonamides had some inhibitory effect upon the growth of virulent human tubercle bacilli had led to the study of sulfones, work starting from the sulfonamides but proceeding in another direction resulted in the finding of the antituberculous action of the thiosemicarbazones (29). One such thiosemicarbazone, Tibione (4-acetylaminobenzaldehyde thiosemicarbazone), was found to have a well established activity in experimental tuberculosis (30). Many chemical variations in the series of thiosemicarbazones have been attempted but no compounds have yet been reported of significantly higher antituberculous activity. The clinical use of these substances never gained wide acceptance in this country, principally because of limited therapeutic efficacy coupled with significant toxicity.

However, investigation of the thiosemicarbazones played an important role in the continued development of antituberculous compounds. Recounting the place of this substance in the jigsaw puzzle of recent antituberculosis chemical reasearch may be of some interest.

In 1945, Chorine of the Pasteur Institute in Paris reported a definite effect of niacinamide on experimental tuberculosis (31). These studies were originally concerned with investigation of the effect of chemical substances in murine leprosy. When the effect of niacinamide on this infection was found, further experiments showed a similar effect in experimental tuberculosis. Since nicotinic

acid, with the same vitamin effect of niacinamide, did not have the antibacterial action, Chorine reasoned (31) that this was an antibacterial effect of the chemical itself. He predicted, indeed, that this observation might be the forerunner of a new class of antituberculous chemicals. The effect of niacinamide was independently reported by McKenzie and her colleagues (32).

In an effort to discover whether the introduction of thiosemicarbazone into the pyridine moiety would prove more efficacious than either of the parent substances, Levandati in France and Grunberg, Schnitzer and their colleagues in this country studied the thiosemicarbazone of nicotinaldehyde (33–34). The therapeutic effect of this substance in experimental tuberculosis was perhaps greater than that of tibione, but not significantly so.

Similar studies went forward in other laboratories (35) since it seemed quite logical to investigate the combination of various pyridine derivatives (nicotinamide is one such) and thiosemicarbazone.

The isomer of nicotinaldehyde thiosemicarbazone (isonicotinaldehyde thiosemicarbazone) was also prepared and studied (34). Fox prepared this substance and found it chemically advantageous to use isonicotinylhydrazine as an intermediate in its preparation. The use of a hydrazine compound (particularly a pyridine derivative) was of interest to Schnitzer who was aware of Aoki's work reported in 1929 that in guinea pigs made anemic by phenylhydrazine, experimental tuberculosis took an attenuated course (36). Kuroya (37) had shown, at that time, too, that methylation of phenylhydrazine in the para position increased the in vitro activity against the tubercle bacillus while substitution in the hydrazine group was unfavorable. Although further work along these lines had apparently not been profitable, yet the knowledge of experimental activity of a hydrazine compound explored over 20 years before, gave interest to the chemical being used as an intermediate in the production process of thiosemicarbazone-nicotinamide compounds.

Because of this same line of coincidental reasoning, Schnitzer and his colleagues tested the intermediate produce, isonicotinylhydrazine. It was found to exert an antibacterial effect in experimental tuberculosis far superior to any substance previously studied (38). "La chance se favorise ce qui est preparé."

Early animal studies indicated that isonicotinylhydrazine might have undesirable toxicologic properties (39) which could limit its human use, and various derivatives were therefore prepared and studied. However, observations in human volunteers (40) indicated that the results of animal studies could not be easily applied to human beings and that, while the various derivatives had valuable properties of their own, isonicotinyl hydrazine was both effective and its effectiveness was not significantly limited by toxicity for humans (41, 42). Extensive clinical chemotherapeutic studies indicated that isonicotinylydrazine could rapidly be transferred from laboratory to clinical usefulness and, as "isoniazid," it has become the most effective agent in antituberculous chemotherapy at the present time.

Other investigations derived from the observations on nicotinamide, but proceeding along other lines, resulted in the development of derivatives of pyrazi-

noic acid. Pyrazinamide has been most extensively studied and has been found (43) to have an important antituberculous chemotherapeutic effect. Although toxicity and the rapid development of resistance are limiting factors, specific indications for the use of this chemical are being developed and it may well achieve a place in antituberculous chemotherapy.

The foregoing paragraphs contain a brief description of the main currents of antituberculous chemotherapeutic research to the present. A number of other substances have also been developed and are occasionally useful in clinical chemotherapy. A number of antibiotics have been so utilized but have proven to be of secondary importance. Among these have been viomycin, oxytetracycline, and tetracycline. Recently, cycloserine has been studied. The use of these substances as well as a number of others will be described later. It may be anticipated that the future will bring an even greater array of potent antituberculous drugs.

MECHANISM OF CHEMOTHERAPEUTIC ACTION

Despite an ever increasing amount of work on the important problem of the mechanism of drug action, it must be admitted that very little is known. Although numerous isolated observations have been made, some as the result of quite ingenious experiments, they are as yet of little assistance in attempting to establish a correlation between chemical constitution and antituberculous activity. They have served, however, to focus attention on the biological problems involved and it is now appreciated that these are of great complexity (44).

Some broad generalizations may be hazarded with regard to the mechanism of action of the sulfones, thiosemicarbazones, isonicotinylhydrazine derivates and pyrazinamide. Here, it seems most likely that one might apply Fildes's theory that the antibacterial activity of a substance is based upon competitive interference with an essential metabolite of the bacteria of similar chemical structure. Such antagonists (metabolites, vitamins, hormones) have been widely studied (45). It is of interest that the theory of competitive interference was based upon Wood's finding that para-aminobenzoic acid, an essential metabolite of many microorganisms, antagonizes the antibacterial effect of sulfonamides.

Application of the Theory of Competitive Interference

In support of the concept of metabolite interference by isoniazid has been the observation that the initial bacteriostasis in the presence of effective concentrations of the drug, is not enhanced by the addition of even massive quantities (46a). Moreover, in culture media isoniazid apparently has a delayed action on the growth of susceptible tubercle bacilli, with bacteria continuing to grow until the bacterial population is approximately double, with cessation of growth occurring at this point. This is similar to the effect of sulfonamides. In contrast, streptomycin has an immediate effect. Pursuing this line of reasoning, it has been suggested that bacterial resistance, when it occurs, would be explained by the assumption by the bacteria of alternate metabolic routes, no longer requiring the metabolite interfered with by isoniazid. In this regard it is of interest to note that, when grown in a media containing isoniazid made radioactive by

the inclusion of C^{14}, susceptible bacteria become radioactive whereas resistant bacteria do not (46a).

Rosen has proposed that because of the structural relationship between isoniazid, niacin and pyridoxine, a possible antimetabolitic effect of isoniazid might be the mechanism for its biologic activity (46b). Although in animal experiments pyridoxine did not exert an inhibiting effect on the protective action of isoniazid (46c), he observed that the neuritis which occasionally occurs with isoniazid therapy may yield to pyridoxine administration (46d), and that pellagra developing during isoniazid therapy had been reported to be relieved with niacin and vitamin B complex. Also, the toxic effects of isoniazid in B^6 deficient rats could be prevented with pyridoxine. Similar interference with other essential intracellular enzyme systems have been postulated. Although no definitive studies are available, certain clinical data add credence to these theories. My own observations indicate that isoniazid toxicity is increased in patients with clinical states often associated with vitamin deficiency, such as malnutrition, debility, constitutional toxicity, liver disease (47). Also, isoniazid neuro-toxicity is enhanced by the simultaneous administration of iproniazid (48).

It has even been proposed that streptomycin might have a similar mechanism of action. Noting that some of the polysaccharides of the tubercle bacillus bear a resemblance to streptomycin, Stacey (49) suggested that the latter ". . . could, therefore, be imagined as a possible blocking group inhibiting the biosynthesis of certain of the tuberculosis polysaccharides". Nevertheless, generally speaking, the competitive interference theory is more difficult to apply to antibiotics, since fewer basic data are available. These data are perhaps more difficult to come by since most of the antibiotics are large molecules and of complex structure. With the antibiotics, as with the simpler chemicals, ". . . it seems still to be the rule that the observation of antibacterial activity precedes the elucidation of the mechanism of activity and that the knowledge of the latter, valuable as it may be, does not further considerably the synthesis of substances having predictable activity" (26).

An apparent exception to the above might be the studies which led to the development of para-aminosalicylic acid (PAS). It was known that benzoic acid greatly increased the oxygen consumption of tubercle bacilli and by so doing apparently inhibited the growth of these bacteria. Study of similar compounds was undertaken and para-aminosalicylic acid showed further abnormality of this biological function. Subsequent clinical investigation indicated significant antituberculous activity (50).

Role of the Host

Difficulties in evaluating the mechanism of drug action are multiplied by the variability inherent in the biological status of the host. These factors include such important ones as acquired and natural host resistance to infection, variations in distribution of the drug in body fluids, excretion and/or metabolism of the drug, metabolic requirements of the host, variations in tissue resistance, and even specific host resistance to the variety of tubercle bacillus. When to these

are added additional variables such as changes in the environment of the host (even putting the rabbit in the erect position changes its resistance), variations in nutrition, age, sex and perhaps race, it can be appreciated that the biological difficulties are immense. Yet, studies in this field might be profitable. FitzPatrick has reported striking prolongation of life in the mouse treated with nicotinamide for a short time *before infection* and suggests that this might point to a mechanism exerted on the host, providing an unfavorable environment for the tubercle bacillus (51). She speculates, further, that nicotinamide may contribute to species resistance, the rat, highly resistant to tuberculosis, having higher nicotinamide tissue levels than mouse or man. Also, she notes that the lung possesses one of the lowest nicotinamide tissue levels of any tissue. One could speculate further that the breakdown of resistance with malnutrition might be related to low nicotinamide levels.

That the host might play an important role in the chemotherapy of tuberculosis is further suggested by the investigation of a series of nonionic surface-active polyoxyethylene ethers. These surface-acting agents may exert powerful suppressive effect in experimental tuberculosis, apparently through the mediation of the host (52). These substances are not bacteriostatic in vitro but are effective in vivo. That the host is involved is not only suggested by this negative factor, but also by the demonstration (53) that monocytes from animals previously injected with one of these substances killed or inhibited intracellular tubercle bacilli, whereas monocytes from untreated animals failed to do this, even in contact with the agent in solution. How these substances enhance the cellular defenses is not known. Owing to liver damage, these substances have not been utilized in man, but the principle established is of more than academic interest. For example, since there is no direct antibacterial effect, bacterial resistance may not occur.

The use of macrophage-tissue culture techniques has provided information on another aspect of the mechanism of drug action. It has long been known that in the sensitized animal most tubercle bacilli are intracellular, within macrophages. It has been proposed, therefore, that successful drug action would presuppose the ability of the drug to penetrate within the macrophage. It has been found (54) that isoniazid penetrates very well, streptomycin poorly and PAS hardly at all. Related to this has been the concept that drug action is at least partly governed by the ability to penetrate the avascular necrotic tuberculous lesion. It has been shown, using C^{14} tagged isoniazid, that this drug penetrates caseous lesions well (55). However, that this cannot always be a crucial factor is evidenced by the failure of micrococcin to exert antitubercular activity in vivo although it has appreciable tuberculostatic activity in vitro. This compound, an insoluble antibiotic, was demonstrated to reach necrotic tissue and its failure to show activity could not be explained on this basis (28). The intermediate effect of the host in the therapeutic utilization of an antituberculous agent has also been proposed as a possible explanation for the observed effect in pulmonary tuberculosis of cycloserine (56a). In an attempt to correlate its weak in vitro activity and its virtual ineffectiveness in experimental animals with its antituberculous action in

humans, it has been proposed (56b) "Possibly cycloserine is chemically modified within the human to a more active form." However, since 70 per cent is excreted unchanged in the urine, this hypothesis is questionable and the mode of action remains for further study.

EFFECT OF CHEMOTHERAPY ON TISSUE RESPONSE IN TUBERCULOSIS

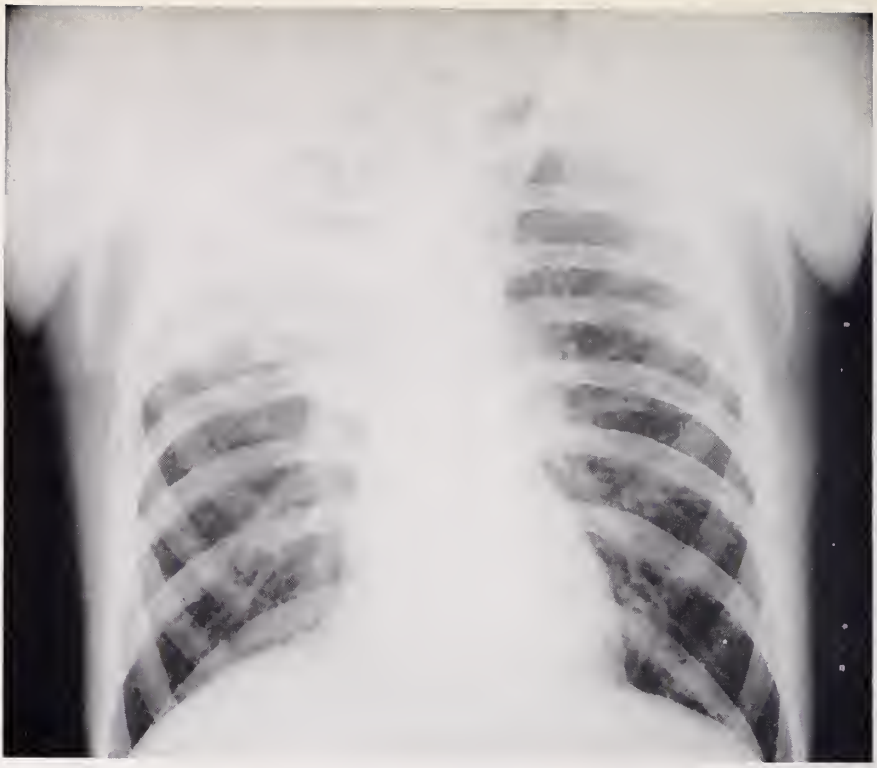
Whether antituberculous chemotherapy is mediated through direct antibacterial action alone or with the addition of alterations in the host's reaction, there is no doubt that such chemotherapy results in profound changes in the disease state. The most gratifying changes are obviously those in the clinical state of the patient and in the evidence of the arrest and subsequent reversal of the disease process. These will be referred to below. However, basic to and underlying such changes and therefore the subject of considerable study has been the alteration in the tissue response to tuberculous infection under chemotherapy. This has been most extensively studied in pulmonary tuberculosis, although pathological data from meningeal, renal and other lesions have also been of interest.

It has been claimed that there are no specific pathological findings under chemotherapy which can be attributed to drug treatment (57). Although it is obvious that the quantitative changes are quite marked, it has been asserted that "Morphologic changes in the lesions are not qualitatively different from those which occur in the natural course of the disease. . . ." (58). Nevertheless, the majority of workers in this field have found that not only are the variations between treated and untreated cases markedly different quantitatively, but qualitative changes are also marked and specific. Thus, it is felt that not only does chemotherapy increase the rate of healing but that the pathologic lesions are different from those in untreated cases.

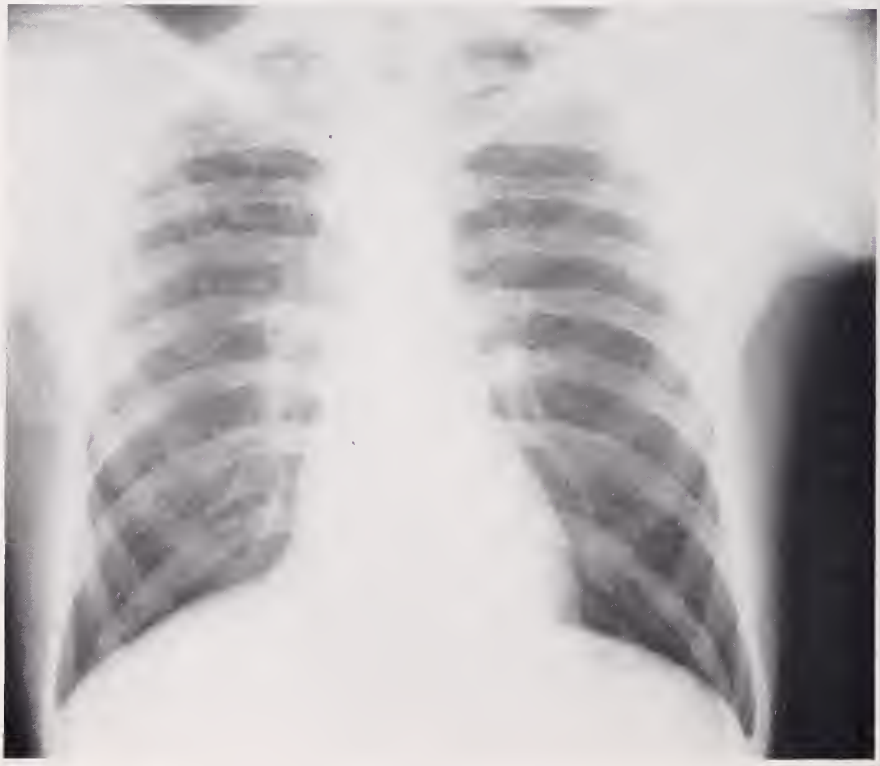
Perifocal Reaction

One of the most easily observed differences and perhaps one of the most important has been the fate of the perifocal reaction in treated and untreated cases (59). The rapid clearing of the perifocal reaction can be easily observed on serial roentgenograms and striking changes can often be seen in a matter of weeks, especially when the disease process is acute and of relatively recent origin (Figs. 1*a–d*). This clearing is of importance since if it does not occur, the perifocal reaction will end in fibrosis and/or necrosis. With chemotherapy the lessened tendency to pulmonary fibrosis simultaneously decreases the possibility of emphysema which ordinarily occurs during the "healing" process, with stretching and tearing of the alveolar septa consequent on contraction of fibrosis.

Decrease in the organization of the perifocal reaction similarly results in a marked decrease in the tendency to massive pulmonary hemorrhage since this commonly occurs from vessels lying tangentially to areas of caseous disease. The elastic walls of these vessels are destroyed by the connective tissue of the organizing perifocal reaction; its absorption with chemotherapy prevents the damage to the vessel wall.

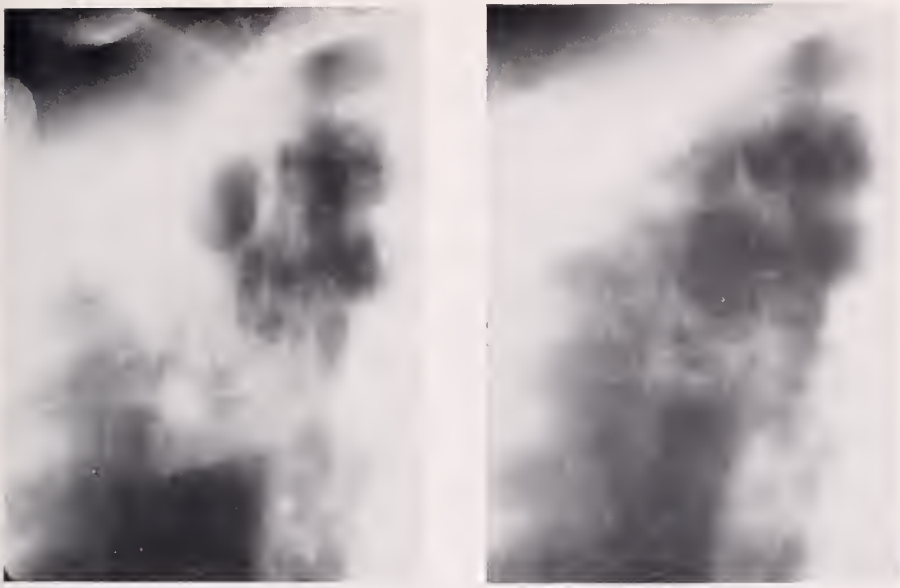


a. R. H. June 8, 1954



b. R. H. Jan. 25, 1956

FIG. 1



c. R. H. June 8, 1954 6 cm. A-P section *d.* R. H. Aug. 28, 1954 6 cm. A-P section

CHEMOTHERAPY: REABSORPTION OF PERIFOCAL REACTION

FIG. 1. *a*) Film of June 8, 1954, showing tuberculous pneumonia in the right upper lobe. Sputum contained tubercle bacilli. A film six months before had been normal. Thus, this represented acute disease. *b*) Treatment with isoniazid, dihydrostreptomycin and P.A.S. resulted in marked reabsorption of the tuberculous infiltration, and reversal of sputum infectivity. This film is of Jan. 25, 1956.

c) and *d*) Of interest is the fact that the pneumonic process can be absorbed rapidly, much of the absorbed infiltration being perifocal reaction. The 2½ months between these two tomographic sections illustrate this well.

Comparative studies (60) suggest that this prevention of the organization of the perifocal reaction is principally seen after isoniazid therapy. With streptomycin the pathological picture remains essentially one of fibrosis, relatively avascular and with only slight regeneration of specialized cells or tissues and with none of the active repair which follows a simple injury or pyogenic infection. With isoniazid, in contrast, increased vascularity is seen, a phenomenon previously not observed in the healing process. This occurs as early as the second week of treatment. In my own experience, it is sometimes evidenced clinically by an increased tendency to bloodstreaked sputum in patients with extensive disease during the early weeks of isoniazid therapy and by a change in the character of fistula discharges from purulent to serosanguinous before complete healing takes place. The increased vascularity is due both to congestion of existing capillary vessels as well as to the formation of new vessels. There are also small hemorrhages in and around the lesions. Thus, it has been stated, "There is nothing in recent lesions following isoniazid like the dense fibrosis after streptomycin" (60). When isoniazid and streptomycin are combined in therapy, the resulting tissue change is that seen after isoniazid.

Specific Cellular Metaplasia

Another significant alteration in tissue response following chemotherapy has been the cellular one. Without chemotherapy, the "specific cellular metaplasia" are usually grouped in tubercles and usually about the periphery of caseous material. With chemotherapy the cellular metaplasia is more extensive, its location more varied and with greater morphological variability of the cells. Bacilli are rarely present in such chemotherapeutically altered lesions. "They are the histological signature of the intervention of chemotherapy" (61). These changes in cellular morphology are much more frequent with isoniazid but have been observed without it. Among the changes in cellular morphology have been a number rarely seen previously in human tuberculosis, including giant cells with Schaumann bodies (62, 63).

The effect of chemotherapy on the perifocal reaction and on cellular morphology is still incompletely known. Data from experimental animals can be applied only with many reservations since it is difficult to reproduce the chronic disease of the (sensitized) human in the experimental animal. Moreover, almost any pathological material is selected by its very nature and uncritical application of the morphological findings to clinical problems may be unwarranted. Caution is necessary both in the interpretation of the acute effect of chemotherapy because of the paucity of material for study, and in the interpretation of findings after longer therapy of chronic lesions either surgically removed or obtained at necropsy, since this material, too, is selective. Such data as have been analyzed would indicate that the effect of streptomycin in advanced lesions was mixed, with regressive changes—principally fibrosis—developing in those portions of the lesions active at the onset of therapy, but with inactive portions showing no changes from old lesions found in untreated patients. Isoniazid therapy, on the other hand, shows resolution in those parts of the chronic lesions of recent activity, as well as loosening and vascularity of surrounding fibrous tissue and some vacuolation of caseation. However, these changes are incomplete, resulting in inadequate healing (60). Additional studies would be welcome in this field, especially with those correlations necessary to explain the clinical observations of frequent healing of both extensive and chronic lesions.

Bronchial Tuberculosis

Two special aspects of tissue reaction to chemotherapy have been studied, of great clinical importance in pulmonary tuberculosis. First, has been the rapid healing effect on bronchial tuberculosis. This single effect has even been considered as underlying most of the major clinical improvement noted under chemotherapy (64). In specimens examined after chemotherapy, tuberculosis of the larger and main bronchi is relatively rare in cases treated with streptomycin or with isoniazid or with combinations of the two drugs (65). This beneficial effect is noted throughout the tracheobronchial tree and includes a marked healing tendency in tuberculosis of the larynx (66) and mouth (67).

Cavity Healing

A second important effect is that on cavity healing. Here, too, reported pathological data must be correlated with clinical problems with a good deal of caution and reserve, since the material is again highly selective and is composed principally of instances of failure of cavity closure. Also, many of the specimens examined were from cases which had received chemotherapy of relatively short duration. For example, in one series studied only 16 per cent had had treatment for more than 12 months while more than one-third of the group had had therapy for less than six months (68). Nevertheless, studies of cavity healing under chemotherapy have provided much valuable data and are of assistance in systematizing therapeutic concepts in clinical pulmonary tuberculosis.

Prior to chemotherapy, when cavities healed it was principally by cavity closure following apposition of the granulating surfaces of the ulcerated bronchus at the bronchocavitary junction. If the cavity contents had previously been largely expelled, a radial or even linear scar would result. Often, however, because of the stenosis of the bronchocavitary junction, some of the cavity contents would remain and become inspissated.

Therapeutically, this knowledge of the mechanism of cavity closure was translated into attempts to close the bronchus leading to the cavity and it was felt that in many instances healing with pneumothorax or with thoracoplasty resulted from just such bronchial closure. When the bronchocavitary junction remained open, it would be very rare for healing to take place.

With chemotherapy, the frequency of cavity closure has tremendously increased and it is this fact which has given chemotherapy its preeminent place in the management of pulmonary tuberculosis. The other effects of chemotherapy, including cure of the toxic state of the patient, removal of constitutional symptoms, and radiological clearing of exudate, would be of limited value were it not for the fact that cavity closure and, usually, consequent disappearance of tubercle bacilli from the sputum, have become frequent and almost predictable results of chemotherapy. Although the frequency with which cavity closure will occur under chemotherapy will naturally vary according to the type of lesion, the size of the cavity, the multiplicity of cavities, the nature of the surrounding infiltration, the thickness of the wall, and duration of the disease, I would estimate, from my own personal experience (69), cavity closure will occur in approximately two-thirds of cases with chemotherapy alone.

In addition to the marked increase in frequency of cavity closure induced by chemotherapy, there have also been noticeable differences in the method of cavity closure. One important difference between cavities treated with chemotherapy and those untreated is reepithelialization of the bronchus at the bronchocavitary junction (70). The lumen of the draining bronchus thus remains patent and the caseous contents of the cavity as well as the necrotic fragments from the cavity wall can be discharged through the bronchus. When cavity closure does occur, with apposition of the cavity walls, much less material is entrapped therein to remain as a residual caseous focus of potential future activity. Moreover, serial roentgenograms in a number of my cases would indi-

a. H. M. Oct. 8, 1954. 8 cm. A-P section.

b. H. M. Nov. 15, 1954 8 cm. A-P section

c. H. M. Dec. 24, 1954 8 cm. A-P section.

d. H. M. Feb. 26, 1956 8 cm. A-P section.

CHEMOTHERAPY: RAPID CAVITY CLOSURE

FIG. 2. *a*) 8 cm. antero-posterior tomographic section at onset of chemotherapy with isoniazid, dihydrostreptomycin and P.A.S. on October 8, 1954. A previous film indicated that this thick-walled $3\frac{1}{2}$ inch cavity had been present for at least six months. *b*) The same tomographic level on November 15, 1954, after 4 weeks of chemotherapy. Rapid decrease in cavity size suggests healing effect on broncho-cavitary junction, resulting in patency and disruption of check-valve mechanism. *c*) Tomographic section on December 24, 1954. Further decrease in cavity size, but residual pericavitary infiltration. Tubercle bacilli no longer present in sputum. *d*) 8 cm. antero-posterior tomographic section on Feb. 26, 1956, after sixteen months of combined chemotherapy, shows only minimal residual infiltrate.

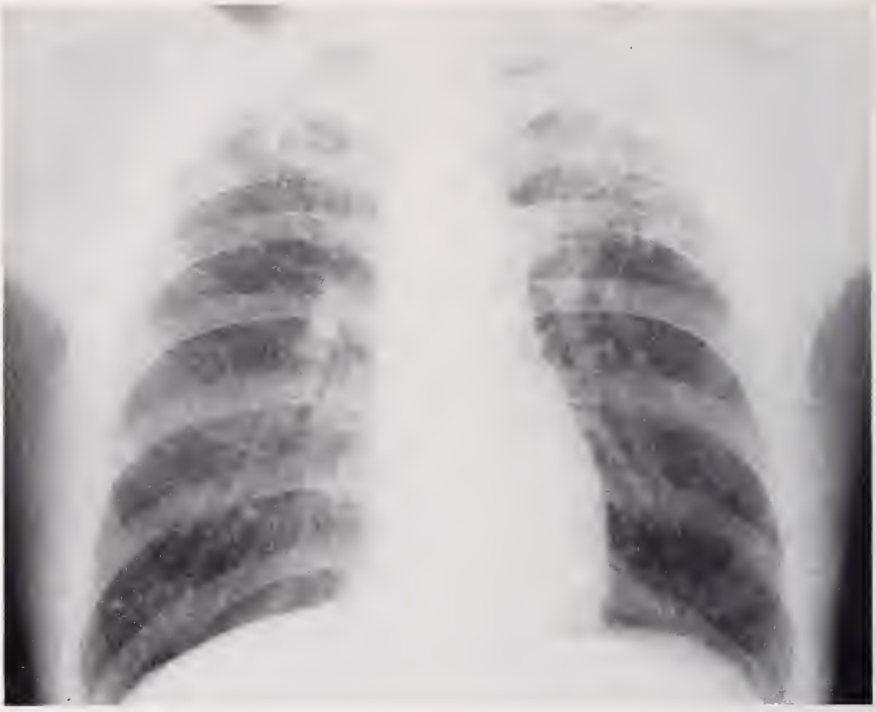
cate that the check valve mechanism at the bronchocavitary junction is disrupted, allowing rapid deflation of the cavity. Instances were not infrequently seen in which large cavities rapidly become concentrically smaller and closed, even when such cavities had been known to be present for some time prior to the institution of chemotherapy (Figs. 2*a–d*).

Another important effect of reepithelialization of the bronchocavitary junction is that this area forms a source for reepithelialization of the lining of the cavity, concomitant with healing of the cavity wall discussed below. However, such reepithelialization of the cavity is usually incomplete, patchy and often does not extend more than a short distance from the bronchocavitary junction. Of course, without chemotherapy, patchy epithelialization of chronic cavities may also be seen but this is associated with caseous necrosis of the remainder of the cavity wall.

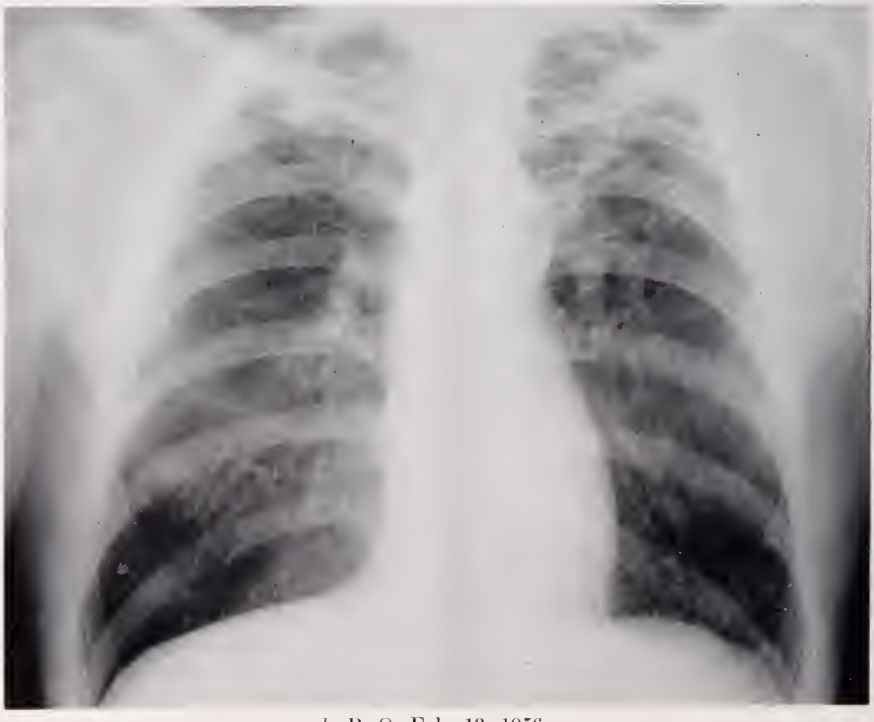
A second important change in cavity healing attributable to chemotherapy has been the effect on the cavity wall. In many instances, there is replacement of the caseous material by ordinary granulation tissue and foreign body granulomata. These walls may end as fibrous linings without any cellular components and may indeed become quite thin and composed of dense connective tissue, with complete disappearance of all signs of specificity of tuberculosis. When cavities occur in the midst of tuberculous pneumonic infiltration, and when cavity healing occurs both by shrinking of the cavity and virtual disappearance of its walls, the roentgenographic appearance may be quite striking and could be aptly termed "disintegration of the cavity wall." This method of cavity healing is not peculiar to the tissue response of any individual but is rather dependent upon the local nature of the disease and its response to chemotherapy. This can be seen from the fact that such cavity healing can occur simultaneously in the same individual as cavity healing by inspissation of another cavity (Figs. 3*a–f*).

The importance of the direct effect of chemotherapy on the cavity wall is emphasized by the observation that the cavity wall may heal in instances in which the bronchocavitary junction is *not* reepithelialized. "A direct action of the chemotherapeutical agent on the cavity wall, in addition to that on the bronchocavitary junction, should be, therefore considered. The latter may be helpful in supporting the dynamics of cavity healing, but does not appear to be essential" (71).

Reepithelialization of the bronchocavitary junction and the healing effect of chemotherapy on the cavity wall are usually, however, incomplete, at least in most instances of relatively short term chemotherapy. It is therefore fortunate that most cavity healing under chemotherapy occurs with obliteration of the cavity lumen so that whether the cavity walls be cleanly healed, or contain foreign body granulomata as small, warty elevations on the fibrous lining, or contain residual areas of caseous disease, the problem is solved by obliteration of the cavity lumen. I have studied a consecutive series of 63 patients with open cavities, and sputum containing tubercle bacilli, all treated by chemotherapy alone (69). Forty-four patients showed cavity closure of all cavities and reversal of sputum infectivity. Six patients showed continued presence of cavities but



a. P. O. Nov. 10, 1955



b. P. O. Feb. 13, 1956

FIG. 3

c. P. O. Nov. 21, 1955, 7 cm. A-P section

d. P. O. Jan. 23, 1956, 7 cm. A-P section

e. P. O. Nov. 21, 1955, 8½ cm. A-P section

f. P. O. Jan. 23, 1956 8½ cm. A-P section

CHEMOTHERAPY: DIFFERENT FORMS OF CAVITY CLOSURE IN SAME PATIENT

FIG. 3. *a)* Film of November 10, 1955 showing bilateral upper lobe tuberculosis. Recent reactivation of long-standing disease. *b)* Film of February 13, 1956, after three months of isoniazid-dihydrostreptomycin-P.A.S. therapy. It is difficult to evaluate chemotherapeutic effect on conventional film.

c) 7 cm. antero-posterior tomographic section showing small cavity in right upper lobe, before chemotherapy. *d)* 7 cm. section after two months of chemotherapy, showing this cavity "closed" by inspissation. *e)* 8½ cm. section, before chemotherapy, of left upper lobe. *f)* 8½ cm. section after two months of chemotherapy show disappearance of cavity with disintegration of cavity wall, in same patient; largely by direct effect on cavity wall and absorption of pericavitary infiltrate. No further sputum infectivity.

persistent absence of tubercle bacilli from the sputum for periods over two years in some cases. In thirteen cases the cavity remained open and tubercle bacilli were present in the sputum.

"Open-healing" of cavities. The fact that in two-thirds of cases in which there was radiological evidence of open cavities, there were also tubercle bacilli in the sputum, indicates that the best healed cavity is a closed one. Nevertheless, the problem of "open healing" of cavities has become a frequent one. The exact incidence is difficult to determine and comparison of the incidence of open healed cavities in various series is hazardous because there are, as yet, no definitive criteria for their classification. Bell (72), for example, in discussing open lesions with negative sputum includes in this group those patients with negative sputum for three months or more. It may be questioned whether reversal of sputum infectivity for a period as short as three months, with an open cavity, should be classified as "open cavity healing". Naturally, when patients so classified are subjected to resectional surgery, the operative specimens could hardly be expected to show well-healed and histologically non-specific cavity walls. Clinical estimates of the incidence of open cavity healing may also be in error unless serial tomograms of the cavity-bearing area are studied, since with the thinning of the cavity wall and the absorption of the contrasting parenchymal infiltration, the cavity may be lost to view on the conventional roentgenogram (73). On the other hand, data collected from pathological studies suffer from unknown factors of selection, including the opinion of the treating physician as to whether or not patients with non-infectious sputum should be subjected to resection.

Appreciating these limitations, it is still useful to review the available pathological data. Thompson (74) studied 240 resected specimens with cavitation at the Chicago Municipal Tuberculosis Sanatorium. Of these 9.6 per cent of the cavities were healed (although minute ulcerations were seen grossly in approximately one-third). At Sea View Hospital, a recent series of 63 pathologically studied specimens showed 11 with smooth-walled cavities, although several of these were apparently bronchiectatic cavities, or bronchogenic defects. That pathological data often fail to reveal the true incidence of open healed cavities can be seen from the fact that at approximately the same time in this institution another group of 7 patients with open healed cavities were under observation and medical management (75).

The true clinical incidence is similarly difficult to come by. Johnson and Hewitt (76) state that they have seen this phenomenon in 22 patients in over a year at their institution of 614 beds. However, the total number of observed patients is not given and the criteria for classification as open-healed cavities is not clearly stated. It would seem prudent not to so classify any patient with a cavity, unless the sputum had been free of bacteria for over a year on smear and culture and the cavity confirmed by tomography.

Approximating these criteria has been a group of cases in the study by Reisner (77). Although the cases treated in his series were not strictly comparable to my own, containing a higher percentage of recent, acute disease, our observations with regard to open-cavity healing have been quite similar (Table I).

TABLE I

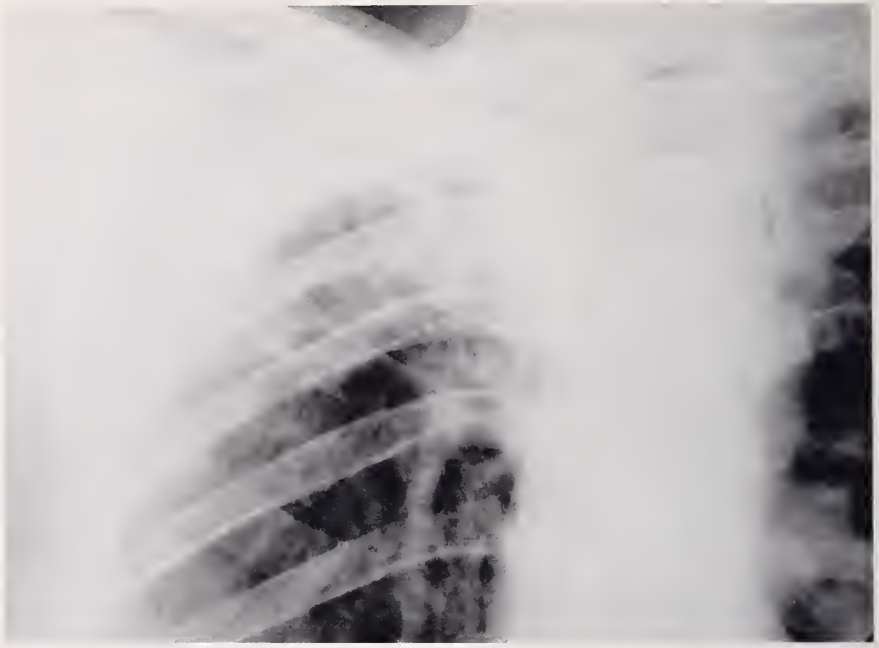
Incidence of "Open Cavity Healing" with Chemotherapy

	Cases with open cavity and positive sputum	Status after Chemotherapy		
		Closed cavity, Negative sputum	Open "cavity"	
			Positive sputum	Negative sputum
Reisner, Peizer and Widelock (77)	64	47	10	7
Selikoff and Rabin (69)	63	44	13	6

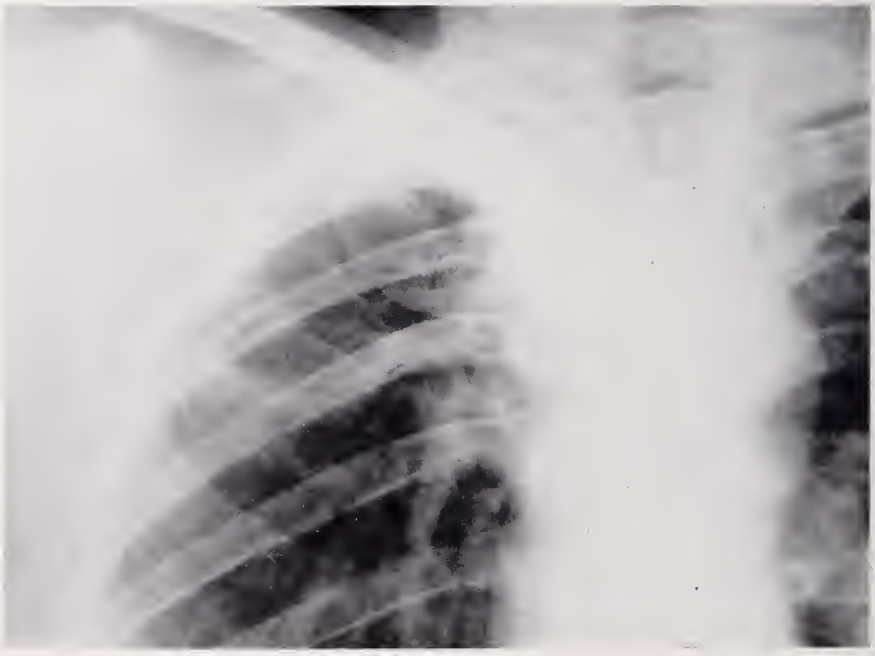
If the above experiences are confirmed, it will be possible to anticipate an incidence of reversal of sputum infectivity with persistence of cavity-like structures in approximately 10 per cent of cases. It is further possible that with longer chemotherapy this incidence will increase. It is not certain whether all of the cavity-like structures seen after chemotherapy are indeed open-healed cavities. Some may represent bleb formation in the area of previously observed disease (78) and this was observed in one case in my series (Figs. 4*a–d*). In other instances, bronchiectatic cavities are present while in still others the residual cavitary shadows are truly completely, or almost completely, healed tuberculous cavities. It may be anticipated that, with further experience, roentgen criteria will be established to enable differentiation between true open-healed cavities and blebs, or unhealed tuberculous cavities.

No reliable data are yet available to indicate what type of disease is most likely to result in open healing of cavities. I have observed it in patients with recent disease as well as in those with disease of some standing, in cavities with thin walls and in two with thick walls, in areas of little surrounding infiltration as well as in areas with a good deal of fibrotic and caseous parenchymal infiltration. Perhaps worthy of comment has been the fact that in each of my cases the sputum became free of bacteria rapidly after the onset of chemotherapy. Johnson and Hewitt (76) comment that open-cavity healing is much more common in Negroes, since 20 of their 22 cases were in Negroes, while their general sanatorium population was about equally divided as to race. I am unable to confirm this from my own data since none of the instances of open-cavity healing in my series was in a Negro although approximately one-fifth of my patients were Negroes.

Open-cavity healing seems to be almost entirely, although not completely, a phenomenon associated with isoniazid therapy. Although cavity healing is not infrequently observed with streptomycin and PAS, open-cavity healing was very infrequent. Thompson, for example, noted that at the Municipal Sanatorium in Chicago none of the specimens from resections in 1949 or 1950 showed evidence of open-healing, and only one case in 1951 was thus recorded. During this period, streptomycin and PAS was the standard therapeutic regimen. In 1953, however, after the introduction of isoniazid, there were thirteen such cases. "It would seem that this type of healing was related to present-day chemotherapy and more specifically to the administration of isoniazid" (68). Altmann records (65) that from 1947 to 1949 inclusive, 193 lung specimens with cavitation from patients



a. J. L. Nov. 6, 1954



b. J. L. Feb. 4, 1956

FIG. 4

c. J. L. Dec. 6, 1954 5 cm. A-P section
d. J. L. Feb. 27, 1955 5 cm. A-P section
e. J. L. June 26, 1955 5 cm. A-P section
f. J. L. Dec. 9, 1955 5 cm. A-P section

"Open Healing" of Cavity with Chemotherapy, "Bleb" Formation

Fig. 4. *a)* Film of Nov. 6, 1954 with cavity in right upper lobe, at onset of combined isoniazid-dihydrostreptomycin-P.A.S. therapy. *b)* Sputum became free of tubercle bacilli after one month of chemotherapy and has remained so. But cavity-like structure *increased* in size in right upper lobe. Film of February 4, 1956.

c–f) Serial tomograms, 5 cm. antero-posterior sections, show gradual increase in size of bleb.

treated with streptomycin were examined at Sea View Hospital. Only one of these showed a smooth-walled cavity. Subsequently, of 46 cases treated with isoniazid alone or with streptomycin, there were eight cases that had clean appearing, smooth-walled cavities.

I have observed one case of open-cavity healing in a patient treated with iproniazid alone.

EFFECT OF CHEMOTHERAPY ON SYSTEMIC MANIFESTATIONS

Those physicians whose familiarity with tuberculosis has been limited to the antimicrobial decade may perhaps inadequately appreciate the ravaging systemic manifestations not infrequently seen with untreated disease. The clinical picture of wasting, debility, anorexia, asthenia, malaise and general toxicity is not often seen now. The infrequent presence on our wards today of the gaunt, hollow-cheeked, coughing patient, flushed with a hectic temperature, is a tribute to the effectiveness of our present chemotherapeutic agents in combating the systemic manifestations of the disease even when the local anatomical healing is incomplete. This is true in varying degrees of each of the major drugs presently utilized.

Although variations exist the therapeutic effect on the systemic manifestations can usually be observed before the roentgenogram shows any change. This therapeutic effect varies directly with the degree of systemic toxicity. The greatest effects are noted in those patients who are highly toxic whereas they may go completely unnoticed in patients who show no evidence of systemic toxicity.

The major drugs can be enumerated in a rough order of ascendency with regard to their chemotherapeutic efficacy on systemic manifestations: PAS, streptomycin, isoniazid, iproniazid. PAS does have some effect on systemic manifestations but this is rarely observed, since the drug is usually not used alone.

Streptomycin and Isoniazid

Although isoniazid appears to have a more powerful effect on systemic manifestations than streptomycin, these effects are probably comparable and both are adequate in a high proportion of instances. In febrile cases, defervescence is usually accomplished within three weeks, with an average of eight to ten days, but occasionally therapy will fail to achieve full defervescence. I have observed reversal to normal temperature within 24 hours in patients who have been continuously febrile for many months. Defervescence may be delayed in the presence of empyema or by concomitant non-tuberculous infection. Once defervescence has been achieved, it usually persists. It used to be noted that when streptomycin was utilized alone in therapy there not infrequently was recrudescence of the fever after the second or third month of continuous therapy, and this would often be correlated with the emergence of streptomycin resistant bacteria and escape of the disease from therapeutic control. This is very uncommon with isoniazid therapy even after prolonged treatment and even in the presence of isoniazid resistant bacteria in the sputum. This observation denotes a major clinical difference between isoniazid and streptomycin when utilized as single drug therapy and is one of the reasons why streptomycin should, if possible, not be used alone while isoniazid may, in certain circumstances, be so utilized (79).

Defervescence is usually accompanied by an equally rapid reversal of general

systemic toxicity. This may even precede the return of the temperature to normal. The appetite is usually normal by the end of the first week and improvement in general strength and well-being is quite marked by the end of three weeks. In those instances in which there has been considerable weight loss, this process is reversed in the first or second week and, thereafter, there is rapid weight gain. Cough and sputum expectoration improve pari passu with the improvement of the systemic manifestations.

Iproniazid

A major exception exists to the above description of the chemotherapeutic effects on systemic manifestations. Iproniazid, the isopropyl derivative of isoniazid, exerts a very much more rapid and very much more marked effect on systemic manifestations of the tuberculous process than does any other antituberculous drug. The reason for this is not known. It seems unlikely to be due to a more vigorous antibacterial effect since in vitro isoniazid is effective in a much higher dilution although this difference is not so great in vivo. One possible explanation might be that iproniazid blood levels are considerably higher than those found with the same dosage of isoniazid. The possibility of a direct action on the host must be strongly considered. This might perhaps correlate with the greater neurotoxicity of iproniazid as well as the considerably narrower therapeutic dosage range. Also, host effect may correlate with the tendency to a "withdrawal syndrome" following iproniazid therapy although this is quite uncommon with isoniazid therapy (80). Finally iproniazid has been noted to have pain-relieving qualities in certain types of metastatic bone lesions as well as an influence in promoting tissue repair (81). Be that as it may, in the treatment of the severely ill tuberculous patient, iproniazid has no peer, at least for the acute phase and until the systemic manifestations have been brought under control. The original observations with regard to this unusual potency (47) have since been amply confirmed (82, 83). The only limiting factor to the successful use of iproniazid in this manner is its toxicity. Major toxicity is uncommon while minor signs of toxicity, although common, are considered "road signs in guidance as to dosage of the drugs" (84). With iproniazid, fever rarely lasts more than a week, weight gain is rapid in onset and marked in degree, on the average doubling that of isoniazid. Similarly, a feeling of well-being makes an early appearance as does renewal of appetite and general strength. As with isoniazid, however, if the patient at the onset of therapy shows no evidence of systemic toxicity, the effect of iproniazid will be minimal or lacking. I have found iproniazid particularly useful in the treatment of patients with disseminated tuberculosis in whom the general toxicity is often excessive in proportion to the visible local pulmonary lesion. However, isoniazid usually can replace iproniazid when the patient has reached a stable course.

LIMITATIONS OF CHEMOTHERAPY IN TUBERCULOSIS

With the successful development of potent chemotherapeutic agents in the past several years the effectiveness of chemotherapy in human tuberculosis has

not been limited by lack of effective antimicrobial drugs. This has been reflected in the high percentage of cures now possible in tuberculosis. It is perhaps no exaggeration to state that approximately 90 per cent of unselected and previously untreated cases can now be controlled with chemotherapy (69). This is true not only for pulmonary tuberculosis but similar results have been recorded in tuberculosis of bones and joints, tuberculous meningitis, genito-urinary tuberculosis, laryngeal tuberculosis, etc. Nevertheless, failure of complete control still occurs in a significant number of patients. Even if this be only somewhat less than 10 per cent, such failures constitute an important problem in a disease as common as tuberculosis. If at this time there are 100,000 new cases of pulmonary tuberculosis each year, a 5 to 10 per cent failure rate with chemotherapy would obviously leave uncured almost 10,000 persons each year, and many of these patients might not be amenable to collapse or excisional procedures and would remain as treatment failures.

It is thus important from a practical clinical point of view to analyze the causes of chemotherapy failure. Moreover, such analysis leads to better utilization of chemotherapy and more effective application of accessory procedures such as surgery or collapse therapy. Sufficient experience has now accumulated to permit tentative efforts at such evaluation. These indicate that limitations of effective antituberculous chemotherapy at the present time stems from three sources: difficulties inherent in the nature of the chemotherapeutic agents, those derived from the nature of the disease under treatment and, finally, those secondary to biological changes in the bacterial population itself.

Drug Toxicity

Fortunately, the chemotherapeutic agents now in use by and large put few stumbling blocks in the way of successful chemotherapy. They are well tolerated, have desirable pharmacological properties, are economically feasible. Moreover, the availability of a number of effective drugs makes inaccessibility to any one of these much less of a problem than might be anticipated.

Still, drug toxicity is of importance in chemotherapy. In all large series this factor has always been present to some degree and in a small but rather constant percentage of patients has prevented successful utilization of chemotherapy. For example, in one series of 443 cases treated by chemotherapy, 11 patients had to stop treatment because of drug reaction (85). Moreover, we have been deprived of the full therapeutic value of a number of drugs, such as pyrazinamide, because of their excessive toxicity.

The frequency of drug reactions varies with the antituberculous drug used. The exact incidence also varies with the conditions of the study, depending on such factors as dosage used, mode of administration, extent of disease treated, concomitant nontuberculous illness, duration of therapy, and the diligence of the investigator in noting and enumerating minor toxic reactions. From my own experience with a series of 108 consecutive personally treated cases (69) I would estimate that minor or major reactions can be noted in almost one-quarter of patients treated but that reactions severe enough to warrant cessation of therapy

to at least one drug occur in about 5 per cent. Of the 108 cases, cessation of therapy was of crucial importance in only one case (Table II).

Streptomycin and dihydrostreptomycin. Streptomycin and dihydrostreptomycin are examples of important antituberculous drugs with toxic properties which can be minimized by chemotherapeutic manipulation. The most important toxicity of these antibiotics has been, of course, eighth nerve toxicity. In the large scale Veterans Administration study, vestibular nerve toxicity, as measured by diminished response to caloric stimulation, was 21 per cent for patients treated with streptomycin and 15 per cent for those treated with dihydrostreptomycin. Audiometrically determined impairment of hearing of all degrees was 25 per cent for those treated with dihydrostreptomycin and 18 per cent for those treated with streptomycin. This included moderate or marked impairment of 10 per cent for dihydrostreptomycin treated patients and 5 per cent for streptomycin treated patients (86a). The toxic action on the auditory division of the eighth nerve is particularly important. When vestibular damage occurs, other mechanisms of equilibrium compensate for the damaged labyrinth and function improves. When there is damage to the auditory division of the 8th nerve, this often is permanent and indeed may be progressive even after the administration of the drug is stopped. There is no satisfactory compensation for the loss of hearing. Since dihydrostreptomycin allows a greater risk of auditory nerve damage, evaluation of toxicity has led to some preference for streptomycin, since their therapeutic potency is equal when they are used alone or with PAS.

The onset of disturbances is most common in the 3rd or 4th week of therapy but it may occur as early as the first 24 hours, or as late as the 8th week. When the patient is kept in bed, it may not be easily noticed, especially if the dysfunction is limited. This is particularly true since nausea and vomiting are rare and may be attributed to PAS. An early premonitory symptom previously unreported has been observed and studied in this hospital: there are often unilateral or bilateral taste changes (subjectively and objectively) before vestibular function can be found grossly disturbed (86b). If therapy is continued after vestibular

TABLE II

Incidence of Drug Toxicity in a Consecutive Series of 108 Patients Treated by Chemotherapy

Drug	Patients	Total reactions	Allergic reactions	Required total cessation of therapy
Isoniazid	96	3	1	1
Iproniazid	12	5	0	0
Streptomycin & Dihydrostreptomycin	86	16	4	0
P.A.S.	87	1	1	1
		25*	6**	2***

* In 23 individuals

** In 5 individuals

*** In the same patient

damage begins, the loss of function is progressive but the tendency to compensation is great and this is often complete, especially if the patient is young. At the termination of therapy, the patient is usually able to navigate without trouble.

Hearing loss should be observed even more carefully. Intermittent tinnitus is often of no consequence but should lead to audiometry studies. If cochlear acuity is diminished, dosage should be reduced or therapy stopped, if possible. Gross hearing testing with a pocket or wrist watch is simple and quick and should be done at each examination of a patient being given streptomycin or dihydrostreptomycin. Periodic audiometry during a course of treatment is also valuable, but does not replace clinical observations.

Numerous other toxic reactions have been reported to streptomycin and dihydrostreptomycin but generally these have either been uncommon or unimportant. Rare deaths have been reported from agranulocytosis, encephalopathy, exfoliative dermatitis. Paresthesias, especially about the lips and gums or other areas of the face are fairly frequent. Drug rashes and drug fever are not. The latter may be accompanied by lymphadenopathy and arthropathy. Contact dermatitis is possible, especially in nurses handling the antibiotics. A word of caution may be offered on the use of streptomycin in patients with diminished renal reserve, as with generalized amyloidosis secondary to the tuberculosis. Here, both the nephrotoxic action of the streptomycin itself plus the heightened blood levels consequent upon the renal disease may lead to serious consequences. I have observed near fatal encephalopathy in a patient with osseous tuberculosis and renal amyloidosis due to streptomycin given one gram twice weekly. When amyloidosis is suspected, its presence should be ascertained either by gingival biopsy (87) or the congo red test (88). I have successfully administered isoniazid and iproniazid in the presence of generalized amyloidosis (47), despite the known importance of renal excretion in the metabolism of this drug. In the presence of renal damage, of any cause, blood levels are not a practical procedure as a guide to streptomycin therapy, so that either alternate therapy should be used or the drug given with considerable caution.

Successful attempts have been made to limit the toxicity of streptomycin and dihydrostreptomycin. Firstly, it has been found that decreased frequency of administration maintains either all or almost all of the therapeutic efficacy but decreases the toxicity. From this observation derives the current practice of administration of streptomycin or dihydrostreptomycin two or three times in the week. This results in lower total dosage, a most important factor in reducing toxicity. When these antibiotics were given at levels of two or even three grams daily, 8th nerve damage was common. With one gram dosage, the incidence is much smaller. There has also been advocated the use of combinations of dihydrostreptomycin and streptomycin 0.5 gram each in the dose and this has given promise of diminishing the toxicity to each antibiotic while their additive effect maintains their therapeutic efficacy. Nevertheless, although this combination has theoretical advantages, toxicity to each branch of the eighth nerve through its use has been seen (89).

Hypersensitivity reactions to streptomycin and dihydrostreptomycin can also

be important. They usually occur early in the course of therapy, in from one to three weeks. Symptoms include fever, skin rashes, malaise, muscle pains, urticaria and headache. These reactions clear within a day or two after stopping the antibiotic. The diagnosis can be confirmed by a provocative test dose of 0.25 gram intramuscularly. It has been recommended that switching to either dihydrostreptomycin (90), or to the streptomycin calcium chloride complex if the sulfate salt had been used (91), will be successful in avoiding the allergic reaction. In my own limited experience I have not found such substitution effective. Moreover, the calcium chloride salt gives more local pain than does streptomycin sulfate. Desensitization can also be attempted but in my own experience this, too, has not universally been successful. Desensitization should be attempted early, since the longer the drugs are continued once hypersensitivity has occurred, the more difficult it is to desensitize these patients. When it is essential to continue the streptomycin therapy despite hypersensitivity and if desensitization is not successful, the use of corticotropin or cortisone to suppress the hypersensitivity reactions may be considered. Successful therapy of this nature has been reported (93). However, there has also been reported the development of severe drug hypersensitivity in a patient taking combined cortisone-streptomycin-PAS-isoniazid (94).

Para-aminosalicylic acid. Similar methods of management may be utilized for toxic reactions to paraaminosalicylic acid. The most serious PAS reactions are those due to hypersensitivity and while these are uncommon they may be fatal (95). The exact incidence of allergic reactions to PAS is uncertain. In one series, they were 2½ per cent (96) but in my own experience they have been more infrequent. Such reactions, when they occur, are as with streptomycin usually seen soon after the onset of chemotherapy, the first symptoms appearing in from one to five weeks. A rise in temperature may be the first sign of a significant hypersensitivity reaction, and any elevation of temperature during the first weeks of chemotherapy should be considered evidence of a drug reaction until proven otherwise. When noted, it should lead to immediate cessation of therapy. The possibility of drug reaction can then be studied by testing with a provocative dose of PAS, although this provocative test dose should not be a large one. In one instance, a test dose of 5.5 grams of sodium PAS was given, followed by a severe reaction and death (95). Skin rash is another important symptom of PAS hypersensitivity and usually follows a preceding pyrexia. Further, hepatitis and jaundice may occur as a result of the hypersensitivity reaction and while this usually follows pyrexia and skin rash, in isolated instances it may occur without such preceding symptoms (91). Other symptoms of hypersensitivity include malaise, joint pains and paresthesia. Löeffler's syndrome has also been observed (96), as has a condition resembling infectious mononucleosis. An instance of Guillain-Barré syndrome has also been reported following an allergic reaction to a good-sized "test" dose (97).

Hypersensitivity reactions to PAS may also be controlled by desensitization. Here, too, desensitization is more easily performed when the hypersensitivity is recognized early. Oral administration of gradually increasing amounts over a two

to three week period, starting with 0.5 gram of sodium PAS, will often accomplish desensitization. Some patients, however, do not tolerate the desensitization procedure (96) and PAS therapy must be discontinued.

The direct anti-thyroid effect of PAS, only slightly weaker than that of thiouracil, explains the occasional occurrence of goitre and myxedema among patients receiving PAS (98). That the goitre is due to the PAS is evidenced by the occurrence of 11 such cases at a sanatorium within a two and a half year period among patients receiving PAS, whereas no goitres were observed among employees or staff of the sanatorium (99). Also, laboratory data (98) demonstrate interference with thyroid function. Such goitres seem to be more common among women, are unrelated to the type of PAS salt used or the dosage administered. In contrast to the allergic reactions with PAS, the goitrogenic effect of PAS is usually not seen for at least several months after the onset of therapy. Fortunately, symptoms respond well to thyroid medication and interruption or cessation of therapy rapidly results in restoration of thyroid function and disappearance of the goitre.

In addition to the above significant, occasionally serious, but infrequent drug reaction to PAS, are the much more frequent but usually less serious gastrointestinal disturbance caused by this drug. The ingenuity, persistence and patience of the physician and patient will usually be rewarded with adequate tolerance. If intolerance is present to one PAS preparation, others can be utilized. When intolerance is present to the acid, calcium or sodium PAS can be given, especially since blood levels following their administration are generally more satisfactory (100). Enteric coated PAS may be utilized, but carries the objection of occasional poor absorption, undesirable with a drug in which variations of blood concentration are already unpredictable. Administration with or after food seems preferable and milk and fruit juices often serve to make it more tolerable. Concurrent use of aluminum hydroxide gel or belladonna preparations is sometimes useful and Thorazine® may also be administered. Very often the patient's own experimentation will provide a mode of administration best suited for him and discontinuance of therapy for short periods with its reinstitution often serves to reestablish tolerance.

Isoniazid. Toxicity to isoniazid can also be separated into drug allergy and drug toxicity. The former is uncommon but does occur. Desensitization can be accomplished by oral administration of gradually increasing amounts of the drug. The initial desensitizing dose should be small. Ten milligrams has been successfully utilized. In general, allergic reactions to isoniazid appear to be less common than those to PAS or streptomycin.

The important drug toxicity of isoniazid is that related to the nervous system. This was not predicted by the early animal studies (39), including those with monkeys (101). This toxicity was, however, noted in early clinical studies (40). Nervous system toxicity is moderately frequent in occurrence and may even affect five per cent of patients being given this drug (102) but the manifestations are usually mild. Apparently, all nervous tissue may be affected, perhaps by competitive metabolic effect. Peripheral neuropathy is the most common mani-

festation and may affect any peripheral nerve. Paresthesias in fingers and toes are usually the symptoms of such toxicity, with burning or tingling. There may be aching "of the bones" with some calf tenderness. Usually, the deep tendon reflexes are not altered but some patients may show exaggeration of these reflexes and I have observed complete loss of deep tendon reflexes in others. Vibratory sense usually remains intact in the presence of paresthesias, but may disappear in severe cases.

Peripheral neuropathy is more common and more severe in debilitated, toxic or older patients, in those in whom iproniazid is simultaneously administered, and, from limited observation, possibly in those with liver disease. Even in such patients, however, rarely is it severe enough to warrant discontinuance of therapy. When this is necessary, improvement is often slow and therapy with pyridoxine (103), Vitamin B_{12}, Vitamin B complex, glutamic acid, BAL, protamide, thiamine chloride and other medications may occasionally be useful but is not infrequently disappointing. Recovery is most always complete and therapy may be restarted in many cases without recurrence of the neuropathy. In some patients, however, this will recur and isoniazid will be unavailable to them.

Autonomic nervous system toxicity may be evidenced by other symptoms, but these are rarely important. Commonly, constipation may be noted as might difficulty in micturition. We have not observed as frequently, with isoniazid, the significant changes of sexual activity that may be noted with its isopropyl derivative, iproniazid. However, these occasionally occur and are usually in the direction of depressed activity and libido.

Cerebral symptoms, although they are the least common of the neurological manifestations of toxicity, are also the most important. The complication most to be feared is psychosis. This may be rapid in onset after the inception of therapy and while recovery usually ensues quickly, this is not always the case. This rare reaction is more common in those patients with a previous history of psychiatric difficulty or unstable personality, whereas patients with organic brain disease usually do not show this toxic manifestation. Therapy should be discontinued immediately upon any evidence of such reaction. In my experience, it can often be later restarted in the same patient, at the same dosage level without any difficulty. The therapeutic use of vitamins of the B complex group has been attempted but reports are too few to evaluate their efficacy, especially since spontaneous recovery is so very common. Convulsions may also occur. These, too, are more common in individuals with previous history of such abnormality, and subside upon discontinuance of therapy and may not recur with its reinstitution. Uncommonly, other central nervous system symptoms occur such as nervousness, apprehension, insomnia, headache, vertigo, and a syndrome of headache, restlessness and peculiar dreams upon withdrawal of medication, especially if this be done suddenly (80).

Toxic symptoms other than those of the nervous system are infrequent. Drug fever has been recorded (104), possibly due to allergy, and occasionally dermatitis is seen, in susceptible individuals, from handling the chemical (105). Rarely, as almost with any drug, hematological abnormalities are seen, including throm-

bocytopenia and leucopenia with agranulocytosis. Jaundice, abnormalities of the urine and purpura have also been observed. These findings are rare and biochemical abnormalities in routine clinical laboratory tests were almost completely absent in a very large series of several thousands of such tests (47). Also uncommon but occasionally troublesome and possibly due to allergic reaction, are occasional instances of bronchospasm with dyspnoea as well as instances of arthralgia, sometimes with joint swelling. These symptoms may occur early in the course of therapy. In my own experience, I have been unable to predict in which patients these will occur. They do not usually require cessation of therapy.

There has also been reported, during the treatment of the acute primary complex in children, a syndrome of febrile exacerbation during the second and third weeks after institution of therapy coupled with perifocal infiltrations or atelectasis on the roentgenogram. These latter were thought to be due to an intense exudative reaction consequent upon isoniazid-induced bacteriolysis, with local liberation of large amounts of tuberculin (106). These findings did not interfere with therapy in these children.

The occurrence of gynecomastia during the administration of isoniazid has been mentioned (107). It is speculated that circulating vitamin B is inactivated by large amounts of isoniazid, with consequent liver function impairment and increase in circulating estrogen. I have not myself observed this abnormality.

Much of the toxicity of isoniazid appears formidable when listed, but in actual practice toxic reactions sufficiently severe to warrant discontinuance of therapy occur in fewer than 1 per cent (69, 102). Actually, the drug is relatively free of toxic side effects, essential in a medication so widely used and requiring prolonged administration. Many of the toxic side effects are related to dosage. This is particularly true of peripheral neuropathy. In one series, the drug was toxic for 1 per cent of patients being treated at a level of three milligrams of isoniazid per kilogram of body weight, whereas of those patients receiving ten milligrams of isoniazid per kilogram of body weight, more than 10 per cent had drug toxicity. Differences in dosage levels of rather minor degree do not result in clinically recognizable differences in toxicity. In the original studies with isoniazid, comparison of drug toxicity in two groups of patients receiving four milligrams per kilogram of body weight and eight milligrams per kilogram of body weight did not reveal significant differences in toxicity (40, 47). However, at dosage levels above this range, toxicity is increased, at least in adults. Children appear to be able to tolerate much higher doses without increase in toxicity. Caution with high doses must especially be observed in patients who are toxic, debilitated, avitaminotic, or elderly. It has been noted that studies of toxicity in monkeys would suggest the clinical use of isoniazid dosage levels far beyond those presently employed (108) and reports of such administration in man have been made (109). My own experience would indicate that high dosage therapy must be approached with a good deal of caution. In a small series of patients treated with doses approximating 20 milligrams per kilogram of body weight (110) prohibitive toxicity was observed, including marked somnolence and psychosis. Peripheral neuropathy, too, is much more common on such high doses, varying from 20 to 37 per

cent (111). Moreover, detailed review of the report of uncomplicated administration of high doses in man (109), reveals that the drug was administered to only five patients. These did not have tuberculosis, and three of the five cases so observed had the drug only for six days. One of the other two developed peripheral neuropathy. At least until wider experience accumulates, doses above 10 to 15 milligrams per kilogram of body weight should be utilized with caution, with the patient under close observation. For general use, dosages in the effective range of three to eight milligrams per kilogram of body weight should be used, especially since isoniazid exerts excellent therapeutic qualities at this level.

The variations of isoniazid toxicity with different dosage ranges has been studied principally insofar as it relates to long-term administration of the drug, since its clinical use is so planned. Insofar as acute toxicity is concerned, the therapeutic index of the drug is very much greater than the above discussion of dosage ranges would indicate. Although in long-term administration the usual daily dose approximates 300 to 600 milligrams per day, evidence is available that the tolerated dose is significantly larger. Of two attempts at suicide with isoniazid reported, one with 8.6 grams did not succeed although neuropathy was severe (112). Another with 15 grams resulted in death due to paralysis of the respiratory center (113).

Iproniazid. Iproniazid resembles isoniazid in its toxicity, but this is present in greater degree. This is unfortunate, since the systemic effect in tuberculosis of iproniazid is much more impressive than is that of isoniazid. Most of the early dramatic reports of rapid and marked symptomatic response to hydrazide therapy were the result of iproniazid administration among the early patients treated (114). Unfortunately, despite the fact that in toxicity trials in dogs iproniazid has much less of a toxic effect on the central nervous system than does isoniazid at the same dosage level (115), in human beings the reverse is true.

With iproniazid, again, the nervous system is the site of predilection for toxic effect. All major divisions may be effected. Peripheral neuropathy may be quite severe and, as with isoniazid, is more frequent in debilitated patients. Muscle twitchings, tremors, difficulties of visual accommodation may occur and are often remarked upon by the patient. Hyperreflexia with or without clonus may occur and it is important for the physician to seek these signs. When they are excessive, they serve as a warning to temporarily discontinue therapy, or decrease the dosage. A frequent dosage range utilized is four milligrams per kilogram of body weight, although in osseous tuberculosis three milligrams per kilogram of body weight has recently been advocated (84). Estimation of total daily dosage utilizing body weight as a guide is much more critical with iproniazid than with isoniazid. Whereas 50 milligrams more or less per day makes very little difference with isoniazid dosage, it might be a significant factor in the toxicity to iproniazid. Iproniazid is a much more volatile drug for the physician to learn to use, although when this is achieved the reward of rapid and lasting therapeutic effect on systemic manifestations will be obtained.

Autonomic nervous system symptoms are also more severe with iproniazid and include blurring of vision, impotence or increased libido, occasional vertigo,

urinary hesitancy, dryness of the mouth, obstipation or constipation, attacks of headaches with flushes (especially with adrenergic drugs), sweating, elevation of blood pressure and palpitations. Nevertheless, these symptoms are not serious and are usually merely an inconvenience. Cerebral symptoms, on the other hand, may be very serious. Indeed, they constitute the toxic limitations to iproniazid therapy. Confusional psychosis, euphoria and headaches may all occur. The "withdrawal syndrome" is much more common and much more severe than with isoniazid, with terrifying dreams, nervousness, restlessness, depression and headache. Although it may be minimized with phenobarbital, it may last from two to four weeks (80). Probably also mediated through the nervous system are occasional pyribenzamine and pontacaine intolerance.

Hypersensitivity to iproniazid may also occur, although its incidence is uncertain. Generally speaking, drug allergy in the chemotherapy of tuberculosis is unpredictable. In my own personally studied series of 108 cases, allergic reactions to drug therapy were noted in five patients. Only one of these five had a known history of clinical allergy. Moreover, in this series there were five other patients who had history of clinical allergy, yet did not suffer an allergic drug reaction during treatment. This would seem to indicate, if confirmed, that previous history of clinical allergy will not be of assistance in anticipating drug allergy reactions.

Treatment of iproniazid drug toxicity resembles that of isoniazid toxicity treatment. Firstly, as noted, dosage should be much more carefully controlled. When reactions occur, therapy should be temporarily halted, or the dosage decreased. Moreover, presently available information would indicate that isoniazid is as effective as iproniazid in the control of the tuberculous lesion, at least in pulmonary tuberculosis. Therefore, in those instances in which iproniazid is utilized to rapidly control the systemic manifestations of the disease, as soon as these are no longer present, it would seem prudent to substitute isoniazid therapy for continuation of treatment. This may not always be possible, however, especially in those situations in which there is evidence that iproniazid is more effective in the control of the disease than is isoniazid (81). For a number of neurological manifestations of iproniazid toxicity, phenobarbital will often ameliorate the symptoms. The "withdrawal syndrome" may be prevented or minimized by gradual, rather than sudden, discontinuance of the medication. When symptoms of the withdrawal syndrome are marked, reinstitution of small doses of iproniazid will often alleviate them. I have observed this effect also in one instance in which symptoms of pollenosis and allergic rhinitis, which had disappeared during iproniazid therapy, recurred following its discontinuance and were again controlled upon the readministration of iproniazid. I have no personal information concerning possible desensitization to iproniazid, but I should assume that desensitization could be accomplished in the rare instances in which such an attempt would be mandatory.

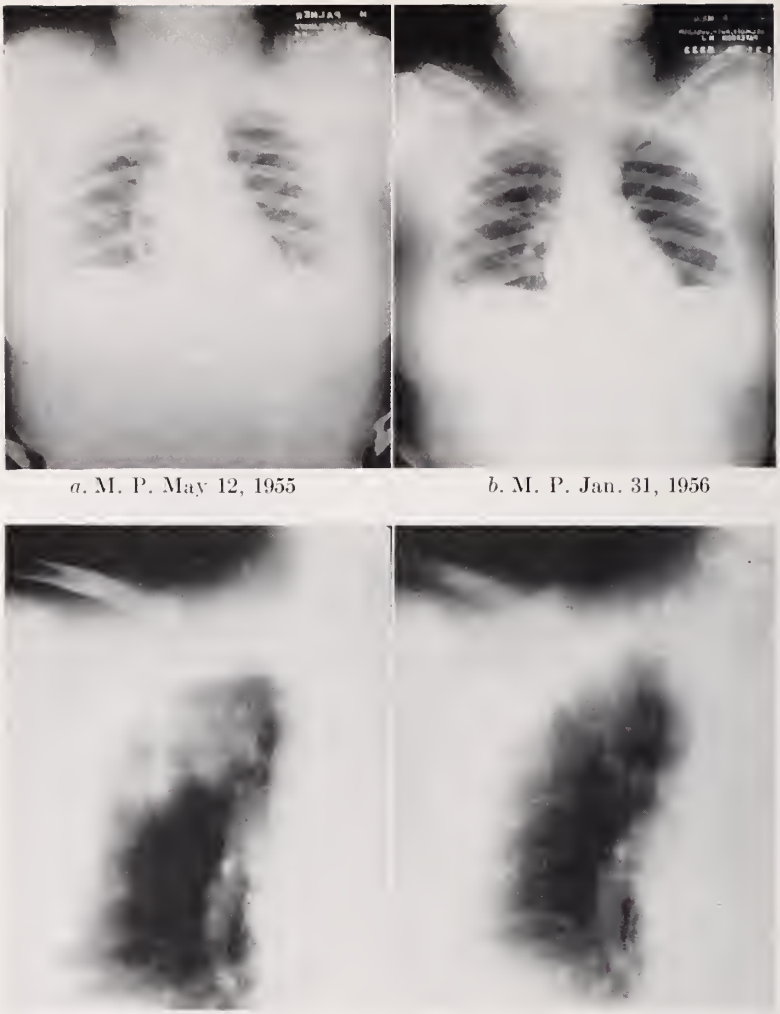
Pyrazinamide. Another example of a potentially potent antituberculous agent, the full utilization of which is denied so far by drug toxicity, is pyrazinamide. Although in the original clinical study of this drug only "mild" toxic reactions were noted, such as joint pains, drug fever and eosinophilia, it was also remarked

that jaundice occurred in two of the 43 patients treated. Liver function tests had suggested parenchymal involvement but prolonged observation following the discontinuance of therapy showed no residual signs of hepatic disease (43b). Nevertheless, subsequent trials showed that this hepatic toxicity was formidable. Of 81 patients treated, 61 for at least three months, there were six instances of drug induced hepatitis (116). One was fatal. Moreover, in the latter case, the hepatitis occurred after only very trivial initial complaints and by the time the presence of hepatitis could be established, the illness became severe and terminated fatally.

These clinical trials had been performed with a dosage level of pyrazinamide of 50 milligrams per kilogram of body weight per day. In an attempt to reduce the toxicity while maintaining therapeutic efficacy, another study was undertaken at a level of 20 to 30 milligrams per kilogram per day. Unfortunately, two patients and possibly a third of the 61 cases studied developed hepatitis. Moreover, the therapeutic efficacy seemed impaired (117). Similar studies with over 300 patients in the Veterans Administration showed abnormal liver function tests in 14 per cent of the patients treated with jaundice in from one to three per cent (118). This hepatic toxicity is difficult to control or predict, since it may come without warning, unlike that occurring with PAS, and may be rapidly fatal. Also, whereas hepatic damage with PAS is usually early in the onset of therapy, hepatitis with pyrazinamide may come as late as six months after the start of treatment. It is unfortunate that techniques have not yet been designed to circumvent this toxicity since, experimentally, the combination of isoniazid and pyrazinamide appears to be the most potent available in antituberculosis chemotherapy (119).

Viomycin. Viomycin also has significant toxicity for humans and this, coupled with its limited therapeutic efficacy, has militated against its wide therapeutic employment. In addition to possible eighth nerve damage similar to that of streptomycin, there may be nausea, vomiting, allergic manifestations, and evidence of renal damage, with proteinuria, cylinduria and mild azotemia. There may be also abnormalities of plasma electrolytes (120). The incidence of viomycin toxicity is perhaps the highest in antituberculous chemotherapy at present. In one group of 125 patients, toxicity occurred in 33 per cent (121), and in another smaller study 59 per cent of the patients showed toxic side effects of varying severity. In this latter group, drug toxicity necessitated discontinuance of therapy in 19 per cent of the group (122). Viomycin toxicity often requires diminution of the dose to a point at which the moderate therapeutic effectiveness of the drug is curtailed. Thus, while toxicity may be decreased by reducing the dose to 2 grams, twice weekly, this simultaneously minimizes its effectiveness. In situations in which it is urgent to employ viomycin alone, especially because of drug resistance to other agents, larger doses probably should be utilized despite the increased risk of toxicity.

Cycloserine. Toxicity with cycloserine therapy is still inadequately studied but appears to be significant. In the first human study with this drug, toxicity requiring cessation of therapy occurred in almost 10 per cent of patients (56b).



a. M. P. May 12, 1955 *b*. M. P. Jan. 31, 1956

c. M. P. May 15, 1955, 9 cm. A-P section *d*. M. P. Dec. 24, 1955, 9 cm. A-P section

CHEMOTHERAPY AS DEFINITIVE TREATMENT: RAPID CLEARING OF EXUDATIVE DISEASE

FIG. 5. *a*) Tuberculous exudative infiltration in roentgenogram of May 12, 1955. Although no cavity could be found on tomography, culture of sputum showed growth of tubercle bacilli. *b*) Roentgenogram of Jan. 31, 1956 showing excellent clearing of infiltration on combined isoniazid-dihydrostreptomycin-P.A.S. therapy. The almost complete clearing is expected in this exudative tuberculous infiltration since absorption predominates, especially with isoniazid therapy. *c* and *d*) Tomographic sections of May 15, 1955 and Dec. 24, 1955 at 9 cm. antero-posterior levels. These sections confirm the healing by absorption rather than fibrosis suggested by the conventional film. No tubercle bacilli have been present in sputum since almost immediately following the onset of therapy.

There were also minor toxic reactions not requiring discontinuance of treatment in several others. These toxic reactions included convulsions and excitatory states as well as confusion. Skin rashes were also noted, while observations are inconclusive with regard to personality or mood changes (123). It may be hoped

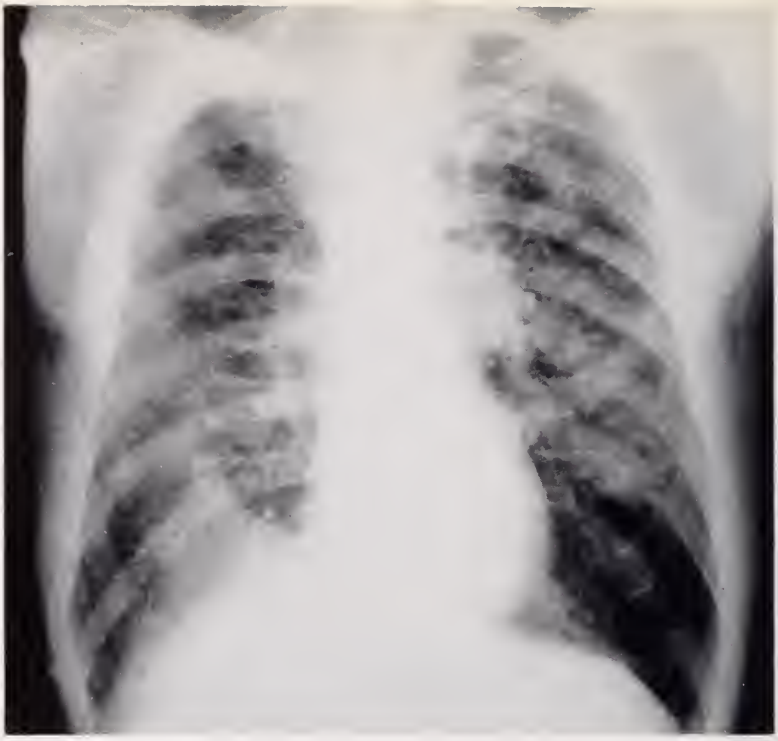
that further studies, including diminution of dosage levels, will demonstrate a lower incidence of toxic reactions.

Nature of the Disease under Treatment

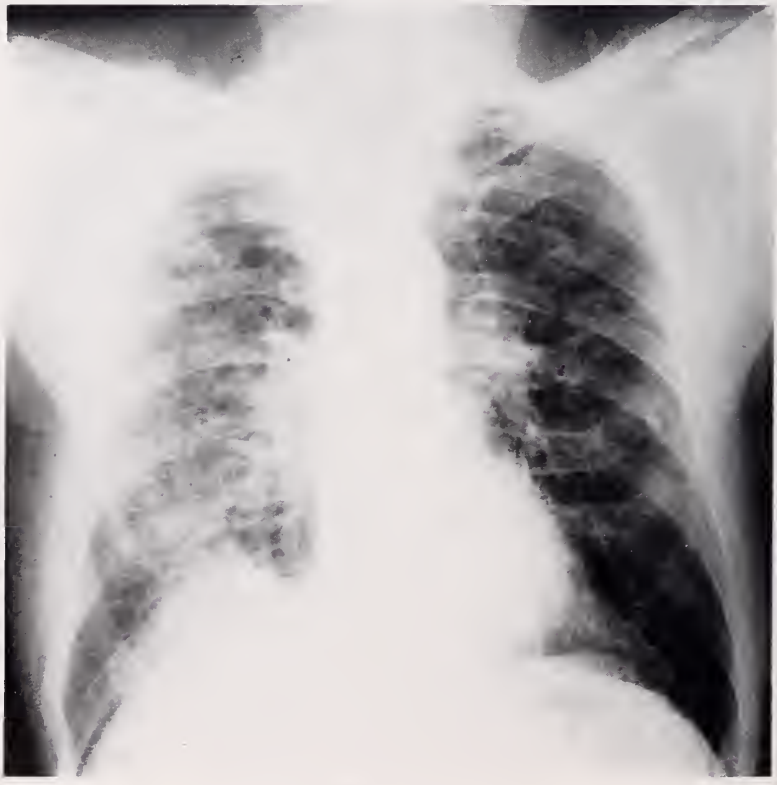
The second factor limiting the chemotherapeutic effectiveness of anti-tuberculous drugs is the presence of pathological changes inaccessible to adequate therapy. This, the nature of the disease under treatment, is probably the single most important factor in determining the success or failure of chemotherapy. Nevertheless, this aspect of the problem of chemotherapy has perhaps been least studied. There are a number of explanations for this apparent paradox. Firstly, investigation of the effect of variation in the disease process upon chemotherapy is not easily amenable to comparative statistical evaluation, which has been the most frequently utilized method of studying problems in chemotherapy. Thus, the large scale studies in chemotherapy conducted by the United States Public Health Service, the British Medical Research Council and the Veterans Administration may be well suited to study the comparative results of such aspects of chemotherapy as variations in dosage, techniques of administration, drug combinations, duration of therapy, and incidence of bacterial resistance, but they do not lend themselves easily to comparison of the most important variable, the nature of the disease under treatment. This would depend upon analysis by different observers of the pathological nature of the roentgenographic abnormality, which is notoriously difficult both of classification and correlation (124). Moreover, the number of variations which occur among patients with tuberculosis is almost as great as the number of cases analyzed. It is probably for this reason that Tucker and Livings conclude their detailed analysis of the Veterans Administration, Army and Navy studies on the Chemotherapy of Tuberculosis with: "There is increasing evidence that the final decision as to what antimicrobial therapy will be prescribed in practical clinical application will depend on variations of the disease and on other factors not included in the large-scale British and United States cooperative studies" (86).

In addition to the problems inherent in the evaluation of the effect of variations in the disease in multi-observer studies, similar difficulties may beset even well organized and close-knit personal observations. This is so not only because the disease process influences the success or failure of the outcome of treatment but additional inter-acting variables are usually present in any series. These include previous treatment, duration of the disease process, utilization of concomitant therapy, dosages and drugs used, incidence of toxicity, the age, sex, derivation and economic status of the patient population observed, drug regimens used, and even, to some extent, the skill of the treating physician. From this array, one can appreciate the difficulties of evaluating the effect of any single variable, even such an important one as the nature of the disease.

Part of the problem is solved for us by the wide therapeutic range of modern chemotherapy. Niceties of differential prognosis are not required when such therapeutic range will encompass most of the observable differences. Range of



a. G. W. Mar. 19, 1954



b. G. W. Feb. 4, 1956

FIG. 6

effectiveness of chemotherapy was unpredicted and is still incompletely appreciated.

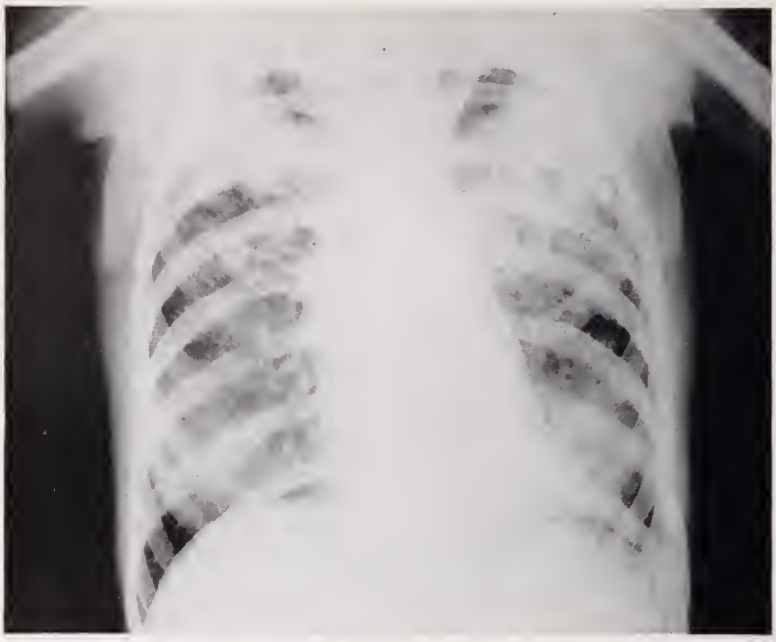
Any analysis of the effective range of chemotherapy must exclude, as far as possible, those limitations of chemotherapy due to drug toxicity or intolerance, or to acquired bacterial drug resistance. When these factors are eliminated, it will be still found that there remains a hard core of cases which predictably are likely to fail to respond to chemotherapy. There will be a much larger group which predictably will respond well in almost every instance to similar chemotherapy. Finally, there is a third group in which chemotherapy will usually be successful but will fail sufficiently often so that prediction is hazardous.

This grouping is important from a practical point of view. The second group obviously requires chemotherapy as the procedure of choice and it can be prescribed with confidence. The third group should be similarly treated, but with close observation for evidence of impending failure so that application of appropriate accessory therapeutic measures can be expeditiously recommended, if required. In the group of anticipated chemotherapy failures, it would be wise to utilize other measures than chemotherapy, if such are appropriate, adding chemotherapy as an auxiliary in each case. If, however, accessory procedures are not suitable for patients in this group of anticipated chemotherapy failures, chemotherapy should nonetheless be advocated, since even in this group a significant number of patients will respond satisfactorily (125). Indeed, it is perhaps unwise to classify any group as anticipated or predicted chemotherapy failures, since this is a relative term and the most that one can say of patients included in this group is that they are less likely to respond to chemotherapy.

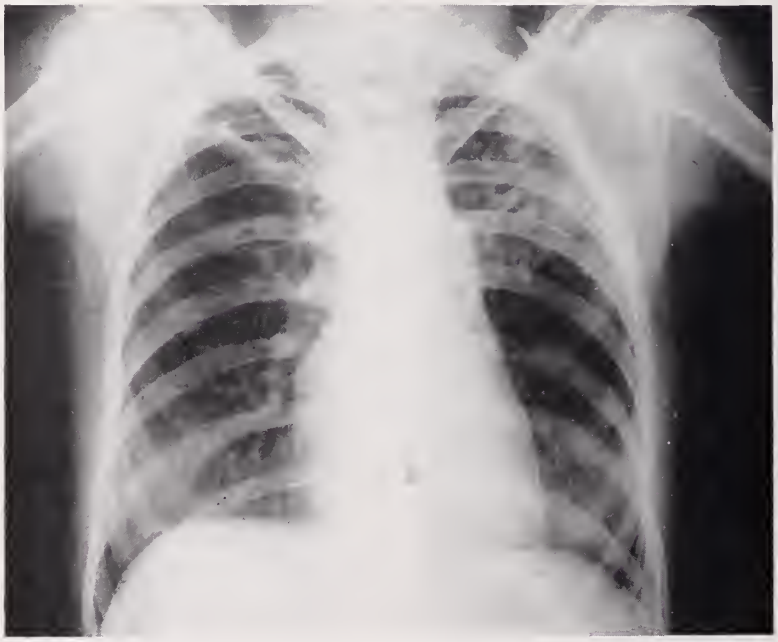
Chemotherapy as definitive treatment. The group of predictable chemotherapeutic success contains most patients with recent disease. Nevertheless, it is uncommon to see pulmonary tuberculosis of a purely exudative, easily reversible nature. Most lesions when seen even relatively early are "mixed" lesions with exudative, caseous necrotic and fibrotic changes. Assumptions with regard to the irreversibility of necrotic and fibrotic elements of these lesions should not be lightly made, since clinical observation with chemotherapy indicates that regressive and absorptive changes take place in many of them. As noted in preceding discussion, data is still inadequate on this point, since lesions regressing under chemotherapy are rarely available for pathological study. Very often, too, the duration of disease is difficult to ascertain. Evaluation must be based in most cases on interpretation of the roentgenographic appearance. An example of an exudative tuberculous lesion which typically healed well is shown in figure 5. Not infrequently, these lesions, even when they are very small, will take a con-

CHEMOTHERAPY AS DEFINITIVE TREATMENT: CLEARING OF DISSEMINATED EXUDATIVE-PRODUCTIVE DISEASE

FIG. 6. *a*) Roentgenogram of Feb. 19, 1954 shows extensive infiltrations in both lungfields in disease of many years duration. This film represents lesions of mixed exudative-fibrotic nature, indolent in course. *b*) Roentgenogram of Feb. 4, 1956, after two years of combined isoniazid-P.A.S. therapy with considerable clearing. Despite the extent of such bronchogenic disseminated lesions, the absence of large conglomerate masses usually allows for good chemotherapeutic response. The patient's sputum has been free of tubercle bacilli since the third month of therapy.



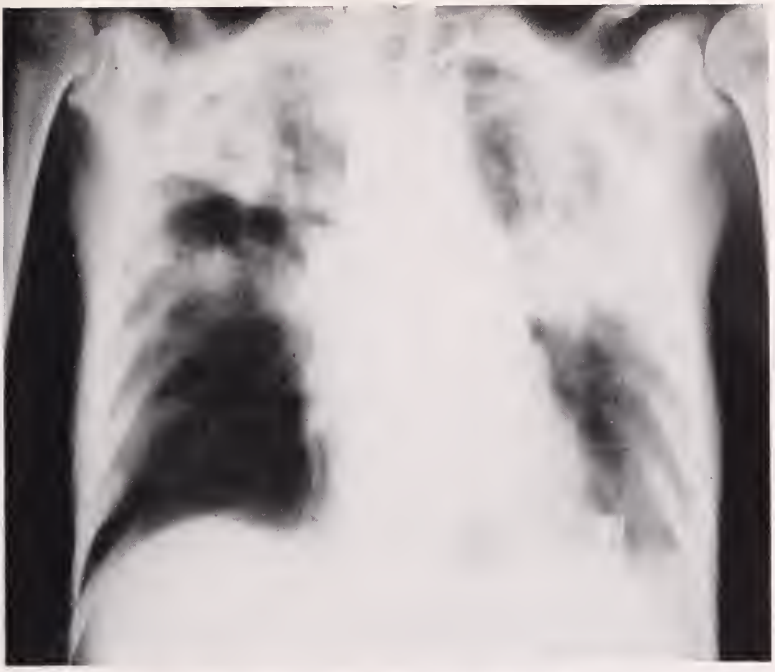
a. S. A. Nov. 30, 1953



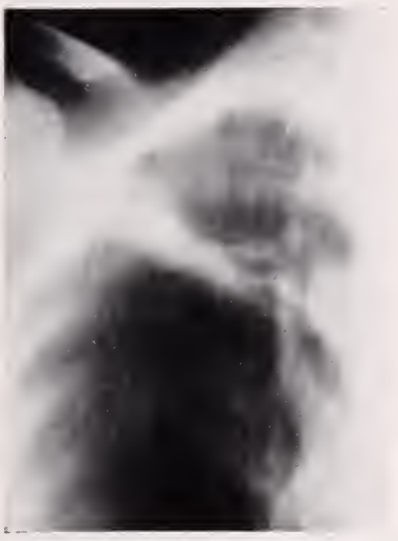
b. S. A. Jan. 26, 1956

TRIAL OF CHEMOTHERAPY: PROLONGED TREATMENT IN EXTENSIVE DISEASE

FIG. 7. *a*) Roentgenogram of Nov. 30, 1953 shows extensive bilateral caseous pneumonic tuberculosis in patient with progressive downhill course of several months duration. Sputum contained many tubercle bacilli on smear. *b*) Combined isoniazid-dihydrostreptomycin-P.A.S. therapy shows marked but still incomplete reabsorption of much of this disease, on roentgenogram of Jan. 26, 1956. Disease of such extent and nature requires prolonged chemotherapy.



c. S. A. Dec. 10, 1953, 7 e.m. antero-posterior section



d. S. A. Dec. 24, 1955, 7 e.m. antero-posterior tomographic section of right upper lobe

e. S. A. Dec. 24, 1955, 7 e.m. section of left upper lobe

FIG. 7—*Continued*

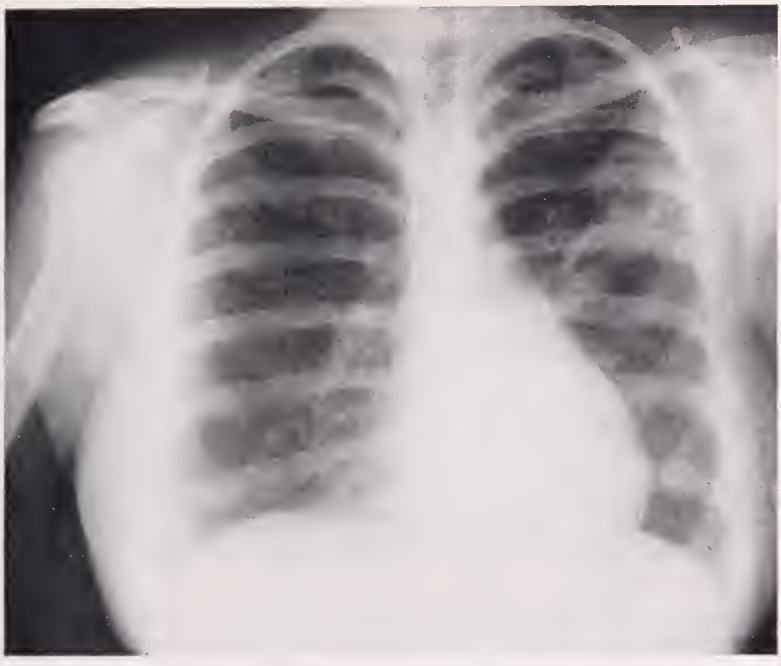
c) 7 e.m. antero-posterior tomographic section of Dec. 10, 1953 emphasizes caseous as well as exudative nature of this infiltration. *d*) 7 e.m. antero-posterior tomographic section of Dec. 24, 1953 indicates that considerable reabsorption is possible in such lesions. Cavity in right upper lobe has healed, but residual infiltration is still present. *e*) 7 e.m. antero-posterior tomographic section of the left upper lobe on Dec. 24, 1955 shows similar regression with residual caseous foci. Culture of sputum on many occasions during the past 16 months have failed to show growth of tubercle baeilli. Chemotherapy continues with isoniazid and P.A.S. and residual lesions are being carefully observed.

siderable time to heal; regression will continue for many months. It is probable that, despite the x-ray appearance, caseous material is present in these infiltrations and they are not entirely exudative. Even when these lesions are scattered bilaterally and are mixed with productive changes, they do well. Figure 6 demonstrates such a response. Many of these lesions represent indolent progression of disease, presupposing good host resistance and providing a highly satisfactory base for chemotherapy.

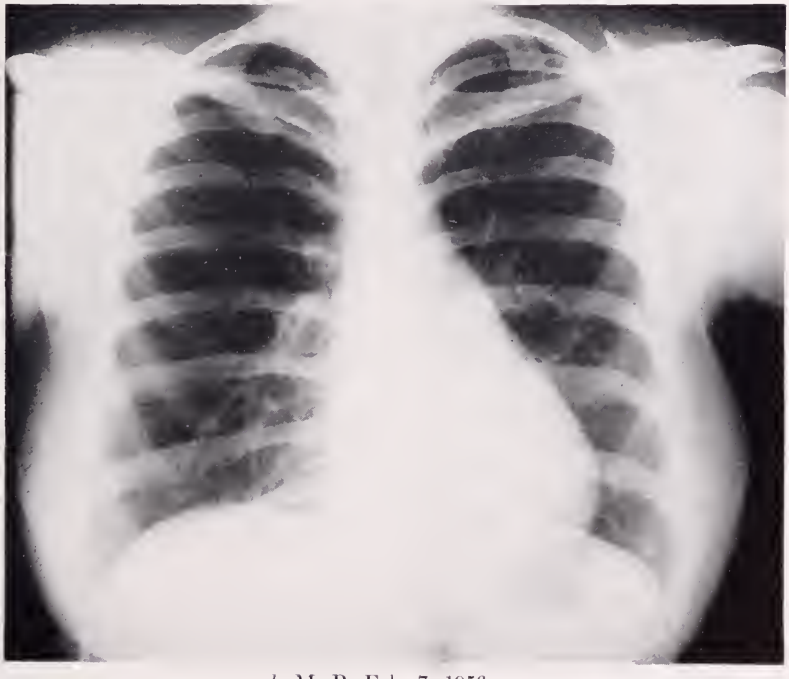
The extent of the infiltration, although not without influence (86), does not invalidate the basic observation that these lesions will heal and figure 7 is an example of such a response. These patients, however, require prolonged chemotherapy since there is much disease to be reabsorbed. Response to chemotherapy with continued regression continues for long periods of time. These lesions are an exception to what is for many cases a good general rule, that chemotherapy response should be judged at approximately six months, with consideration of the addition of accessory therapy at that time. These lesions, on the contrary, will continue to regress after six months and chemotherapy should be continued under close observation so long as regression is observed. Although as a general rule sputum conversion will occur before the end of six months of chemotherapy in cases in which such treatment will be successful, in patients with extensive disease of recent origin, loss of sputum infectivity may not occur until the tenth or twelfth month of therapy.

The presence of cavitation, similarly, need not prevent a good prognosis in patients with recent disease, although chemotherapy usually results in more rapid reabsorption of the pericavitary infiltration than in cavity closure. The pericavitary infiltrate may show marked absorption by the end of the second or third month of treatment, whereas the cavity may not close until after several additional months of chemotherapy. In other instances, the cavity will close simultaneously with the reabsorption of the pericavitary infiltrate (Fig. 8).

Pulmonary infiltration which is evidence of hematogenous dissemination also responds well to chemotherapy (Fig. 9). The prognosis of the patient generally is good. Not only will the disseminated pulmonary lesion heal, but there is usually arrest of the (extrapulmonary) source of dissemination. In many instances, this primary source cannot be ascertained even though genito-urinary, osseous, pelvic and glandular foci are carefully sought. Chemotherapy should be continued in these cases for a long period of time and the response of the pulmonary lesion, which is often very rapid, is not a guide in these cases for estimation of duration of therapy. This must rather be decided upon the basis of our knowledge of the presence of other, perhaps not clinically demonstrable, disseminated disease, as well as the source for the hematogenous dissemination. Properly applied chemotherapy for these lesions must contain isoniazid. With this drug utilized either singly or in combination, there has been no case reported of the development of meningeal tuberculosis during treatment of hematogenous tuberculosis. This is not true of chemotherapeutic regimens omitting isoniazid (79). It is probable that the rationale for the success of chemotherapy in disseminated "miliary" tuberculosis lies in the fact that these lesions are always of recent origin.



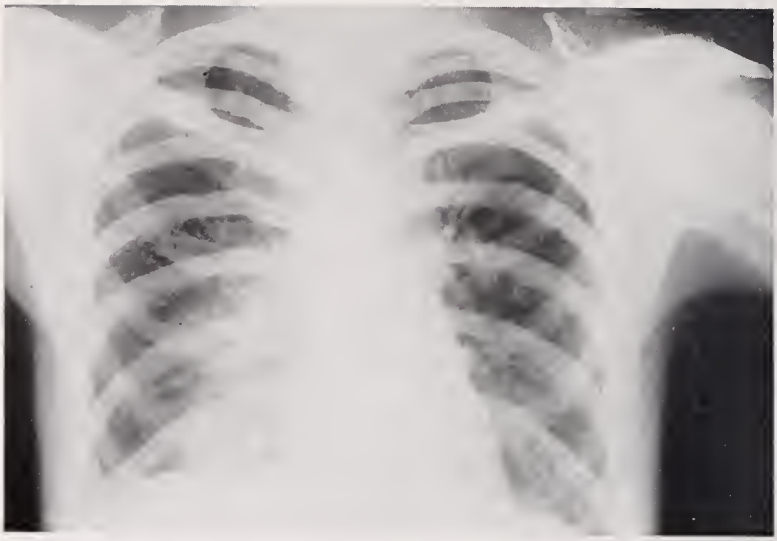
a. M. B. Nov. 22, 1954



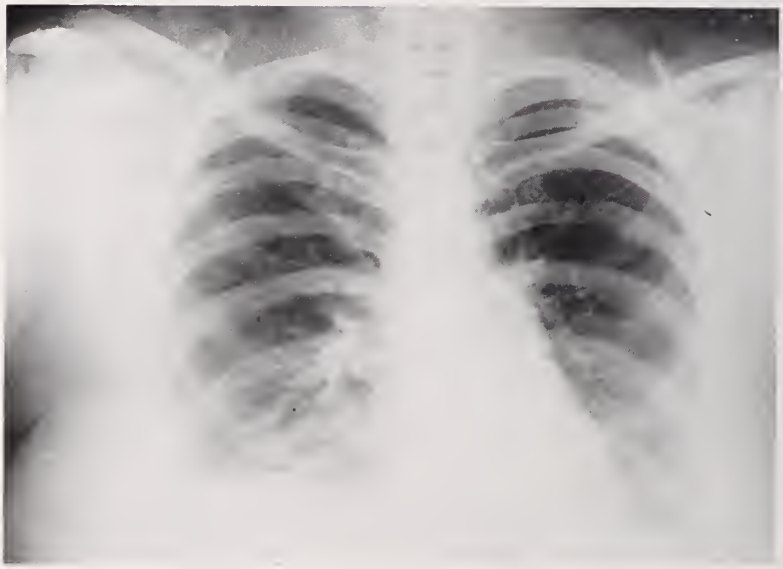
b. M. B. Feb. 7, 1956

TRIAL OF CHEMOTHERAPY: RAPID RESPONSE IN RECENT CAVITARY DISEASE

FIG. 8. *a*) Roentgenogram of Nov. 22, 1954 shows moderately large cavity in left upper lobe. However, roentgenographic appearance is that of recent disease and chemotherapy is effective in most such lesions. Chemotherapy was combined isoniazid-dihydrostreptomycin-P.A.S. *b*) Film of Dec. 7, 1955 shows only linear residual scar to mark site of previous cavity. Sputum examination showed disappearance of tubercle bacilli during the second month of treatment although cavity did not finally close until the end of the third month.



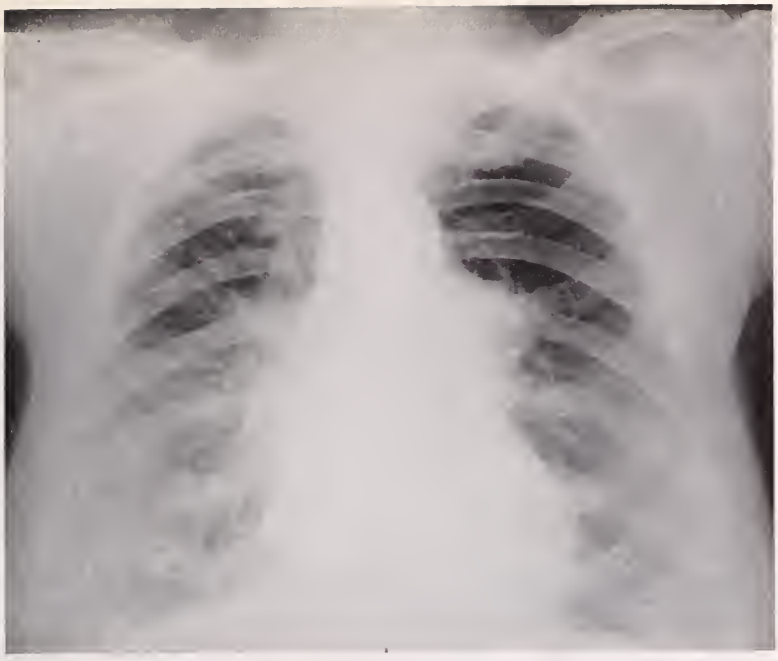
a. B. H. Nov. 12, 1952



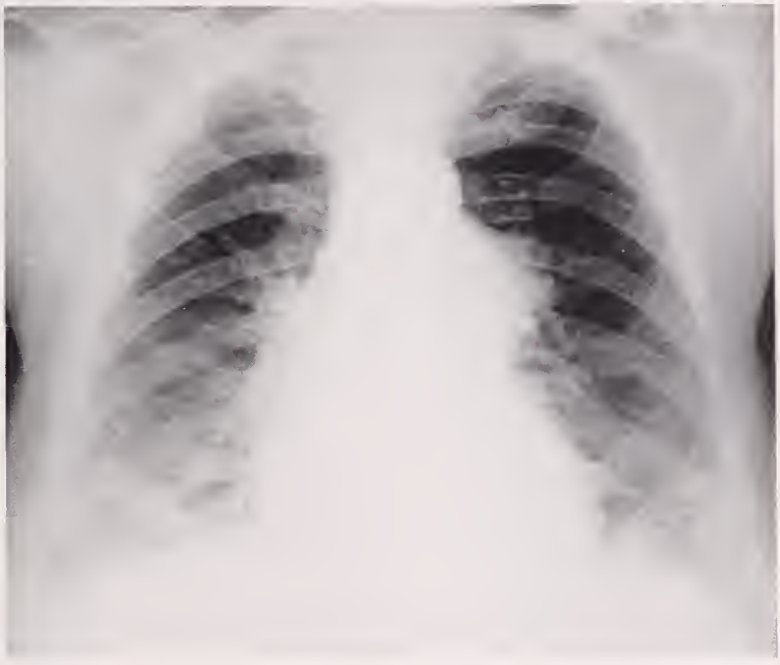
b. B H. Sept. 14, 1955

Effectiveness of Chemotherapy in Hematogenous Disseminated Tuberculosis

Fig. 9. *a*) Roentgenogram of Nov. 12, 1952 shows scattered bilateral infiltrations and mediastinal adenopathy in a patient with disseminated tuberculosis. Tuberculous peritonitis was also present. *b*) Following two years of combined isoniazid-dihydrostreptomycin-P.A.S. therapy roentgenogram shows complete clearing. Extrapulmonary foci similarly no longer give evidence of their presence. Isoniazid therapy is particularly useful in such cases. Not only does rapid healing result, but unlike other drug treatment, meningitis does not occur with isoniazid therapy.



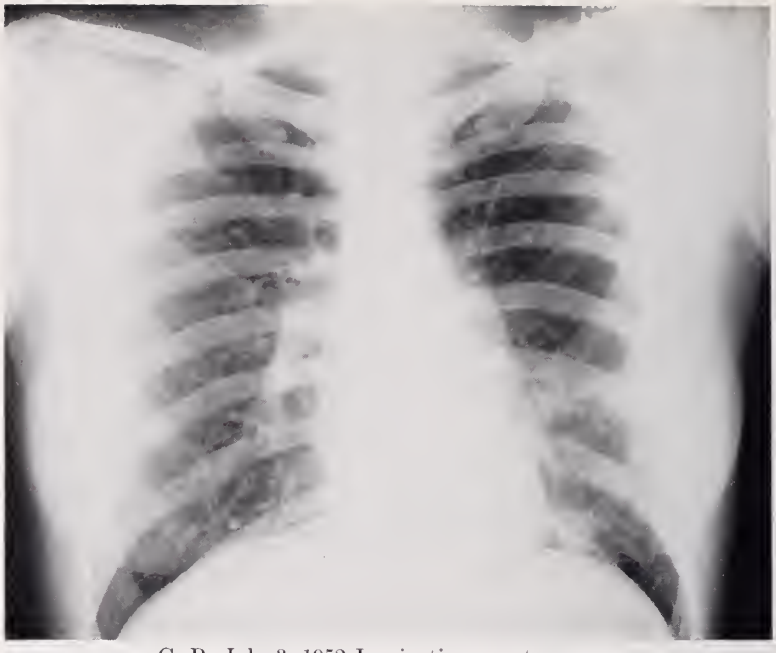
a. C. K. Dec. 19, 1953



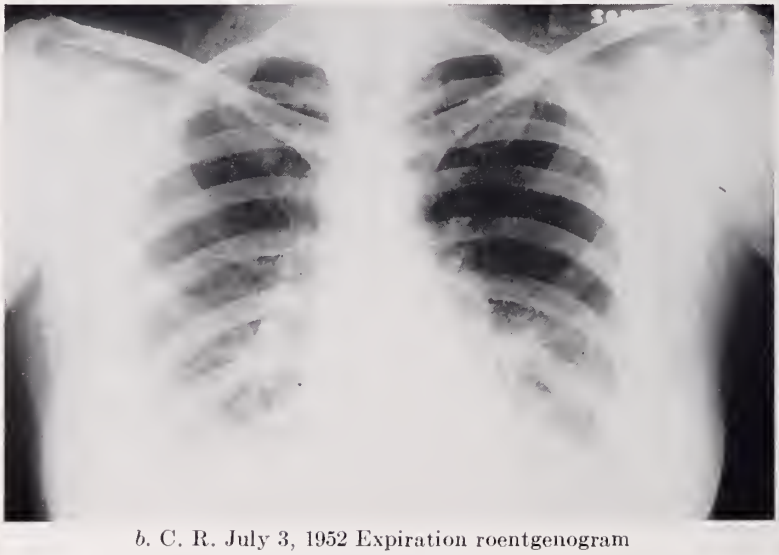
b. C. K. Feb. 23, 1956

Chemotherapy of Tuberculous Endobronchitis

Fig. 10. *a)* Roentgenogram of Dec. 19, 1953 shows large caseous node at left hilum with peri-hilar infiltration in the right lung. Bronchoscopy showed caseous tubercuIous endobronchitis. *b)* Two years of combined isoniazid-dihydrostreptomycin-P.A.S. therapy resulted in healing of the endobronchial disease although the caseous adenopathy remains practically unchanged. Nevertheless, with the healing of the endobronchial disease, the patient became asymptomatic and no tubercle bacilli could be cultured from sputum or gastric contents. The patient continues under observation. Endobronchial tuberculosis characteristically responds well to chemotherapy.



a. C. R. July 3, 1952 Inspiration roentgenogram

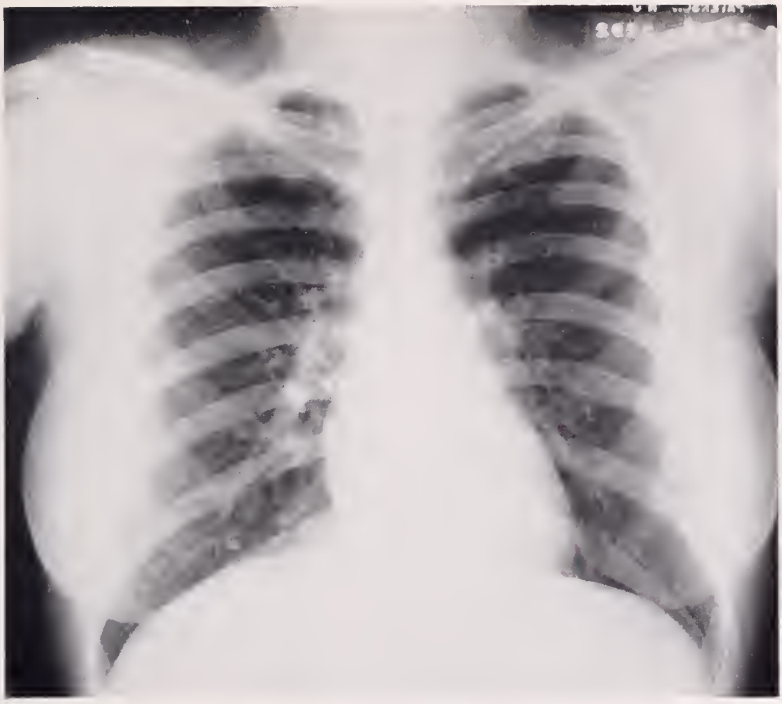


b. C. R. July 3, 1952 Expiration roentgenogram

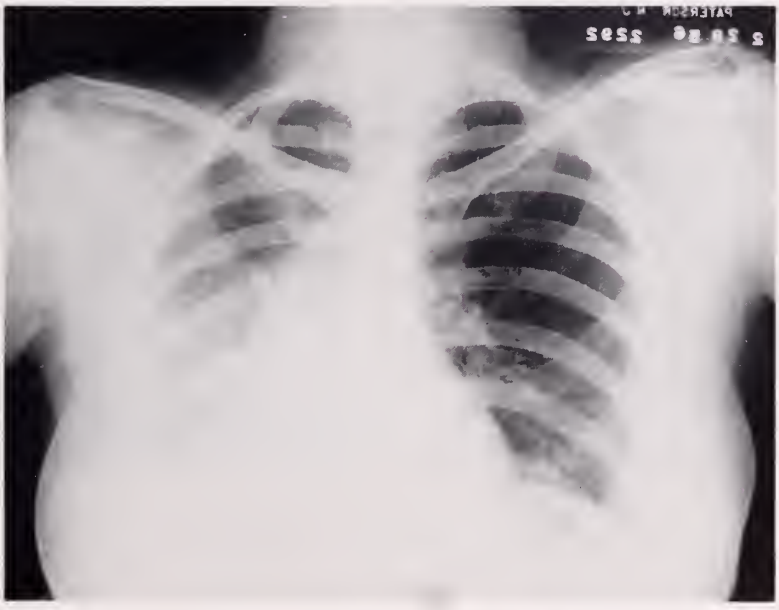
CHEMOTHERAPY OF TUBERCULOUS ENDOBRONCHITIS: RESIDUAL BRONCHOSTENOSIS

FIG. 11. *a)* Roentgenogram of July 3, 1952 shows some parenchymal infiltration in the left lower lobe. It should be noted that this film, taken during inspiration, showed some shift of the mediastinum to the left. This suggests bronchial obstruction in the left lung. Smear of sputum contained tubercle bacilli. *b)* Expiration film taken at the same time shows shift of the mediastinum to the right, confirming the presence of bronchial obstruction. Bronchoscopy showed this to be due to caseous endobronchitis.

c) 18 months of combined isoniazid-dihydrostreptomycin-P.A.S. chemotherapy resulted in absorption of the disseminated infiltration in the lower lobe and cure of the tuberculous endobronchitis, confirmed on bronchoscopy. Culture of the sputum failed to grow tubercle bacilli after the first month of therapy. This roentgenogram was taken during inspiration on Feb. 29, 1956. *d)* An expiration film of the same day shows that while the active tuberculous disease responded well to chemotherapy, as bronchial tuberculosis usually does, the bronchostenosis remained.



c. C. R. Feb. 29, 1956 Inspiration roentgenogram



d. C. R. Feb. 29, 1956 Expiration roentgenogram

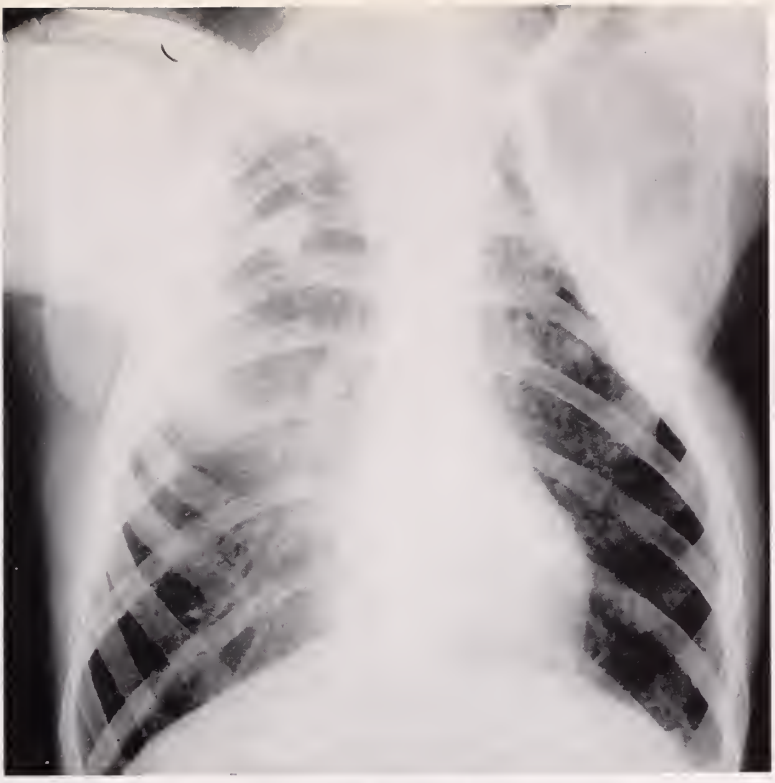
FIG. 11.—*Continued*

Pleural disease of recent derivation also responds well to chemotherapy: possibly, this is due to good diffusion of isoniazid into the pleural cavity (126). However, there usually is an underlying caseous tuberculous focus in the lung, sometimes the result of an hematogenous dissemination. This pathogenic concept is important in formulation of the treatment of tuberculous effusions (127).

Bronchial disease responds well to chemotherapy, whether as the "unseen lesion" in caseous pneumonic tuberculosis or in instances in which it forms the major lesion. Although one may be confident that bronchial tuberculosis will respond well to chemotherapy, the management of patients with significant bronchial tuberculosis may also depend upon other factors. Where parenchymal disease is present, evaluation of its probable response to chemotherapy may overshadow the expected response of the bronchial tuberculosis in the overall management of the case. Also, healing of the bronchial tuberculosis with chemotherapy will not alter bronchostenosis due to fibrosis and this may be important in lowering the resistance to secondary infection, even in the upper lobes. Finally, extensive tuberculous bronchiectasis must be catagorized as a distinct entity and cannot be equated with tuberculosis limited to major bronchi. When bronchostenosis does not exist and the disease is essentially limited to a large bronchus, with little parenchymal infiltration, chemotherapy will be effective (Fig. 10). Even should bronchostenosis be anticipated, chemotherapy may still be the definitive management for the patient since, with the tuberculous disease controlled, the bronchostenosis may not trouble the patient (Fig. 11).

The nature of the pulmonary disease is of greater consequence than its precise location. Disease awkwardly placed for collapse therapy may respond perfectly well to chemotherapy. Moreover, toxic constitutional symptoms do not prevent successful chemotherapy; highly toxic patients often show the most dramatic response. Also, in contrast to experiences in the pre-chemotherapy era, "excretory tract" tuberculosis will not hinder the control of the disease. Laryngeal tuberculosis often used to herald progressive terminal deterioration. This is no longer true and the laryngeal disease heals concomitantly with the pulmonary lesion (128). Similarly, intestinal tuberculosis, with its debilitating effect in the seriously ill patient, was a frequent and serious accompaniment of uncontrolled pulmonary tuberculosis. Now, it too heals as the pulmonary lesion is controlled by chemotherapy. Also, the presence of generalized amyloidosis does not prevent the successful utilization of chemotherapy. Instead, the incidence of generalized amyloidosis as a result of pulmonary tuberculosis has been markedly reduced, and it may become as uncommon in this disease as it has in syphilis. Study of possible reversal of generalized amyloidosis as a result of successful chemotherapy would be valuable. Finally, it should be noted that diabetes does not prevent successful response to chemotherapy (129).

Exceptions to satisfactory chemotherapeutic response in recent disease may occur in patients with very large cavities or with multiple cavitation. Although many of these cases will respond well, a significant number will not and chemotherapy in these patients must be considered a trial of therapy rather than a definitive procedure.



a. J. P. May 24, 1952

b. J. P. May 26, 1952. 5 c.m. antero-posterior tomographic section

c. J. P. May 10, 1953. 5 c.m. antero-posterior tomographic section

TRIAL OF CHEMOTHERAPY: CAVITY CLOSURE IN LONG-STANDING CASEOUS LESION

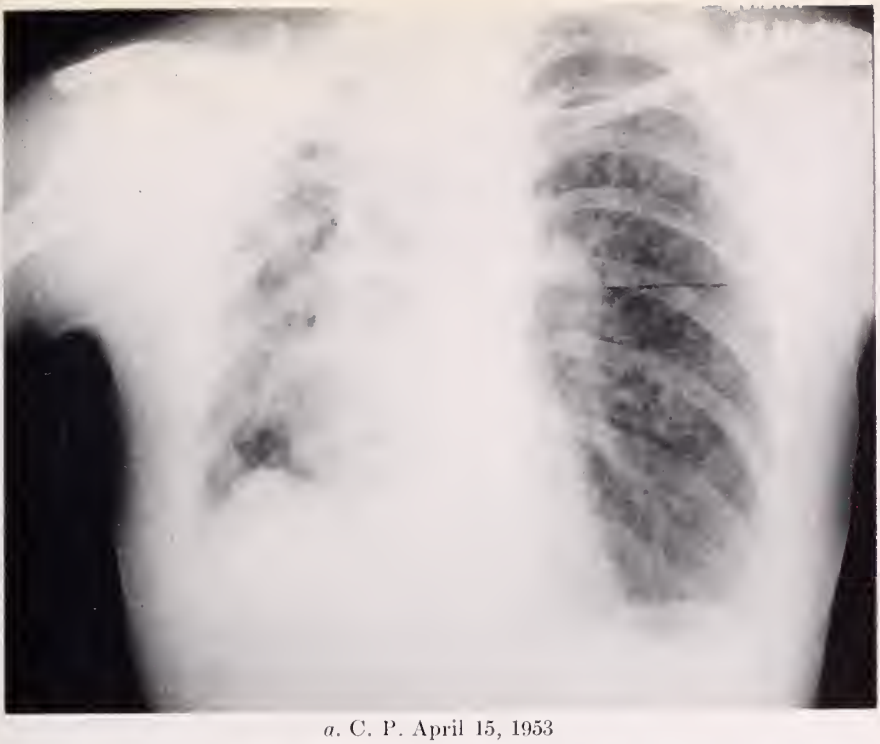
FIG. 12 *a*) "Thoracoplasty failure", Disease of six years duration. Sputum still contains tubercle bacilli, believed to be excreted from cavities known to be present in left upper lobe before thoracoplasty. Note caseous nodular infiltration in right upper lobe. This contralateral lesion had been present for a number of years and was therefore believed to be stable. *b*) 5 c.m. antero-posterior tomographic section shows a small cavity in the nodular caseous lesion in the right upper lobe on May 26, 1952. *c*) Tomographic section at same level on May 10, 1953. Isoniazid and iproniazid therapy resulted in disappearance of tubercle bacilli from the sputum after the fourth month of therapy, with simultaneous closure of the small cavity. Cavities may close in caseous lesions, especially if they are small. The patient continues well under observation.

Trial of chemotherapy. A second large group of patients is composed of those cases in whom response is less certain but in whom it still occurs very frequently. It is in the management of this group that the greatest variation in chemotherapeutic regimens exists. This is not necessarily a disadvantage and different regimens are utilized, each to meet a particular facet of the disease or a special problem. It is here, too, that competitive surgical or collapse procedures are important, since many of the patients in this group are also amenable to successful treatment by such procedures.

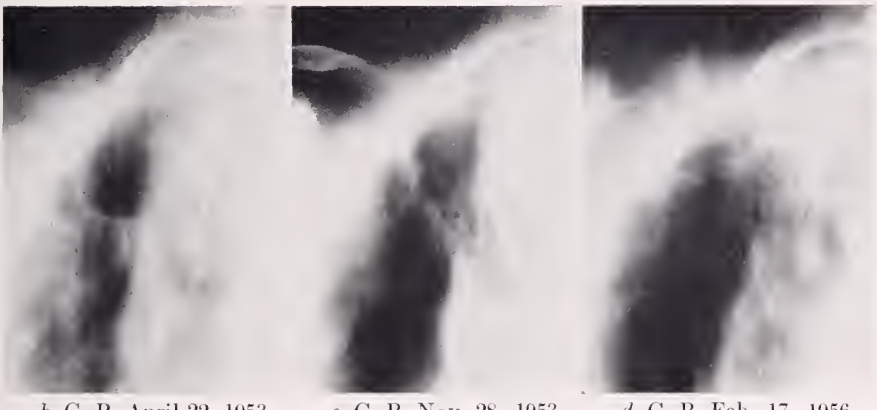
It would appear reasonable to propose that all patients in this group be given at least a trial of chemotherapy, since most of these patients will show successful response and no further treatment will be necessary. Secondly, pulmonary disease is always more extensive than the visualized roentgenographic lesions (130). Partial resection or collapse achieves mechanical control only of the major visible lesions. Yet the remaining disease, without chemotherapy, is active and potentially capable of extensive progression. Therefore, chemotherapy is required in any case for all patients with active disease even if excision or collapse procedures are to be utilized. This is not to say that careful judgment is not required in the management of the patients in this group. On the contrary, it is here that skill, judgment and experience are most necessary. Since there are as yet no adequate criteria for the reliable prediction of chemotherapeutic failures in most of the cases of this group, close observation must be maintained, and the physician must be prepared to utilize accessory therapy expeditiously in the event of failure of chemotherapeutic response. It is difficult to prepare a rule of thumb to cover all patients of this group, although of assistance is the knowledge that the essential feature of the pathological lesions in these cases is that they are "mixed" lesions, with varying degrees of caseous necrosis, fibrosis and exudation. Different areas of the lesions may have their own evolution: progression may be observed in one part of the lesion with simultaneous healing by fibrosis in another.

With the widening experience with chemotherapy, many more cases may be classified in the group in which a trial of chemotherapy is justified. Observation indicates that a range of lesions much wider than originally anticipated, will respond satisfactorily to chemotherapy. In particular, this is true of many lesions with caseation. Were this not so, chemotherapy would play a much less significant role in the therapy of tuberculosis.than it has assumed. There are few cases indeed, the lesions of which are largely exudative when seen for therapy. The very large majority of lesions are "mixed" when seen. These lesions have exudative elements and also fibrosis but much of their structure is caseous. Yet the overall success of chemotherapy includes control achieved in many such cases. Moreover, analysis of results of chemotherapy does not indicate that failure is often due to the presence of caseous infiltration, but rather to specific aspects of such infiltration. For example, multiplicity of cavities is more important in causing failure of chemotherapy than is the extent of caseous infiltration. Retreatment (with possible drug resistance) will statistically yield many more failures than similar caseous disease without previous treatment.

Observations such as these make it inadvisable to accept without reservation



a. C. P. April 15, 1953



b. C. P. April 22, 1953. 8 c.m. antero-posterior tomographie section

c. C. P. Nov. 28, 1953. 8 c.m. antero-posterior tomographic section

d. C. P. Feb. 17, 1956. 8 c.m. antero-posterior tomographic section

TRIAL OF CHEMOTHERAPY: CAVITY CLOSURE IN LONG-STANDING FIBRO-CASEOUS DISEASE

FIG. 13. *a)* Roentgenogram of April 15, 1953 showing disease of several years duration with extensive fibro-caseous infiltration in the right lung and bronchogenic dissemination in numerous areas of the left lung. Tubercle bacilli present in large numbers on smear. It might be assumed, a priori, that chemotherapy would have little effect on such lesions. Nevertheless, experience shows that many such lesions will show good response and trial of chemotherapy is therefore warranted. *b)* Tomographic section at 8 c.m. antero-posterior of April 22, 1953 shows large cavity in the right upper lobe not well seen on a conventional film because of the extensive surrounding fibrocaseous infiltration. Patient was placed on prolonged combined isoniazid-dihydrostreptomycin-P.A.S. therapy. *c)* 8 c.m. tomographic section on Nov. 28, 1953 shows the cavity to be one-half its former size. Examination of the sputum failed to show tubercle bacilli after the third month of treatment. *d)* 8 c.m. tomographic section on Feb. 17, 1956 shows complete cavity closure, which had been present following the 11th month of chemotherapy. Right upper lobe is shrunken and fibrotic. Patient is clinically well but continues isoniazid-P.A.S. therapy.

assertions such as those of Keers (131), who stated, "The evidence available at present indicates that the maximum effect of chemotherapy is exercised at the stage of exudation and local cell proliferation, ... In the presence of caseation its effect is much less . . . in larger and older caseous lesions the effect of chemotherapy is negligible." Keers is correct in noting that "older and larger" caseous lesions do not respond as well as acute exudative lesions. Nevertheless, many do respond well and a trial of chemotherapy is warranted. It may be that further experience will enable us to more sharply delimit which of these lesions is likely to respond. But, as noted above, such information is not now available and in its absence almost all such lesions should have the benefit of a trial of chemotherapy.

Trial of chemotherapy is often successful in this group of patients whether or not cavitation is present. Most lesions with single cavities respond well to chemotherapy. This is true not only when such a cavity is present in the midst of fresh exudative disease but is true in many cases in which the surrounding infiltration is fibrocaseous in nature (Figs. 12, 13), although such surrounding infiltration makes it somewhat less likely that cavity closure will occur. It is stated that the presence of giant cavities (132) and indeed those three centimeters or over (72) are indications of potential drug failures. However, a trial of chemotherapy is indicated since many such lesions will respond well (Fig. 2). Nevertheless, a significant number will fail to do so and such lesions therefore should be observed carefully so that alternate treatment can be applied at an opportune time, if necessary.

Similarly, caseous nodular lesions have been presented as representing a pathological state unable to respond to chemotherapy. However, here too a priori reasoning must yield to observation. ". . . it has now become a commonplace experience with phthisiologists to have seen the disappearance under chemotherapy of a nodular lesion long present and always considered 'productive' " (89). This has been my experience as well (Fig. 14). These lesions may take a longer time to show regression and reabsorption than do obviously exudative lesions, but this merely qualifies the duration of chemotherapy and does not negate its effectiveness.

The ability of caseous lesions to respond to chemotherapy even applies to lesions of considerable extent including those of caseous lobular pneumonia or caseous pneumonia involving considerable portions of the lung (Figs. 15, 7). Here also, regression is relatively slow and requires many months. Often it is incomplete, and residual foci remain. The management of such residual foci is presently the subject of considerable discussion and is referred to elsewhere (69).

In the above paragraphs evaluation has been attempted principally from a practical clinical point of view, using as the criterion the achievement by the patient of a clinical state of a stable, inactive lesion, without sputum infectivity, and with minimal or no risk of reactivation of the disease. This attitude justifies also the recommendation of a trial of chemotherapy for the occasional patient still seen with "thoracoplasty failure". These patients, most of whom were treated many years ago with thoracoplasty, are sometimes seen clinically well, essentially asymptomatic but with occasional recovery of tubercle bacilli by

culture or guinea pig inoculation of the sputum or gastric contents. The practical problems in treating such patients are considerable since not only are they clinically well symptomatically but long observation also indicates that their prognosis for life is good and the likelihood of progression of their disease is small. Moreover, for those whose sputum contains tubercle bacilli only upon culture but fails to show organisms on smear, the potential for infection of others is small (133). Until recently, it was difficult to recommend therapy for such patients. Revision of the thoracoplasty often failed and bedrest added little to the treatment of these indolent lesions. When large caseous lesions with multiple cavities can be demonstrated under the thoracoplasty, excision of the destroyed lobe or lung is logical. But very often such disease cannot be demonstrated. When no no definite cavitation can be made out under the thoracoplasty, utilizing such techniques as tomography and early morning tilt films, and if contralateral disease can be ruled out (Fig. 11), a trial of chemotherapy is worthwhile. I have treated three such patients with chemotherapy with success in each instance. It is possible that the occasional positive culture in these cases is due to endobronchial tuberculosis in the collapsed lung under the thoracoplasty, which responds well to chemotherapy.

Anticipated chemotherapy failure. The third group of cases, into which may be categorized those lesions in which failure of chemotherapeutic response may be predicted with some degree of assurance, is a heterogenous one. Very extensive infiltrations of long duration with marked fibrosis in addition to caseation would be so classified (Fig. 16). This is not to say that patients with such lesions should be denied chemotherapy but rather that such lesions indicate that chemotherapy is unlikely to be a definitive treatment and that, if possible, it should be planned as part of an overall therapeutic regimen which might contain other available accessory procedures as would be applicable. Since these lesions are often those which not only fail of complete therapeutic response but also will eventuate in a high incidence of bacterial drug resistance, the timing of chemotherapy in these cases is a matter for competent clinical judgment. Where no accessory therapy is available because of the extent, nature and bilateral character of the disease, it may still be advisable to utilize isoniazid-PAS therapy since first, one cannot predict with certainty that chemotherapeutic failure will result and, secondly, the continued administration of isoniazid, even with the presence of drug resistant bacteria, will often protect the patient against progression of his disease. It is a common observation that spread of disease even in patients with extensive lesions is much less common under isoniazid therapy, with or without the presence of drug resistant bacteria.

When such extensive pulmonary destruction is anatomically localized, the possibility of potential chemotherapeutic failure should dictate the early utilization of other therapy, usually excisional surgery. Preoperative and postoperative chemotherapy would then be utilized. Similarly, with our knowledge that the beneficial effect of chemotherapy on bronchial tuberculosis does not include the dilation of a stenotic lesion, extensive pulmonary infiltration distal to such bronchostenosis, especially if bronchiectasis is present, may indicate the early use of

a. M. S. July 21, 1953. 7½ c.m. antero-posterior tomographic section

b. M. S. June 21, 1954. 7½ c.m. antero-posterior tomographic section

c. M. S. Dec. 24, 1955. 7½ c.m. antero-posterior tomographic section

CHEMOTHERAPY: REABSORPTION OF CASEOUS NODULAR INFILTRATION

FIG. 14. *a*) 7½ c.m. antero-posterior tomographic section on July 21, 1953 illustrates poorly encapsulated caseous nodular infiltration at the left apex. Culture of gastric contents showed tubercle bacilli. *b*) 7½ c.m. antero-posterior tomographic section on June 21, 1954, after almost one year of combined isoniazid-dihydrostreptomycin-P.A.S. chemotherapy, shows considerable reabsorption of caseous infiltration but residual caseous nodular lesion is still present. *c*) Continued chemotherapy resulted in further reabsorption of the caseous nodular disease with residual infiltration on 7½ c.m. antero-posterior tomographic section of Dec. 24, 1955. Culture of sputum no longer showed tubercle bacilli after the onset of chemotherapy. The serial tomograms are examples of the range of chemotherapeutic effectiveness in which caseous lesions show regression, in addition to those of an exudative nature. However, such regression is slower, requires more prolonged chemotherapy and may be incomplete, with residual nodular infiltrations. With persistence, however, extensive reabsorption is possible.

excisional surgery. With many of the lesions in this group, the problem is often a complex one and occasionally the final decision is strongly influenced by the results of pulmonary function studies. Finally, although there is still inadequate data on this subject, the presence of other complicating pulmonary disease may make response to chemotherapy less successful. This may be true of pneumoconiosis. Although the tuberculosis death rate has decreased sharply in the last several years, this decrease has not been so marked when occupational disease of the lung coexisted with the pulmonary tuberculosis (134).

Often militating against the success of chemotherapy in pulmonary tuberculosis is the simultaneous presence of empyema, either pure tuberculous empyema or mixed-infection empyema. Although the underlying pulmonary disease in such cases may respond well to chemotherapy, depending upon the nature of the lesion, and fistulae close, the empyema itself often fails to show significant healing tendency. Chemotherapy in these cases makes its contribution in the control of the toxicity of the patient, which in pre-chemotherapy days was often marked Also, chemotherapy, either by controlling the underlying pulmonary disease or by preventing its progression, tends to localize the problem to the empyema and the residual underlying pulmonary disease. But since complete control of the disease is not achieved, control must be planned with the operation of pleuropulmonary resection, introduced by Sarot (135). Depending upon the disease present, this may take the form of resection of the residual empyema alone, or

simultaneous resection of the empyema and the significant underlying pulmonary disease, whether this be achieved by segmental resection, lobectomy or pneumonectomy (136). Pleuro-pulmonary resection has revolutionized the treatment of pulmonary tuberculosis complicated by empyema. Although chemotherapy has reduced sharply the number of occasions in which its use is required, when empyema is present, chemotherapy cannot substitute for this operation.

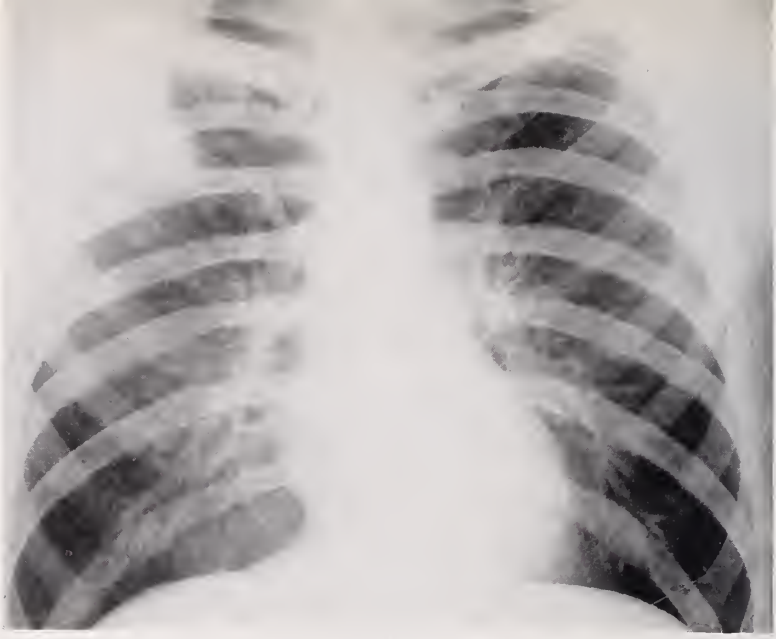
Bacterial Drug Resistance

Adaptation of microorganisms to antimicrobial agents was described even before the development of chemotherapy (137). When the first antimicrobial drugs were introduced by Ehrlich, he simultaneously noted that the trypanosomes so affected could become resistant to the dye stuffs used, by prolonged exposure. "Since that time, the phenomenon of drug resistance has accompanied the development of chemotherapy like a faithful shadow and the history of chemotherapy is also a history of drug resistance" (138).

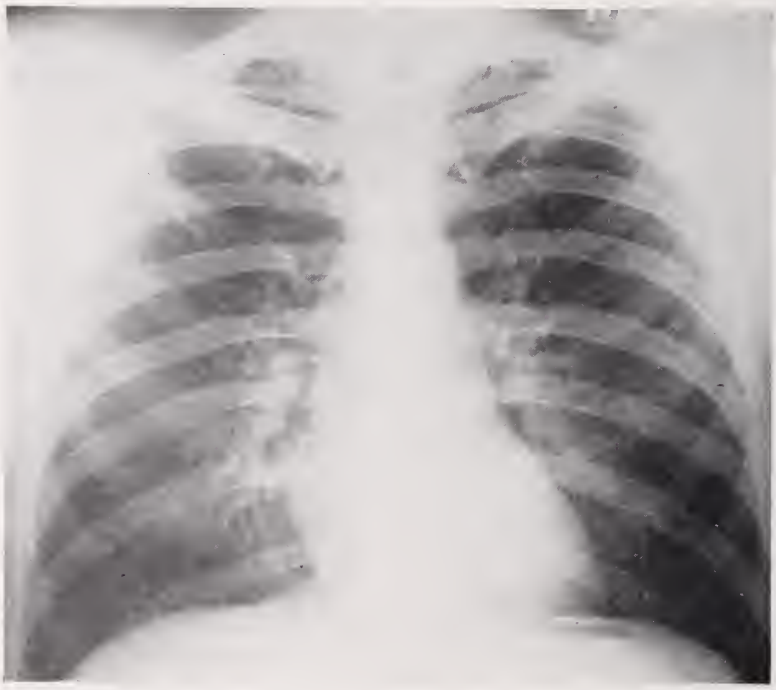
Streptomycin resistance. The progress of modern antituberculous therapy has similarly been characterized by the phenomenon of drug resistance. Soon after streptomycin was introduced as an antituberculous agent, the development of drug resistance to it in vitro was found (139, 140). Almost simultaneously, streptomycin resistant bacteria were isolated from patients under treatment with this antibiotic, some of the cultures studied being from among the first patients treated with streptomycin (141). These findings were not unexpected and had indeed been predicted not only by the scattered reports of the development of drug resistant bacteria during the previous several decades (16) but also by the finding of bacterial drug resistance to the sulfonamides and penicillin in the preceding several years.

That this development of drug resistance by tubercle bacilli to streptomycin was important was inferred from the early finding that such streptomycin resistant bacteria were able to produce streptomycin resistant infection in animals (142). This was soon mirrored by clinical observations in which it was found that patients from whom streptomycin resistant bacteria could be isolated often did not continue to respond to further streptomycin therapy (143, 144). The full impact of this problem was realized when it was found that drug resistance was common during streptomycin therapy. Thus, in large-scale studies, daily administration of streptomycin resulted in bacterial drug resistance in more than half of those patients still bacteriologically positive after 120 days of therapy (145). Bacterial drug resistance was also found during streptomycin therapy of disseminated tuberculosis (146).

Early efforts to circumvent this difficulty were based on the observation that in vitro, the presence of a sulfone might retard the development of streptomycin resistance and it was suggested that the possibility existed of delaying the emergence of streptomycin resistant strains (140). Meanwhile, the principle of combined drug treatment, previously established by Ehrlich (147), was revived (148). The applicability of this concept to antituberculous therapy had to wait the development of a suitable drug able to be combined with streptomycin. PAS pro-



a. T. I. May 2, 1955



b. T. I. Feb. 27, 1956. 10 c.m. antero-posterior tomographic section

TRIAL OF CHEMOTHERAPY: CASEOUS SEGMENTAL PNEUMONIA

FIG. 15. *a*) Caseous segmental pneumonia on roentgenogram of May 2, 1955. Sputum contained tubercle bacilli. *b*) Combined isoniazid-dihydrostreptomycin-P.A.S. therapy resulted in considerable reabsorption of disease, evidenced by the roentgenogram of Feb. 27, 1956. Chemotherapy continues, with the expectation of further reabsorption. Culture of sputum failed to yield tubercle bacilli after the fourth month of chemotherapy.

c. T. I. May 2, 1955. 10 c.m. antero-posterior tomographic section

d. T. I. July 1, 1955. 10 c.m. antero-posterior tomographic section

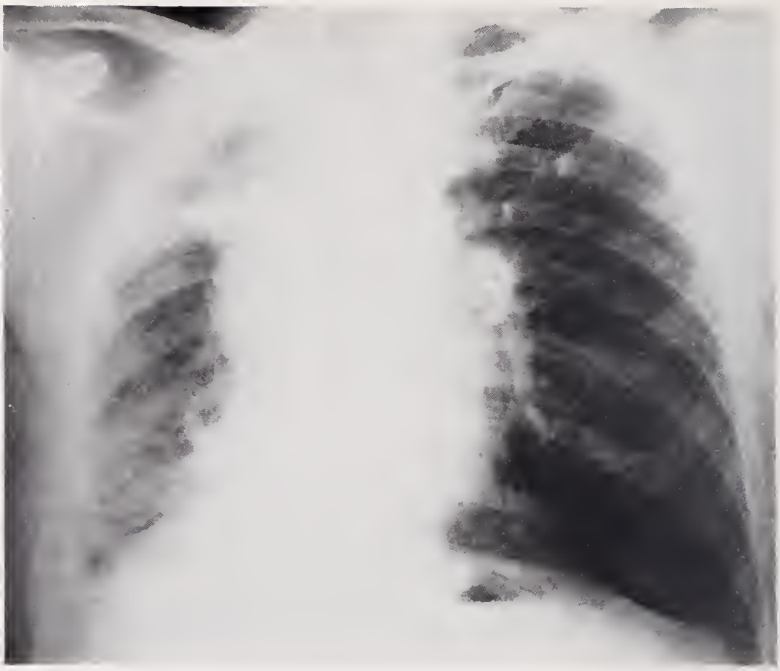
e. T. I. Feb. 27, 1956. 10 cm. antero-posterior tomographic section

FIG. 15—*Continued*

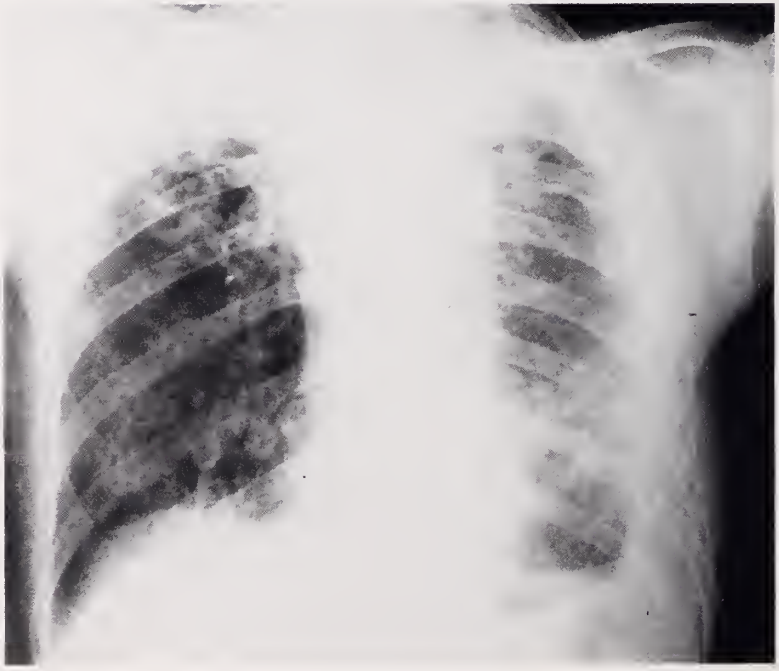
c) Tomographic section, 10 c.m., on May 2, 1955 shows cavity within caseous lesion. *d*) Tomographic section at same level on July 1, 1955 shows decrease in cavity size. Cavities within caseous areas may fail to close as rapidly. Cavity closure in general is frequently influenced by the nature of the infiltration, as well as by cavity size, multiplicity of cavities, thickness of cavity wall. *e*) Tomographic section again at 10 c.m. antero-posterior level on Feb. 27, 1956 shows cavity closure.

vided this accessory agent (149). The effects of PAS and streptomycin were shown to be additive in vitro (150) and in vivo (151). It remained only to demonstrate that the theoretical advantages of combined therapy could be produced by the simultaneous administration of PAS and streptomycin. This was soon found in vitro (152) and clinically in the therapy of human beings (153).

Nevertheless, even with the concomitant administration of PAS the development of bacterial drug resistance to streptomycin remained sufficiently common to constitute an important limiting factor to such chemotherapy. It was believed that PAS delayed or prevented streptomycin resistance on a genetic basis. Since, it was felt, streptomycin resistant variants during streptomycin therapy arose by mutation during the multiplication of tubercle bacilli and since there was a markedly lessened biological possibility of a mutant occurring resistant to both streptomycin and PAS, the opportunity for the development of drug resistance was small. Nevertheless, concern with regard to the possibility of drug resistance led to reluctance at first to continue administration of even approved combinations of drugs for more than limited periods of several months. With increasing experience in chemotherapy, however, this rule was not so rigidly held. It was realized that most of the early data on bacterial resistance was derived from patients with acute, rapidly progressive, active disease with extensive caseation and large cavities. Treatment of this type of disease is more likely to result in the development of drug resistance since there are many actively dividing tubercle bacilli, with greater chance of mutation. Moreover, the arrest of the disease requires much longer therapy, with greater opportunity for resistant mutants. Once, however, patients with less extensive disease undertook treatment, the



a. H. D. Feb. 20, 1955



b. J. J. Mar. 4, 1952

FIG. 167

incidence of the development of drug resistant bacteria fell, since the disease in many of these patients came under control long before there was opportunity for the development of resistant bacilli.

Isoniazid resistance. Apprehension with regard to bacterial resistance engendered by the experience with streptomycin was transferred to isoniazid when that drug became available, and the expected occurrence of drug resistant variants during therapy, or even before, appeared to confirm this concern. It was consequently urged that the techniques found useful in delaying streptomycin resistance be applied to isoniazid therapy. These included courses of therapy of limited duration, insufficient for development of resistance; the use of combined chemotherapy; the early use of accessory therapy when available, as soon as drug resistant bacteria were found; and variations in dosage and administration calculated to minimize the possibility of the emergence of drug resistance.

Nevertheless, experiences during the past four years indicate that isoniazid resistance cannot be equated experimentally, biologically, or clinically with streptomycin resistance and that the peculiarities associated with isoniazid resistance have important clinical connotations requiring study and analysis.

Most important was the clinical observation that the finding of isoniazid resistant bacteria did not necessarily indicate the probability of clinical deterioration of the patient. This observation was reported as the result of the first clinical studies with isoniazid (154) and has been confirmed since (155–157, 79, 81). Moreover, it was noted that relapse in patients with miliary tuberculosis under treatment of isoniazid was exceedingly rare or did not occur, in contrast to relapse under similar conditions in patients treated with streptomycin (158).

A possible explanation for this clinical observation was suggested by the observation that isoniazid resistant mutants of tubercle bacilli had diminished pathogenicity for guinea pigs (159, 160). This attenuated pathogenicity was correlated with a biological change in these bacilli, with deficiency in endogenous catalase activity (161). Some isoniazid resistant bacteria retained adequate endogenous catalase activity ("catalase positive resistant bacteria"), but clinical correlation (156) failed to reveal any difference in the course of patients harboring such resistant bacilli in contrast with "catalase negative resistant bacteria."

Long-term data is still inadequate for final formulation of the relationship between these laboratory observations and the clinical management of patients under isoniazid therapy.

A second facet of the problem which qualifies any analysis is the fact that the

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Anticipated Chemotherapy Failure: Extensive Fibro-Caseous Tuberculosis

Fig. 16. Examples of long-standing extensive fibrocaseous tuberculosis which often respond poorly to chemotherapy but will occasionally result in chemotherapeutic control of the disease. Because of this, especially when accessory therapy such as excision or collapse is not available to the patient, chemotherapy should be utilized. Even should control of the disease not be achieved, continued isoniazid administration minimizes the likelihood of progression of the disease. *a*) 73 year old man with long-standing disease; inadequate pulmonary ventilatory capacity prevented right pneumonectomy. The development of bacterial resistance is more frequent in such disease with prolonged administration but failure of chemotherapy is due to the nature of the lesion and not to the development of bacterial resistance which follows and does not cause the chemotherapy failure. *b*) Bilateral fibrocaseous extensive pulmonary tuberculosis. Present chemotherapy is often inadequate to fully control lesions of this nature.

incidence of isoniazid resistant bacteria in the overall chemotherapy of tuberculosis is much lower than was observed during early streptomycin therapy. This is simply because the disease is usually arrested and, after a course of therapy, there are relatively few patients who continue to show tubercle bacilli in their sputum. Patients who no longer have tubercle bacilli in their sputum could hardly be expected to yield resistant bacteria. Thus, in the recent studies reported from the Fitzsimmons General Hospital, 104 patients were treated with streptomycin, isoniazid and PAS. After eight months of chemotherapy, 97 per cent of cultures were negative. Of the 96 patients available for bacteriological study, 93 no longer showed tubercle bacilli in their sputum whereas three cultures still showed tubercle bacilli. And only one of these three showed a drug resistant strain to either streptomycin or isoniazid (162).

Similar experiences have been reported elsewhere (77). In this latter series, of 107 patients with recent disease only six, after chemotherapy, yielded resistant bacteria. Moreover, "there was no apparent correlation . . . between the degree of in vitro resistance and lack of adequate therapeutic response, as judged by the roentgenographic findings." In this series as a whole, 99 of the 107 cases achieved control of their disease with chemotherapy and the remaining eight all underwent surgical resection successfully. Thus, in this series also, the development of drug resistance failed to constitute a significant problem. It would appear from these and similar observations that the best solution to the problem of drug resistance is chemotherapeutic control of the disease. The converse, however, is also true: failure to achieve chemotherapeutic control is often correlated with the emergence of drug resistant bacilli. It does not necessarily follow that such emergence underlies the failure to achieve control. Rather, clinical observation would indicate that drug resistant bacilli will eventuate from the same type of lesion that is refractory to chemotherapy. This occurs by virtue of its duration, multiplicity of its cavities, size of the cavities, or extent of fibrosis and caseation.

Delay and prevention of drug resistance. It is precisely in patients with extensive refractory disease that every effort should be made to minimize, delay or prevent drug resistance, since it is essential for them that their bacteria retain drug sensitivity for as long a time as possible, inasmuch as chemotherapy, to be successful, must be prolonged in such cases. Accumulated experience suggests a number of prophylactic measures. First, with very extensive disease, especially if localized, a trial of chemotherapy is warranted, as noted above, but should not be unduly prolonged in the absence of satisfactory progressive response, and alternate therapy should be applied as indicated. This is especially true if cavitation persists despite chemotherapy, with sputum infectivity, for more than four to six months. Judgement in these cases should be clinical and not based upon laboratory data. The latter may be time consuming and subject to varying conclusions. For example, the growth of drug resistant bacilli from sputum samples does not at all indicate that the total bacterial population of such a sample is composed of drug resistant bacteria. On the contrary, recent studies would indicate that often only a small proportion of such a bacterial population would be so constituted, and that this proportion could vary from time to time (163).

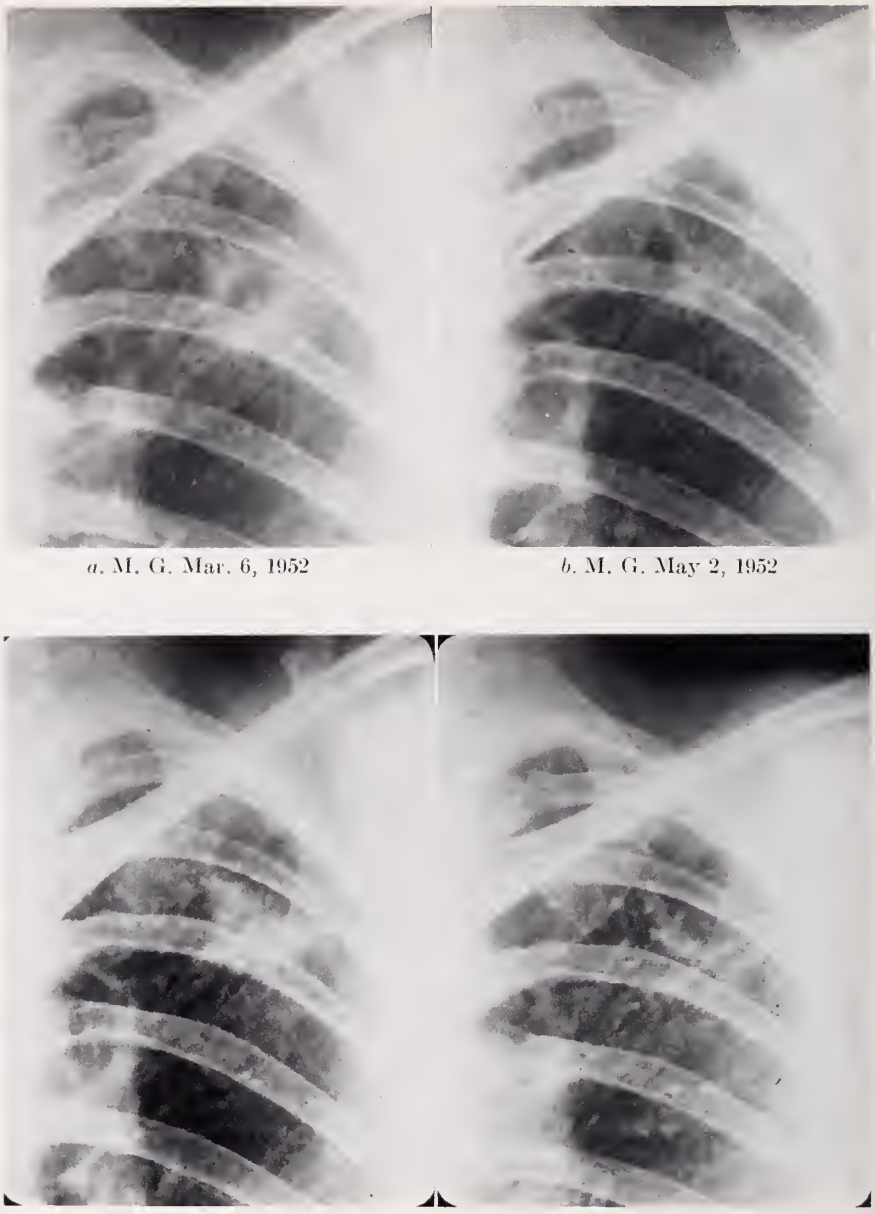
A second and most important measure in the attempt to delay or prevent the

emergence of drug resistant bacilli, is the utilization of combined chemotherapy. Although the necessity of such treatment for universal application has been questioned (79) its applicability for most patients seems warranted (Fig. 17). In my opinion this is so not only because of the reduced incidence of emergence of drug resistant bacilli—such mutants will be found in significant numbers even with combined drug therapy (164) but because such combined therapy is also more effective in achieving control of the disease. Moreover, it is yet to be claimed that the presence of drug resistant bacteria are an advantage to the patient. Even though, as noted, there is no definite correlation between clinical deterioration and the presence of isoniazid resistant bacteria in the sputum, it would appear reasonable to agree with the conclusion derived from the British Medical Research Council's study on isoniazid drug resistance that . . . "as it is possible that isoniazid resistance is a direct disadvantage to the patient in some way which has not been demonstrated in this study, it would be wise to continue to regard the development of isoniazid resistance as indicating some loss of clinical effectiveness toward the drug. . . ." (157).

A number of drug regimens appear to be efficacious in decreasing the incidence of drug resistance, all based on the observation that isoniazid is effective in preventing streptomycin resistance, streptomycin is effective in preventing isoniazid resistance and that PAS is useful in minimizing both streptomycin and isoniazid resistance (165). Thus, almost all possible combinations of the presently available chemotherapeutic agents have been utilized, most of them effectively. It is difficult on the basis of statistical analysis alone to select the "best" regimen. It would appear, however, that the therapy of choice must include isoniazid (86). Isoniazid-PAS has been frequently utilized and found effective. My own preference, subject to variations in specific cases, is for triple drug therapy, utilizing isoniazid-dihydrostreptomycin and PAS (69). Some data is available to indicate that the use of daily streptomycin in combination with isoniazid is a superior regimen in the prevention of drug resistance (166).

Whatever the regimen utilized, it would appear that chemotherapy should be continuous and uninterrupted, except in the rare instances in which streptomycin or PAS (167) is used alone. When tetracycline or oxytetracycline are utilized, the same principle would hold, although this might make for gastrointestinal or other difficulties, especially when the effective dose of 5 grams a day is utilized (168). Moreover, a corollary to continuous therapy would be the requirement that adequate dosage be maintained. Not only would this yield more effective chemotherapy and, consequently, a lessened risk of the emergence of drug resistant bacilli, but it might diminish the possible risk of antagonism of isoniazid and streptomycin found experimentally in mice with subtherapeutic doses of isoniazid and streptomycin (169) and possibly related to previously noted in vitro antagonism (170). Higher dosage has also been proposed as a means of preventing the emergence of catalase-positive resistant bacteria (156). My own clinical observations would support the theoretical desirability of continuous uninterrupted therapy: analysis of my results of chemotherapy would suggest that continuous therapy decreases the risk of its failure (69).

Chemotherapy in the presence of drug resistance. Management of the patient



a. M. G. Mar. 6, 1952

b. M. G. May 2, 1952

c. M. G. Oct. 9, 1952

d. M. G. Feb. 24, 1956

MANAGEMENT OF BACTERIAL RESISTANCE WITH COMBINED CHEMOTHERAPY

FIG. 17. *a*) Roentgenogram of Mar. 6, 1952 shows cavity in left upper lobe, present on serial films for two years. Single drug therapy with isoniazid instituted. *b*) Rapid cavity closure (with disappearance of tubercle bacilli from the sputum) on the roentgenogram of May 2, 1952. *c*) Stability of the regression on serial films was interrupted on the roentgenogram of Oct. 9, 1952 with reexacerbation in the region of the infiltration. Dihydrostreptomycin and P.A.S. were added to the therapeutic regimen at this point. *d*) There was again rapid regression of the lesion and combined chemotherapy was continued for two years. Stability of the healing has continued during the post-chemotherapy observation period, as evidenced by the roentgenogram of Feb. 24, 1956.

with drug resistant bacteria is sometimes difficult. Firstly, as noted, the presence of isoniazid resistant bacteria in the sputum should by no means lead to the discontinuance of isoniazid therapy. Streptomycin-PAS resistance, on the other hand, have much more exact correlations with ineffectiveness of drug therapy and the appearance of bacteria resistant to these drugs, especially with clinical correlation, might warrant their discontinuance although here, too, caution is necessary. Future observations may result in modification of this stand. It has been noted that spontaneous variations occur in the percentage of the bacterial population which shows loss of drug sensitivity (163). Instances have been reported in which sputum cultures, once growing highly resistant bacteria, subsequently, without treatment, showed bacteria of low resistance (171). It is speculated that sensitive bacilli or those with a low degree of resistance, might grow faster than more resistant bacilli. Since the diseased areas of the lungs, especially if treatment is not too prolonged, contain bacilli of varying resistance, the more resistant ones may be replaced with susceptible bacilli, once treatment is stopped. This could speak for "rest periods" in chemotherapy or might suggest alternate therapy. The subject remains a matter for future study.

The administration of secondary drugs such as oxytetracycline, tetracycline or viomycin is sometimes useful in continuation or retreatment therapy of patients with bacteria resistant to other drugs. Generally, the results of such treatment have been inadequate. The use of higher dosage ranges of isoniazid and streptomycin might be occasionally useful in patients with bacteria of a low degree of resistance. Quantitative correlations are, however, lacking and such variation of treatment would be on an empirical basis.

The presence of drug resistant bacteria at the onset of retreatment therapy might affect the choice of treatment, with chemotherapy less to be depended upon. This variation, however, raises its own problems since it has been reported that surgery carries greater risks in patients with drug resistant bacteria (172), even when such resistance is present to only two drugs (173).

The presence of drug resistant bacteria has also created the possibility of a public health problem. Although there have been isolated reports of infection with drug resistant bacteria which failed to respond to subsequent chemotherapy to the disadvantage of the patient, the overall problem has not been a significant one. First, because at least to the present, the incidence of new infection with such resistant bacteria has been small and, secondly, the majority of patients infected with resistant bacilli can nevertheless be treated successfully (174).

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THE MANAGEMENT OF PULMONARY TUBERCULOSIS

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Chemotherapy has become the mainstay in the treatment of pulmonary tuberculosis. The rapid introduction of chemotherapeutic techniques into clinical use and the accumulation of concomitant basic data, are happy examples of effective collaboration between laboratory disciplines and clinical medicine.

This important development has simultaneously made necessary the re-evaluation of many of the therapeutic concepts distilled from the past several decades, during which rest and collapse procedures were the only available treatment.

PRINCIPLES OF CHEMOTHERAPY OF PULMONARY TUBERCULOSIS

Sufficient experience has now been accumulated to warrant formulation of new concepts based upon contemporary chemotherapeutic advances. Although such formulations are necessarily tentative, in view of the progress in this field, it is felt that the following principles will be useful not only for current practice but will have continued validity.

1. *All patients with active pulmonary tuberculosis should have chemotherapy.* Even when a tuberculous pulmonary lesion appears localized and eminently suitable for collapse or excisional procedures, systemic therapy is essential because tuberculous infection is always more widespread than is apparent. Not only does treatment of the local lesion alone ignore other pulmonary involvement, in bronchi or in small parenchymal bronchogenic foci not demonstrated by x-ray, but it also leaves unaffected the extra-pulmonary foci of hematogenous dissemination, clinically mute, but widely present (1).

2. *Isoniazid should be included in every chemotherapeutic program.* Not only is this drug the most effective medication available at present, but it is similarly unique in its ability to prevent hematogenous dissemination of tuberculosis (2). In addition, there is evidence that the healing process is associated with less anatomical derangement and is more complete with isoniazid (3).

3. *Combined drug therapy is preferable to the use of a single agent.* There is some evidence that this statement will not prove to be invariably correct. Nevertheless, it seems preferable to emphasize the rule rather than the exceptions.

4. *Chemotherapy should be continuous and prolonged.* Pathological study of resected specimens following chemotherapy has shown this to be desirable, and correlates with clinical observations of the time required for cavity closure and reabsorption of infiltration.

PRESENT STUDY

We have utilized, both for analysis and illustration, a consecutive series of 108 cases of active pulmonary tuberculosis observed personally and treated by

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one of us. Although the results of this analysis are integrated with the reported experiences of others in the formulation of our opinions, a review of this series appears particularly profitable. First, it is the longest consecutive series currently under observation in which isoniazid therapy has been utilized. The first patient entering this series began therapy four and one half years ago, on October 5, 1951, shortly after the completion of toxicity studies (4) and only three days after the institution of the first trials of this group of drugs (5). Most of the patients have been observed for more than three years. This prolonged observation is particularly useful from the point of view of the study of possible chemotherapy relapse.

Of particular value in the study of this series of cases is the fact that all patients had "ambulatory therapy". None were hospitalized for chemotherapy. This affords an opportunity to study this aspect of present-day chemotherapy. Also, although a number of chemotherapeutic regimens were utilized, the large majority of patients were treated with a triple-drug regimen. Very few significant series of patients utilizing this regimen have been reported, despite its clinical popularity.

Only two cases have been lost to observation. Similarly adequate follow-up, unfortunately, has not been achieved in other large series. In one of the most extensive studies, for example, at 18 months only 37 per cent of those potentially observable were actually under observation. Even if those lost to observation because of change of regimen, toxicity, drug resistance or clinical decision, are not included as lost to observation, there was still a loss of 30 per cent at 18 months (6). Moreover, in our analysis we have excluded as a variable in chemotherapy the effect of collapse therapy or surgery. In contrast, in the large scale Veterans Administration's study from 1949 to 1951 (7), approximately 71 per cent of all patients had some form of collapse therapy. In the second study, 1951 to 1952, 46 per cent had collapse therapy or surgery. Although this does not necessarily invalidate the value of a comparative study of several regimens of chemotherapy (8), it does make difficult the estimate of the overall chemotherapeutic efficacy of these regimens.

Finally, analysis of this series has included the important variable of the nature of the disease under treatment. Such evaluation has unfortunately been omitted from many large series reported, probably because of the difficulty in accurately recording and evaluating different types of the disease under treatment. It is perhaps because of this difficulty that Tucker concludes his exhaustive analysis of the chemotherapy study conducted by the Veterans Administration, Army and Navy, with "There is increasing evidence that the final decision as to what antimicrobial therapy will be prescribed in practical clinical application will depend on variations of the disease and on other factors not included in the large scale British and United States Cooperative Studies" (6).

OVERALL RESULTS OF CHEMOTHERAPY IN THE MANAGEMENT OF PULMONARY TUBERCULOSIS

It is perhaps no exaggeration to state that in previously untreated patients, approximately 90 per cent can achieve arrest of their disease by chemotherapy

TABLE I

108 consecutive cases of active pulmonary tuberculosis; chemotherapy including isoniazid; ambulatory management

Overall results [6 months–4½ years]

A. Present status:
- 98 sputum negative with controlled disease
  - 3 died: non-tuberculous (gunshot, coronary occlusion, brain tumor)
  - 3 have "sterile cavities".
- 10 failed to achieve adequate control of disease
  - 2 died of tuberculosis
  - 8 continue therapy.

B. Sputum status
- 22 had negative sputum. All continue negative.
- 86 had tubercle bacilli in sputum
  - 76 became negative
  - 10 remained positive

C. 70 patients had open cavities.
- 56: cavities closed, negative sputum
- 14: residual cavitation
  - 10 positive sputum
  - 4 negative sputum

TABLE II

Results of chemotherapy

Evaluation of nature of disease	Success	Failure
Alternate therapy possible	65	6*
No other therapy available; poor prognosis	16	7
Chemotherapy with accessory therapy (surgical or collapse)	7	0
	88	13 = 101†

* 1 successfully retreated with chemotherapy; 4 subsequently successfully treated by surgery and collapse; 1 awaiting surgery.

† 7 patients of the 108 in this series were treated by primary surgical or collapse measures without trial of chemotherapy.

alone (Table XV). When the disease is of short duration and of limited extent, it is likely that a higher percentage of satisfactory results will be obtained and such series have been reported (9, 10). With the use of accessory surgical treatment for the management of chemotherapy failures, experiences have been reported with control achieved in 100 per cent of cases (10). Therapeutic measures now available, therefore, will result in control of almost all cases of newly discovered tuberculosis.

Of 108 patients in this series, 98 have achieved control of their disease and 10 have failed (Table I). Seventy-one of the 108 patients were regarded as most suitable for chemotherapy. This, utilized alone, proved successful in 65 of these cases and failed in six (Table II).

The overall success of therapy in this series is exemplified by the results in

TABLE III

Analysis of patients and response to therapy

		Effect of treatment on sputum status			Effect of treatment of cavitation		
		Negative sputum, remained negative	Positive sputum		Cavity closure	Residual cavitation	
			Became negative	Remained positive		Sputum positive	Sputum negative
Age							
15–24	(15)	4	9	2	7	2	0
25–39	(52)	10	40	2	26	2	4
40–54	(28)	6	19	3	17	3	0
55+	(13)	2	8	3	6	3	0
	108	22	76	10	56	10	4
Male	52	9	35	8	26	8	0
Female	56	13	41	2	30	2	4
	108	22	76	10	56	10	4
White	84	18	57	9	42	9	4
Negro	21	4	17	0	12	0	0
Oriental	3	0	2	1	2	1	0
	108	22	76	10	56	10	4

control of sputum infectivity and cavitation. Twenty-two patients in this series had no tubercle bacilli in their sputum at the onset of therapy—all remained negative.* Of 86 patients with infectious sputum, 76 no longer are positive after therapy and 10 remain with bacilli in their sputum (Table III). Similarly, 70 patients had cavities clearly visible on x-ray. After therapy, 56 no longer had such cavitation while in 14 instances there was failure of complete cavity closure. Ten of these 14 patients also continued to have tubercle bacilli in their sputum (Table III).

Analysis of various factors having influence on the effect of chemotherapy, are contained in Tables IV–IX. Inspection of these tables will be profitable, since they analyze the importance of such variables in chemotherapy as extent of disease, nature of the disease, influence of the pre-therapy course of the disease, the number of cavities and their size.

PROBLEMS AND PRINCIPLES IN THE MANAGEMENT OF ACTIVE PULMONARY TUBERCULOSIS

Choice of Chemotherapeutic Regimen

The choice of a chemotherapeutic regimen is no longer a simple matter. With almost a dozen drugs having some effect on tuberculosis and with near as many

* "Negative sputum" in this report signifies repeated negative cultures of the sputum and gastric contents, as well as negative smears of the sputum for tubercle bacilli.

TABLES IV–IX

Results of chemotherapy: evaluation with regard to nature of the disease under treatment

		Roentgenographic Change				Sputum Status			Cavity		
		Improvement					Positive Sputum			Open	
		Moderate–Marked	Minimal	No change	Worse	Negative Sputum remained negative	Became negative	Remained positive	Closed	Positive sputum	Negative sputum
IV. Extent of disease											
Minimal	14	8	6	0	0	13	1	0	0	0	0
Moderately advanced	36	23	11	2	0	5	29	2	20	2	2
Far advanced	51	31	9	6	5	4	36	11	24	11	4
	101	62	26	8	5	22	66	13	44	13	6
V. Extent of disease											
Unilateral	50	30	12	6	2	16	35	5	21	5	3
Bilateral	51	32	14	2	3	6	31	8	23	8	3
	101	62	26	8	5	22	66	13	44	13	6
VI. Pathologieal Evaluation											
Exudative	8	7	1	0	0	5	3	0	3	0	0
Fibro-caseous	49	21	21	5	2	11	32	6	15	6	4
Caseous-pneumonic	41	31	4	3	3	3	31	7	26	7	2
Hematogenous	3	3	0	0	0	3	0	0	0	0	0
	101	62	26	8	5	22	66	13	44	13	6
VII. Previous course											
Progressive	56	45	6	1	4	11	38	7	31	6	2
Indolent	44	16	20	7	1	11	27	6	13	7	4
Regressive	1	1	0	0	0	0	1	0	0	0	0
	101	62	26	8	5	22	66	13	44	13	6
VIII. Cavitation											
Single	48	37	7	2	2	0	41	7	37	7	4
Multiple	15	8	3	1	3	0	9	6	7	6	2
	63	45	10	3	5	0	50	13	44	13	6
IX. Cavitation											
Smaller than 3 cm	30	23	5	1	1	0	27	3	27	3	0
Larger than 3 cm	33	22	5	2	4	0	23	10	17	10	6
	63	45	10	3	5	0	50	13	44	13	6

valid surgical procedures, we are almost embarrassed by the richness of our therapeutic resources. Moreover, evaluation of the results of various regimens sometimes yields no clearcut differences. This is particularly true when isoniazid is included in the treatment. Isoniazid by itself is so effective that ". . . it is extremely difficult to demonstrate that anything added to isoniazid is really exerting an influence" (11). With so many variables present, in so kaleidoscopic a disease as tuberculosis, "It is not the available statistical methods which are at fault, but the lack of sensitive techniques for the identification of pulmonary lesions of sufficient comparability to permit fine comparisons by the statisticians" (12).

It may well be, as Muschenheim insists (13), that no single regimen of drug treatment will prove optimal for all cases, but that different regimens will be found especially suitable for different forms of the disease. To the present, there has been a tendency to straitjacket choice of therapeutic regimen, with recommendations of "the best" regimen. Partly, this has been the unintended but perhaps inevitable result of the influence of the large scale cooperative studies in Great Britain and the United States. We think the comment by Muschenheim is pertinent,—"The point is not, however, that the control studies have merely confirmed what could be anticipated. It is rather that the influence of this type of investigation on clinical thought becomes so great that clinicians generally have come to distrust their own observations and judgment until these have received statistical sanction" (13).

One of the advantages of present chemotherapy is that it will yield a broad base of successful results no matter what the variations in its application. Many such variations are utilized, each in an attempt to meet a particular facet of the disease or a special problem, or in studies to evolve a generally more potent effect of the drugs. Much of the current discussion in antituberculous chemotherapy hinges about these variations—the basic observations on the success of chemotherapy, widely accepted, are no longer a subject for discussion or require verification.

The principal drugs utilized at present in chemotherapeutic regimens are isoniazid, streptomycin, dihydrostreptomycin and paraaminosalicylic acid. Iproniazid and pyrazinamide are potentially useful drugs with individual problems and applicability. Also utilized, though with less effectiveness, are viomycin, oxytetracycline, tetracycline and perhaps, cycloserine. The sulfone derivatives and the thiosemicarbazones are not widely utilized, at least in this country. The pharmacological properties of these drugs, as well as their toxicity, mechanism of action, chemotherapeutic effect and relation to drug resistance, are discussed elsewhere (14) and will be referred to only briefly in this report.

In general, combined drug treatment is preferable to therapy with a single drug. Until the advent of isoniazid, there was no question about the validity of such a concept. Not only was there an additive effect in the utilization of two or more chemotherapeutic agents but it was found that the difficult problem of the development of bacterial drug resistance could best be handled in this manner. The genetic possibility of the occurrence of a mutation likely to be resistant

to more than one drug is small. This explained the enhancement of the value of streptomycin by the addition of PAS. With regard to these two drugs, the advocacy of combined treatment still holds.

The problem is not quite so simple, however, with isoniazid. Although bacterial drug resistance to isoniazid does develop, it does not have the same clinical significance as the development of resistance of streptomycin. Not only is chemotherapy more effective with isoniazid, with consequent reduction of the opportunity for the development of bacterial drug resistance, but when such resistance does develop, there is not the clinical deterioration of the patient which follows the development of streptomycin resistance. For this reason, it has been maintained that single drug therapy with isoniazid may be acceptable.

This advocacy of single-drug isoniazid therapy does not appear unreasonable in certain special circumstances. Its use in prophylactic therapy, as with tuberculosis in pregnancy (15), might be valid. Similar prophylactic administration to patients with quiescent tuberculous lesions prior to surgical operations, or concomitantly with steroid hormone therapy (adrenocorticotropic hormone, cortisone), or its use prophylactically in children with recent tuberculin conversion, would appear justified. In all of these instances, there is little or no active multiplication of bacteria, with the possibility of development of resistant mutants. Similar concepts might conceivably govern its use in lesions of minimal extent and of an exudative nature, where rapid control of disease is expected with little opportunity for the development of drug resistance. In the latter case, however, combined therapy would certainly be of no advantage and the use of isoniazid alone might be characterized as an exercise in the estimation of a minimal effective therapy.

In more extensive lesions, the advocacy of single drug therapy is beset with greater difficulty. There is both experimental and clinical evidence of the additive effect of dihydrostreptomycin (16) and probably streptomycin (17) when added to isoniazid. Secondly, although isoniazid resistance, as noted, does not have the same unhappy prognosis as streptomycin resistance, it certainly cannot be considered an *advantage* to the patient. It is difficult not to agree with the conclusion derived from the British Medical Research Council study on isoniazid drug resistance that ". . . as it is possible that isoniazid resistance is a direct disadvantage to the patient in some way which has not been demonstrated in this study, it would be wise to continue to regard the development of isoniazid resistance as indicating some loss of clinical effectiveness toward the drug . . . ." (18).

Because of these considerations, it would seem treatment with more than one drug is generally preferable. It is our opinion that for most cases, at the present time, triple drug therapy should be employed. For purposes of clarity, a number of advantages of such a regimen may be enumerated.

1. It is effective. Observations of the effect of chemotherapy on tuberculosis elsewhere in the body indicate that triple-drug therapy is superior. In renal tuberculosis triple-drug therapy has been found advantageous (19). Even those who recommend two-drug therapy, often add that where the disease is especially

serious all three presently available effective drugs should be used (20). Triple-drug therapy is also advocated in "miliary" and other forms of disseminated tuberculosis.

2. A frequently repeated objection to triple-drug therapy is that this regimen commits all presently available effective resources at one time. It is felt that utilizing only two drugs might be more serviceable. Thus, streptomycin-PAS or isoniazid-PAS are recommended, each being an effective therapeutic regimen, although isoniazid-PAS would seem to have the advantage of greater therapeutic response. "Either pair has the added virtue of reserving one of the two more potent drugs for possible future needs" (21).

This position does not gain validity by frequent repetition. We believe it is open to serious criticism. Utilization of one pair would not necessarily reserve one of the potent drugs for possible future use. Should resistance develop—and this is the main fear—to either streptomycin, if that be used in the combination, or to isoniazid if that be used, there remains a strong probability of development of PAS resistance. Should it then be desired to revert to the second pair of drugs, PAS would no longer be available as an agent to prevent resistance to the second drug. This would be particularly disadvantageous if streptomycin were the second (reserve) drug. Since its use without PAS is of limited value (14) and since the use of isoniazid similarly without the protective action of PAS, would also result in bacterial drug resistance, two-drug therapy may not provide an effective "reserve".

3. The advocates of two-drug therapy have developed their position principally in an effort to minimize the disadvantages of bacterial drug resistance. ". . . . the choice of a regimen for the individual patient is a decision which may depend chiefly on the risks of bacterial resistance. . . ." (22). However, on genetic grounds, the possibility of development of bacterial drug resistance is even less likely with triple-drug therapy than with treatment with two drugs. When approached from this point of view, it would appear that triple-drug therapy would be even more attractive.

In view of the foregoing, it would almost appear incumbent upon those who advocate less than full utilization of presently available chemotherapeutic resources to justify their theoretical position by observed data. We are unaware of reported experiences which would show the successful predicted use of "the reserve combination".

It is difficult to believe that such experiences will be forthcoming. First, prolonged chemotherapy results in relatively few failures. Secondly, when such failures occur it is our experience that the cause of the failure lies primarily in the nature of the disease under treatment (Table XIII) and generally not to the unavailability, for a sufficiently long period of time, of effective chemotherapeutic measures. Moreover, failure of chemotherapy in most series have been followed by accessory procedures, such as surgical excision, and not by the substitution of an alternate chemotherapeutic regimen.

This analysis of the utilization of triple-drug regimens might perhaps have less relevance should there be developed a fourth active antituberculous drug, effective in the prevention or delay of bacterial drug resistance. In that case a

TABLES X–XI

Results of chemotherapy

Variation with chemotherapeutic regimens and duration of therapy.

No.		Effect on Sputum Status			Effect on Cavity [63]		
		Negative sputum, remained negative	Positive sputum		Cavity closure	Residual cavitation	
			Became negative	Remained positive		Sputum positive	Sputum negative
	X. Regimen						
5	INH	1	3	1	2	1	0
3	INH-PAS	2	1	0	0	0	0
79	INH-DHSM-PAS	15	55	9	37	9	5
2	INH-DHSM	1	1	0	0	0	0
5	IPNH	2	3	0	2	0	1
5	INH-IPNH-SM-PAS	1	2	2	2	2	0
2	INH-IPNH	0	1	1	1	1	0
		22	66	13	44	13	6
	XI. Duration						
	6 mos.	1	0	3	0	2	0
	6–11 mos.	8	13	4	10	5	0
	12–17 mos.	7	20	2	12	3	2
	18–24 mos.	4	18	0	12	1	3
	25+	2	15	4	10	2	1
		22	66	13	44	13	6

true "reserve" would be available. Even then, it would have to be shown that the total therapeutic effect is not significantly reduced by omitting one of the drugs. At the present time, cycloserine is being studied from the point of view of its utilization in combined therapy as a means of preventing or delaying bacterial drug resistance (23). Should it prove to be of value in this regard, it may become the fourth required drug, especially if its known toxicity can be circumvented.

No significant modification in the usual doses of the drugs commonly used is required with combined-therapy. At least 1 gram of streptomycin twice a week should be administered in order to avoid the experimentally observed antagonism with isoniazid in low concentrations (24). For this same reason, it may be preferable to use dihydrostreptomycin, with which such antagonism has not been observed (16). Adequate dosage of isoniazid, towards the upper end of the 4 to 8 milligrams per kilogram of body weight per day range, is advisable. This seems preferable, especially, since it is at least as effective (25) and might prevent the development of catalase positive resistant bacteria (26). Adequate dosage of PAS should be sought. Although it does not appear that dosages over 10 grams per day offer much advantage, this level should be attained if possible, since PAS blood levels are variable and irregular.

Since iproniazid is particularly useful in patients with significant systemic toxicity, its use here is desirable (27, 28). Isoniazid should be substituted when the systemic manifestations have been controlled (14). The place of pyrazinamide in chemotherapeutic regimens is not yet determined, because of its toxicity. It may be useful in short-term treatment, as operative cover in patients with bacterial drug resistance to other drugs, or in other instances in which alternate chemotherapy is unavailable because of resistance or toxicity. The combination of isoniazid and pyrazinamide is a particularly interesting one since it is the only combination which appears to destroy *all* tubercle bacilli in experimental lesions (29) and has also been found effective clinically (30). However, because of its toxicity, it is not suitable as a chemotherapeutic regimen for wide use.

Toxicity of isoniazid, streptomycin and PAS is sufficiently low to minimize this factor in selection for use in drug therapy combinations. Among those clinicians (31–33) who have found triple-drug therapy advantageous, toxicity has not been considered important.

Duration of Therapy

The problem of duration of therapy can be studied from two points of view; from the standpoint of the control of the disease and the duration of treatment required for prevention of relapse. An estimate of the time required for control the disease is important for practical management of the patient but the desideratim of treatment is to prevent relapse.

Our experience has shown that antimicrobial therapy of only several months duration is inadequate from either point of view. With streptomycin and PAS, not only is stability not achieved for a number of months but also it has been shown that hematogenous dissemination may continue (1). Study of excised specimens yields histological evidence of activity with short term therapy (34). Bacteriological study of these specimens has shown significantly reduced bacterial viability in residual lesions with increased duration of chemotherapy (35).

Analysis of the present series indicates (Tables XI, XII) the value of long-term chemotherapy. None of the patients with prolonged treatment suffered a relapse. The single case of reactivation following discontinuance of chemotherapy, occurred in a patient who had only six months of treatment. Upon retreatment with drugs, he responded well and has again achieved control of his disease. Other available data conform to our experience (36, 37). When therapy is continued for one to one and a half years, reactivation is quite uncommon (33). The experience in our institution in the treatment of tuberculous lymphadenitis has been similar. Here, too, reactivations occurred only in those patients with short term chemotherapy (38).

We would make the following recommendations with regard to duration of therapy. A *minimum* of one year of chemotherapy is necessary. However, this short period should not be regarded as the duration of choice. The length of treatment is a matter to be decided for each patient and is dependent upon clinical judgment. Certainly, as long as regression of the lesion is observed on

TABLE XII

Time of sputum conversion

79 Cases with positive sputum: Primary chemotherapy. Evaluation of influence of several factors

	Month						Remained Positive
	1	2	3	4–6	7–9	10–12	
A. *Cavity*							
1. (48) *single*	20	10	4	5	2	0	7
2. (15) *multiple*	1	2	3	2	0	1	6
	21	12	7	7	2	1	13
B. *Cavity size*							
1. Smaller than 3 cm	16	4	2	2	2	0	3
2. Larger than 3 cm	5	8	5	5	0	1	10
	21	12	7	7	2	1	13
C. *Activity allowed at onset of therapy*							
0	0	0	2	0	0	0	1
1+	2	1	0	1	0	1	1
2+	10	6	3	3	1	0	6
3+	9	5	1	1	1	0	4
4+	8	4	3	3	1	0	1
	29	16	9	8	3	1	13
D. *Therapy*							
INH	2	0	1	0	0	0	1
INH-PAS	1	0	0	0	0	0	0
INH-DHSM-PAS	24	13	7	7	3	1	9
INH-DHSM	1	0	0	0	0	0	0
IPNH	1	1	1	0	0	0	0
INH-IPNH-DHSM-PAS	0	2	0	0	0	0	2
INH-IPNH	0	0	0	1	0	0	1
	29	16	9	8	3	1	13

the roentgenograms continued chemotherapy is mandatory. Once there is roentgenographic stability, a further period of six months of chemotherapy may be adequate, provided the sputum is negative and there is no evidence of cavitation.* If the sputum is positive, or a cavity persists with a negative sputum, chemotherapy should be continued. The chemotherapeutic regimen may be changed as soon as roentgenographic stability is attained provided the sputum is negative. In such instances, streptomycin or dihydrostreptomycin may be discontinued and only isoniazid and PAS given.

* No lesion is considered cavity-free without confirmation by sectional radiography.

If for any reason therapy has been stopped too soon and observation indicates reactivation of the disease, an additional course of treatment may be given. Reviews of serial roentgenograms sometimes reveal that the activity seen is not purely a reactivation; rather, stability had not yet been achieved so that premature discontinuance of therapy had resulted in progression of the disease. In such instances, restarting therapy can be considered a continuation of the previous treatment. Serial tomography (39) is particularly valuable in making a more accurate decision as to the stability of the lesion.

Even if true reactivation has occurred, another course of chemotherapy is often indicated. If the original treatment was of short duration, the possibility remains that bacterial drug resistance is not a factor. Moreover, even if resistance was present during the previous course of therapy, it may have decreased, with the passage of time, to the point where therapy may again be effective (40). Judgement as to the degree of resistance, furthermore, may have been erroneous since there are varied degrees of sensitivity and resistance among the bacteria in any single sample (41). For these reasons, a second course of chemotherapy may be successful. Failure of retreatment could be followed by suitable accessory therapy, if this be applicable.

Drug toxicity is not usually a significant factor in determining the duration of therapy. Most drug reactions, especially those due to the drug allergy, occur early in the course of treatment. This has been well documented with regard to isoniazid, PAS and streptomycin (14) and it is true of cycloserine as well. An exception is pyrazinamide, with which liver damage also may occur late in therapy. Eighth nerve damage with streptomycin or dihydrostreptomycin may be late, but usually is noticed before the eighth week. Neither in our series nor in others reported (42), has toxicity been a contraindication to long term treatment.

Of crucial importance, and yet to be adequately reported, will be an analysis of the late results of chemotherapy insofar as reactivation of residual lesions is concerned, with and without prolonged chemotherapy. From the study of our own data it appears that such experience will not be easy to evaluate. Because of the many variables, unless a considerable number of recurrences are available for study, it will be difficult to isolate the effect of duration of therapy on the frequency of reactivation from other equally important factors.

Two such factors to be considered are the nature of the original disease and the type of residual lesion. Experiences gained in the pre-chemotherapy era are difficult to apply at present. For example, because of the beneficial effect of chemotherapy on healing at the bronchocavitary junction, there is less inspissated material in the closed cavity than in previous years (14). Moreover, with the rapid clearing of the perifocal reaction under the influence of chemotherapy, healed lesions currently show less fibrosis than in the pre-chemotherapy period. These evidences of more complete healing of residual foci as a result of chemotherapy suggest that the residual foci following treatment will prove less apt to reactivate than those in the pre-chemotherapy era.

Moreover, it will be undoubtedly difficult to isolate the effect of the duration of chemotherapy from the effect of host resistance, which may continue to have an

effect after once chemotherapy is stopped (43). What effect the chemotherapy may have on the patient's own immunity is at present unknown (44).

THE CHEMOTHERAPEUTIC MANAGEMENT OF ACTIVE PULMONARY TUBERCULOSIS

Chemotherapy as a definitive treatment. The variability of pulmonary tuberculosis makes difficult the grouping of patients for the various forms of treatment. Classification of lesions can be made so exact as to include one patient in each group. Therefore, as a practical measure, it is preferable to seek common denominators, rather than differences. There will then be but a few large categories, for which plan of management need be formulated. Naturally, the distinctions between the various categories will be indistinct and the classification of the borderline cases will depend upon experienced clinical judgment.

There is a large group of patients for whom chemotherapy alone may be expected to serve as definitive treatment. Into this group would fall most patients with recent disease. Selection of this group depends largely on roentgenographic interpretation. This group is represented by lesions which because of their pathological nature may be considered to be "reversible". It should be emphasized, however, that it is uncommon in clinical tuberculosis to see pulmonary tuberculosis of a purely exudative nature. Most lesions when seen even relatively early are "mixed" in character with exudative, caseous and fibrotic elements. Yet clinically, with chemotherapy, these lesions show regression and healing. Current thinking with regard to healing of caseous lesions is undergoing a change (14).

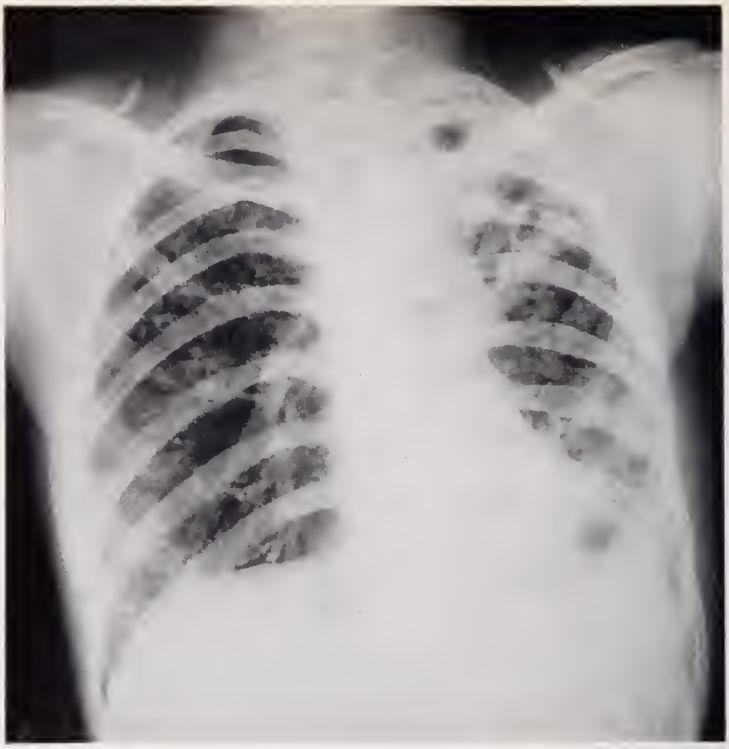
Extent of the lesions, although important, does not negate the basic observation that recent disease is amenable to chemotherapy, although such chemotherapy should be more prolonged (Fig. 1). Extensive lesions provide a good example for the necessity of long-term chemotherapy. Progressive resolution may continue for two years or more.

The simple presence of cavitation also does not contraindicate the selection of chemotherapy as a possible definitive procedure. This is especially true when only one cavity is present. As can be seen from Table VIII, 37 of 48 single cavities closed under chemotherapy and only seven remained open with positive sputum. The nature of the pericavitary infiltrate, however, is important. When this is extensively fibrosed, the possibility of cavity closure is perhaps decreased. Usually, the pericavitary infiltrate will show regression before the closure of the cavity.

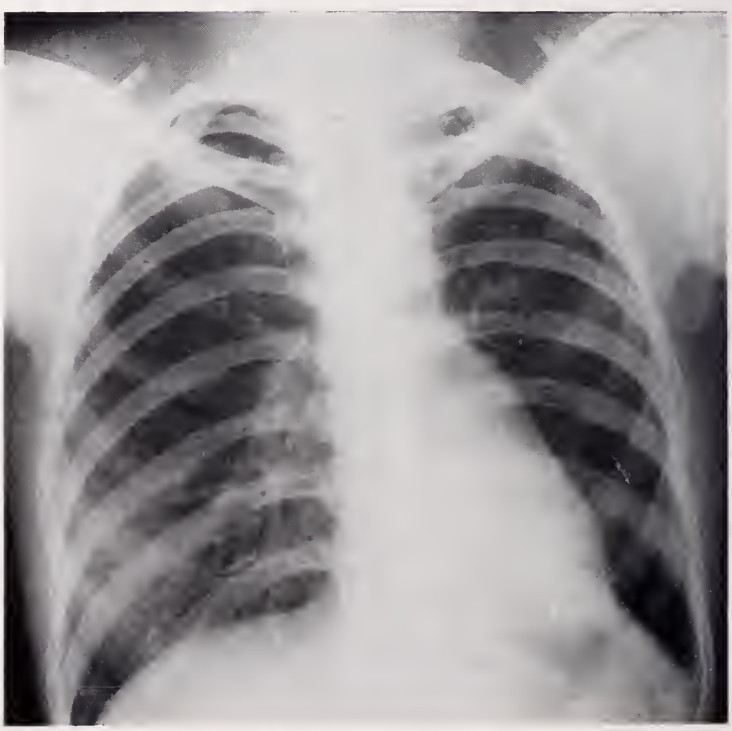
Diffusely disseminated lesions, whether bronchiogenic or hematogenous, do well with chemotherapy, if the individual lesions are small. The rapid healing of these lesions by chemotherapy prevents extensive fibrosis and restores and maintains good pulmonary function.

Tuberculous endobronchitis also responds well to chemotherapy, but bronchostenosis due to fibrosis is not affected (14). The infected element in extensive tuberculous bronchiectasis may be eliminated but the anatomical alterations remain.

Exceptions to the general rule that chemotherapy is successful in recent dis-



1a. M. McG. Dec. 15, 1952.



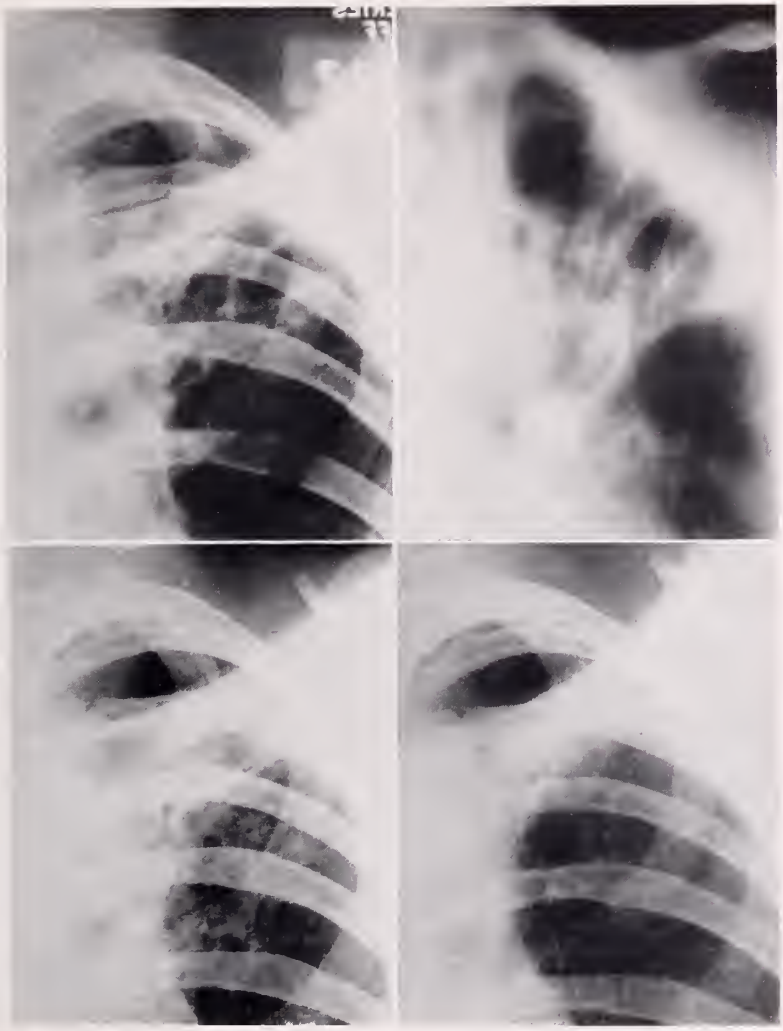
1b. M. McG. Jan. 28, 1956.

FIG. 1. RESULT OF CHEMOTHERAPY IN EXTENSIVE DISEASE

1a. Dec. 15, 1952. Extensive bilateral infiltration. However, this has the appearance of relatively recent disease. Chemotherapy is often successful in such cases. *1b*. Jan. 28, 1956. Marked clearing under combined chemotherapy with isoniazid-dihydrostreptomycin-PAS. Chemotherapy must be prolonged in disease of such extent.

1c. M. McG. June 11, 1953.

1d. M. McG. June 11, 1953, tomographic section.



1e. M. McG. Dec. 8, 1953.

1f. M. McG. Nov. 10, 1954.

1c. Detail of left upper lobe on June 11, 1953. Demonstrates the extensive involvement. *1d*. Well shown in tomographic section of same date. *1e*. Left upper lobe, Dec. 8, 1953. Further healing. *1f*. With continued chemotherapy, film of Nov. 10, 1954 shows progressive resolution. These serial films illustrate that there can be no hard and fast rule as to duration of therapy in disease of considerable extent. It should be continued as long as response is obtained.

ease occur in the group of patients with very large cavities or with multiple cavitation. Table VIII indicates that of 15 patients in our series with multiple cavitation, six failed to show complete cavity closure and retained sputum infectivity. Moreover, it can be seen from Table IX, that of 30 cavities smaller than 3 centimeters in diameter, 27 showed cavity closure, while of 33 measuring

over 3 centimeters, only 17 showed cavity closure. Therefore, patients with large cavitation should not be included in a group in which chemotherapy is regarded as a definitive procedure. While chemotherapy may still be recommended, it should rather be considered a trial of treatment, with careful observation for possible failure and the substitution of alternate therapy.

Trial of chemotherapy. A second large group of patients consists of those in whom control of the disease by chemotherapy is not as likely as those in the first group, but in whom the treatment is successful sufficiently often to warrant a trial. It is precisely in this group of patients that therapeutic concepts vary the most. Common to most patients in this group is the "mixed" nature of the lesions which show varying degrees of caseous necrosis, fibrosis and exudation. These lesions are usually of considerable duration and, as a consequence, may vary in character in different portions. Some areas retrogress while others simultaneously heal by fibrosis. Review of the previous course of these patients often shows reabsorption of exudative elements with breakdown of caseous areas, resulting in cavitation.

There is a group of patients in whom the decision as to whether to use chemotherapy or resection or collapse treatment is difficult. These include cases with localized caseous lesions with cavitation. Nevertheless, a trial of chemotherapy would appear reasonable for most patients in this group. Experience indicates that most will achieve control of their disease by chemotherapy and for those who fail, alternate procedures are available. Chemotherapy is required, in any case, for all patients with active disease even if excision or collapse is contemplated. Moreover, control is required of the "unseen lesion" in the bronchi and in other parts of the lung, secondary to previous bronchogenic dissemination.

With widening experience, the indications for inclusion of patients into this group have been extended. Previously held concepts about the irreversibility of caseous lesions no longer appear valid. Figure 2 shows an example of a case with caseous disease in the upper lobe of at least three years duration which, nevertheless, showed regression under chemotherapy. In this group, too, the nature of cavitation is important with less likelihood of success with multiple cavities and those of very large size. The mixed, fibrocaseous character of many of the lesions in this group necessitates prolonged chemotherapy for proper healing. Regression is relatively slow, is often incomplete, with residual lesions. The management of such residual lesions is discussed below.

Anticipated chemotherapy failure. Chemotherapy failure can sometimes be anticipated from the observed nature of the disease. This group consists principally of cases of extensive disease of long duration, with much fibrosis and caseation. When such disease is further complicated by large multiple cavities, the failure of chemotherapy becomes even more likely. If the extensive pulmonary disease is localized, it may be amenable to surgical therapy. In these cases, chemotherapy is utilized pre- and postoperatively, for its known beneficial effect on the endobronchial tuberculosis as well as for the control of unseen lesions in other areas of the pulmonary parenchyma.

Nevertheless, when alternate therapy with a greater likelihood of success is not

possible, chemotherapy should be utilized to its full extent. While chemotherapy may not be a definitive treatment, it may, by clearing of contralateral lesions or control of the reversible portion of the disease, make possible surgical therapy in the future. While chemotherapy often fails in these cases—many patients will respond well, sometimes unexpectedly (45, 46). In addition, it is a common observation that even in extensive disease, in which full control is not achieved by the drugs, spread of the infection is much less common when isoniazid is used.

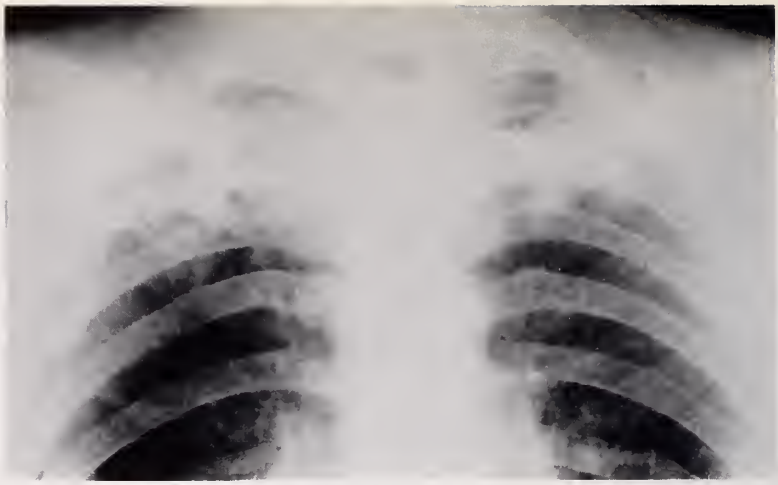
An estimate of the response that can be expected in the various categories can be obtained from perusal of Table II. Of 71 patients who could be classified in group 1 or group 2 (chemotherapy predictably definitive or at least worth a trial) there were only six instances of failure, and of these six, five had subsequent successful management either with retreatment, resection or collapse, and the sixth is waiting excision with every likelihood of success. Of 30 patients who could be classified as anticipated chemotherapy failure, seven were judged suitable for excisional or collapse therapy and were successfully treated thereby. Twenty-three, however, had no other therapy logically available and were consequently treated by chemotherapy alone. In 16, this treatment was successful.

Prophylactic chemotherapy. A certain number of patients are suitable for prophylactic therapy. These are patients with inactive disease entering periods of actual or anticipated stress, such as pregnancy, operations, etc. That this might be an advantageous use of chemotherapy is illustrated by a series of patients undergoing gastrectomy, in which 2 per cent of 356 patients subsequently developed active pulmonary tuberculosis (47, 48).

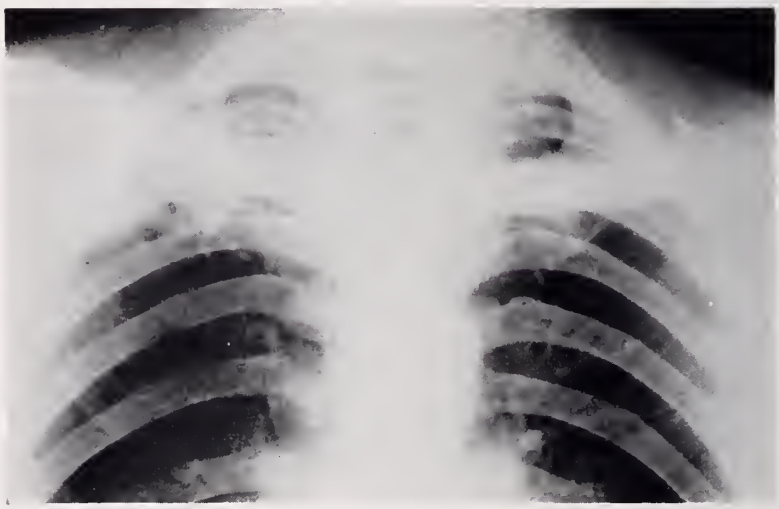
ANALYSIS OF FAILURES OF CHEMOTHERAPY

Analysis of the 13 cases of failure of chemotherapy in this series proved fruitful (Table XIII). In five patients the nature of the disease was such that it was predicted that chemotherapy would fail. In the other eight it was thought that chemotherapy had a reasonable chance for success. Of the latter group, drug allergy precluded adequate chemotherapy in one case. In another, there was inadequate duration of therapy. Three patients failed to respond and re-evaluation of these cases still provides no clue for the failure. We suspect that the reason lay in the nature of the disease but this was not obvious on roentgenogram. Finally, in three cases therapy had been interrupted.

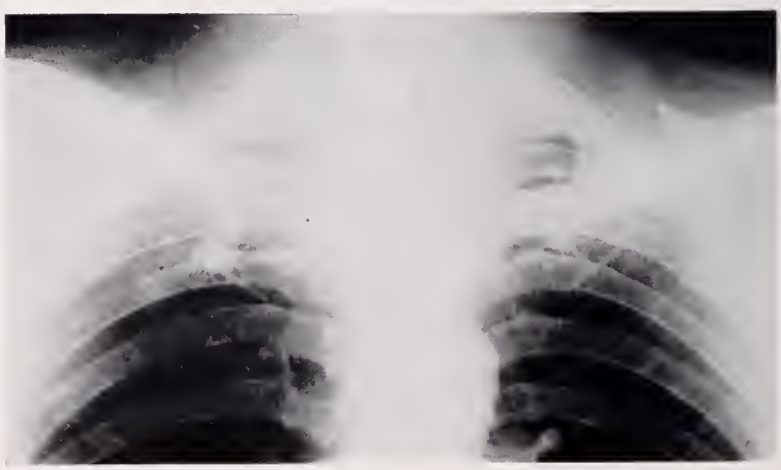
This latter point is worthy of some comment. Although continuous therapy is generally recommended, the basis for this recommendation has not been documented. Therefore, we have studied all patients in our series in whom for various reasons therapy was discontinuous. Analysis of this group of patients is contained in Table XIV. It will be seen that eight patients of the 108 in the series did not have continuous chemotherapy. In one case, as noted, this was due to drug allergy while in the other seven, lack of patient cooperation was the cause, in three cases because the patients "felt well", and because of the irresponsible nature of the individual in the other four. Six of these eight patients did poorly. Although in three of the six the nature of their disease might have made success unlikely in any case, this was not the case in the other three. Although no firm



2a. M. M. March 22, 1954



2b. M. M. October 20, 1951



2c. M. M. March 14, 1956

2d. M. M. April 3, 1954

2e. M. M. April 18, 1956

FIG. 2. RESORPTION OF CASEOUS LESIONS UNDER CHEMOTHERAPY

2a. March 22, 1954. Bilateral upper lobe fibroeaseous lesions. At beginning of treatment. *2b.* Film of October 20, 1951. Disease has been present for at least three years. *2c.* Nevertheless, with chemotherapy, reabsorption is possible in many instanees of fibrocaseous disease. Film of Mareh 14, 1956 shows considerable clearing. Patient continues under combined ehemotherapy. *2d.* April 3, 1954. Tomogram showing caseous lesions more clearly. *2e.* Tomogram section at the same level on April 18, 1956. Healing with chemotherapy, with residual lesions.

TABLE XIII

Analysis of failures of primary chemotherapy

Inadequate course of therapy	1
Nature of the disease-predicted	5
Drug allergy	1
Failure of expected response to adequate therapy	3
Interrupted therapy	3
	13

TABLE XIV

Effect of discontinuous chemotherapy: 8 patients of 108

Reason for discontinuous therapy		
Lack of patient cooperation		7
"Felt Well"	3	
Irresponsible	4	
Allergy		1
Results of interrupted therapy		
Continued deterioration		1
Reactivation of disease		5
No apparent ill effect		2

TABLE XV

Results of chemotherapy: evaluation of effect of previous chemotherapy

	No Previous Chemotherapy		Previous Chemotherapy	
	Success	Failure	Success	Failure
Primary chemotherapy	65	3	23	10
Primary surgery or collapse	3	0	4	0
Total	68	3	27	10

conclusions can be drawn from study of this small group, it would appear that continuous therapy, as advised in theory, has a practical basis.

There is a greater incidence of poor results in patients undergoing retreatment. It is likely that there are two reasons for this: first, retreatment connotes long duration of disease. Secondly, with previous treatment, there is greater opportunity for the presence of bacterial drug resistance. These facts are emphasized by analysis of Table XV. Of the 108 patients in this series, 71 had had no previous chemotherapy. In this group, there were three failures and 68 successes. In contrast, of 37 patients who had previously had chemotherapy, there was failure in ten and success in 27. By failure is meant lack of reversal of sputum infectivity and/or unsatisfactory x-ray change.

MANAGEMENT OF RESIDUAL DISEASE

The success of chemotherapy in moderate or far advanced disease has made much more common the important problem of the residual lesions. With exten-

sive disease, especially of caseous or fibrocaseous nature, resorption and healing with chemotherapy is rarely complete and lesions usually fibrocaseous in nature, remain evident on the roentgen film.

In some cases, these residual lesions are not a problem in management. When they are very small and hardly visible on x-ray, one is quite content to merely observe them. When they are extensive and bilateral, the indication for therapy is clearcut, i.e., continuation of chemotherapy for a prolonged period of time, or close observation. However, most residual lesions fall between these two groups.

Medlar was often able to trace open bronchi leading to necrotic foci in the residual lesion and therefore considered them potentially dangerous. It was therefore felt that surgical excision of these residual lesions was a highly desirable procedure (49). The first surgical procedure for residual foci following this concept was performed in October 1950 (50) and the procedure rapidly became widely popular, especially, but not exclusively (51), among surgeons.

Enthusiasm for this procedure has not been universally shared, however. Jerome Head, for example, objected (52) ". . . . is a patient on whom the pathologist can demonstrate a walled off focus of tuberculosis or a minimal tuberculous infiltrate which is not healed entirely in the center, clinically tuberculous or clinically threatened? I do not believe so. I believe we must insist on our rights as clinicians and that in these matters we must refer to experience and statistics." Similarly, O'Brien (53) cautioned "Right now it is difficult to get a patient out of a hospital or a sanatorium without resection of some sort."

In the last several years enthusiasm for the indiscriminate resection of residual lesions has been much more reserved. As has been stated by the Committee on Therapy of the American Trudeau Society, "At the present time the excision of non air-containing nodules either filled in or unsloughed, in patients with negative sputum bacteriology during prolonged antimicrobial therapy in pulmonary tuberculosis can neither be recommended nor condemned. There is now less enthusiasm than formerly for such surgery because of the known results of bacteriological study of surgical specimens and apparent success of long-term therapy" (54).

It is presently felt that prolonged clinical observation will be required of patients who have had adequate chemotherapy and who are left with residual lesions, before decision can be made as to the desirability of excision of residual lesions (22). Such studies to date have given no answer. Studies of alternate patients with resected and non-resected residual foci, with a three-year follow-up have shown no significant difference in the relapse rates of the two groups thus far (55). In one of the Veterans Administration's hospitals participating in this study, there were 85 cases, resected and unresected, studied from June 1953 to December 1954. A recent review showed two clinically benign "relapses" in each group. "As yet, no factual data are available that permit surgical policy to do more than improve what appears to be an already favorable outlook" (50).

Indeed, we hesitate to believe that projected studies of this sort will give more than an approximate answer to what is essentially an individual problem of each case. In investigations of this problem it will be difficult to isolate such

variables as the nature of the original disease or the nature of the residual lesion. Yet both are obviously important. Moreover, numerous other variables exist and are equally difficult to isolate. The duration of the previous chemotherapy would be of importance. For example, the very first case operated upon had only had four months of previous chemotherapy. The residual disease in such a case would obviously differ from the residual disease of a patient who had had three years of chemotherapy. D'Esopo (22) noted that in patients who had been treated with PAS and streptomycin twice weekly for four to eights months, residual lesions were found to have viable bacteria in approximately 50 per cent of instances. In contrast, when daily streptomycin was utilized with PAS for the same period of time, only 8 per cent of the excised residual lesions had viable bacteria. The possibility of reactivation would differ with each type of residual lesion. Whether or not cavities had previously been present, their size and number, and the possible existence of drug resistant bacteria in them prior to closure, provide additional variables. Considering all these possibilities, and the relatively small number of reactivations that occur, one can appreciate how difficult it will be to be able to state with any degree of certainty whether surgical excision of residual lesions is worth while.

As experience with excision of residual lesions has increased, problems have arisen. Morbidity after surgery is not inconsequential (32). Whereas mortality is quite low and the operation therefore considered safe, it has been correctly commented that ". . . . the indications for operation should be *necessity* and not *safety*" (56). In one series of post-resection relapse, in eight of nine cases the relapse was characterized by the appearance of new shadows at or near the site of operation. With the ninth relapse there was a pleural effusion on the same side. "Since in each case the disease became active again at or near the operation's site, it is suggested that the surgeon's knife may have been in part responsible for the relapse. This was true even in patients having continued chemotherapy at the time of operation, even with drug sensitive organisms. In five of the nine patients, there was no open cavity at the time of operation so that cavitary spread could not be considered" (56).

A further difficulty with surgical removal of residual foci has been the realization that while "the removal of all palpable disease, the theoretical aim, is accomplished in approximately two-thirds of the cases" (50), removal of palpable disease is no index of removal of *all* disease. This has been brought out clearly in the study by Logan (34) who examined 43 resected specimens. Disregarding the diseased areas, 101 blocks of tissue were taken from what was macroscopically and radiologically (including tomography) normal lung. He found "the most surprising feature of this study was that, in sections of the lung taken from areas which appeared on roentgenographic and macroscopic examination to be normal lung, almost every slide showed evidence of tuberculosis. In less than half the cases, the disease appeared to be healed and in one-quarter of the cases it was active, although there was no clinical evidence of activity." It should be noted that the specimens taken were from patients who had previously had preoperative chemotherapy.

In our opinion, *routine* excision of a residual focus is unwarranted. The indication for excision should depend on an evaluation of the individual case. Good clinical judgment will indicate a number of situations in which it should be recommended.

1. *A large residual caseous mass.* If such a lesion is brought under control with difficulty and with indeterminate stability on roentgenograms, we would suggest excision, if there is no contraindication.

2. *Hemorrhage from a residual fibrocaseous lesion.* This sometimes is best treated by excision, especially if the lesion from which the hemorrhage occurs is extensive. One such case occurred in our series and is illustrated in Figure 3.

3. *A large residual inspissated cavity.*

4. *An inspissated cavity with previous drug resistant bacteria.*

5. *Residual lesions at the site of previous large multiple cavitation* might be considered for resection. However, this does not constitute an absolute indication.

6. *Bronchostenosis* after healing of endobronchial tuberculosis if there is recurrent non-specific infection.

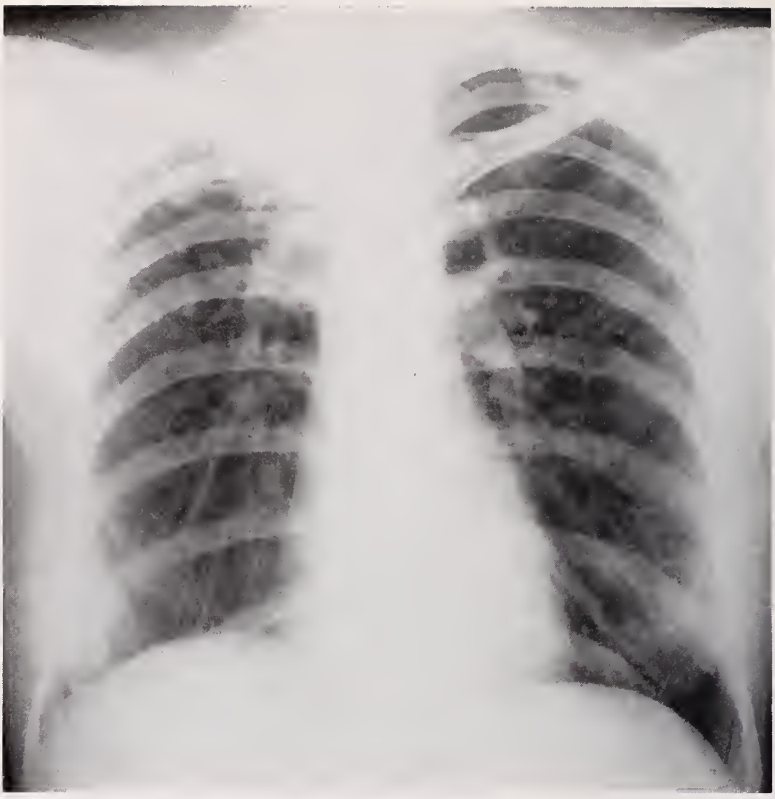
7. *Anticipated failure of potential retreatment* might be considered an indication for resection of residual disease. This would be considered in patients who had significant drug toxicity during chemotherapy, in patients with significant bacterial drug resistance before control of the disease, patients with bilateral residual lesions, in whom one side at least should preferably be under good control, poor risk patients such as those with mental illness, alcoholism, or diabetes, and in special circumstances such as members of air crews with potential stretching of parenchyma during rapid or explosive decompression or rapid acceleration (57).

8. *Empyema* is an important indication for resection of residual disease, either pleural disease alone or together with the pulmonary disease (58), if this be present. Figure 4 represents one such case in this series.

MANAGEMENT OF THE OPEN "STERILE" CAVITY

The problem of a special type of residual lesion, the open "healed" cavity, has recently arisen. The anatomical nature of such open healed cavities has been discussed elsewhere (14). It is related to the effect of chemotherapy on cavity healing. In contrast to pre-chemotherapy days, obstruction of the bronchocavitary junction need not necessarily occur as a requisite preliminary to cavity healing. With reepithelization of the bronchocavitary junction under the influence of chemotherapy, the bronchus to the cavity remains open and the caseous cavitary contents are discharged through it (59). This, coupled with chemotherapeutic action on the cavity wall (60), leads to the persistence of cavities without tubercle bacilli in the sputum.

Open healing of cavities was rarely observed prior to the introduction of isoniazid therapy. Although cavity healing occurred with streptomycin and PAS therapy, *open* cavity healing was very infrequent. With streptomycin-PAS therapy, it was found at the Municipal Sanatorium in Chicago that none of the specimens from resections in 1949 or 1950 showed evidence of open healing and



M. P. Jan. 9, 1955.

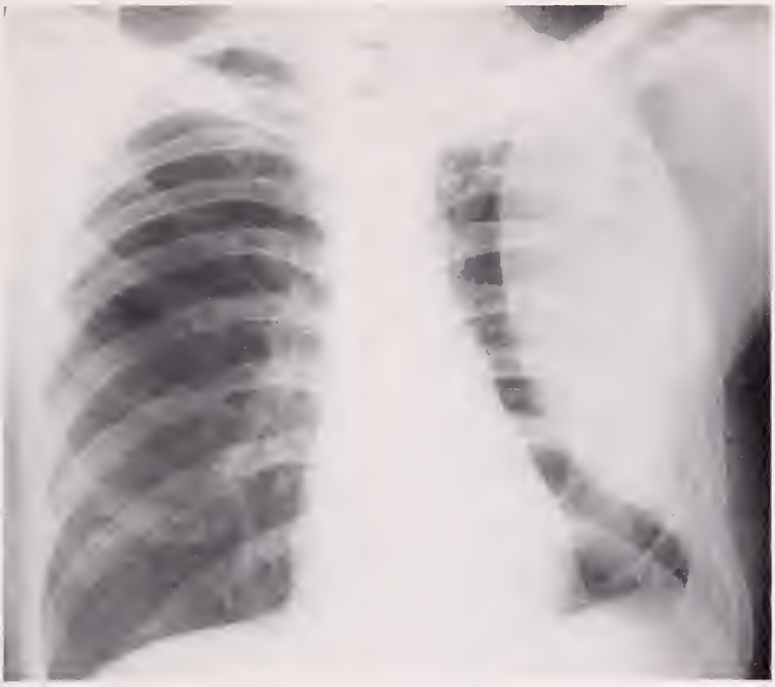
FIG. 3. INDICATION FOR RESECTION OF RESIDUAL LESION

Jan. 9, 1955. Large residual lesion with hemoptysis. Infiltration of the right upper lobe. Although the lesion was stable on serial films and no tubercle bacilli were present in the sputum, severe hemorrhage from this residual lesion provided an indication for its resection.

only one such instance was found in 1951. In 1953, however, after the introduction of isoniazid, there were 13 such cases (61). Similarly, at Sea View Hospital, of 193 lung specimens with cavitation from patients who had streptomycin-PAS therapy, only one specimen showed a smooth-walled cavity. In contrast, eight of 46 specimens from patients treated with isoniazid, with or without streptomycin, showed open healing (61A).

The exact incidence of open healing of cavities with chemotherapy is difficult to determine. Although Johnson and Hewitt (62) state that they found 22 examples of open healing of cavities in their hospital of 614 beds in over a year, they do not give the total number of patients observed, from which incidence might be approximated.

Criteria for the designation of "open healing" have not been established. The possibility of an active lesion should always be suspected and no cavity should be designated as an example of open healing unless the sputum had been



A. P. March 28, 1955

FIG. 4. INDICATION FOR RESECTION OF RESIDUAL LESION: EMPYEMA

March 28, 1955. Large encapsulated empyema with a residual inactive caseous focus in the left upper lobe. Tubercle bacilli were found in the empyema and in the pulmonary focus. Such residual lesions should be treated by pleuropulmonary resection, with excision of the empyema as well as removal of the residual pulmonary focus.

free of tubercle bacilli for at least one year on smear and culture, and the presence of the cavity is confirmed by tomography.

In the series under study, there were 63 patients with open cavity and tubercle bacilli in the sputum. After chemotherapy, there were 44 instances of closed cavity and negative sputum, and 19 instances of residual cavitation. Thirteen of these continued to show tubercle bacilli in the sputum. Six patients, despite careful search, were no longer found to have infectious sputum. It would seem, therefore, that if our experience is repeated elsewhere, approximately 10 per cent of patients with cavitation and tubercle bacilli in the sputum may, with chemotherapy, be expected to show "open cavity" healing. Similar incidence has been found in another consecutive study (10).

It is not at all certain that all cavity-like structures seen on roentgenograms are true cavities. Some are bullae rather than true pulmonary cavities (63, 64), occasionally occurring near the site of cavities which had disappeared (65).

The question of the proper management of open-healed cavities is still unsettled. Additional data will be required before decisions based upon adequate experience can be formulated. A number of variables will require study, in-

cluding the duration of chemotherapy and its nature. Pathological examination of resected specimens indicates that, in some instances, especially those with short-term chemotherapy, the cavity walls are incompletely healed. Thus, while clinically these would seem to be open-healed cavities, they cannot be so regarded anatomically.

Varied management was applied in the six cases we observed. One such cavity was successfully closed by pneumothorax therapy. One was resected. Four have been observed with continued chemotherapy for periods of 16 to 28 months and each of these four has remained well.

Figure 5 is an example of open-healed cavitation in our series. Although a cavity has been clearly present throughout this patient's treatment, there have been consistently negative sputum examinations for the past 18 months. The cavity has become somewhat smaller. Figure 6 shows serial roentgenograms of another patient in our series with an open-healed cavity. At the onset of chemotherapy, a large cavity in the left apex became inspissated and then emptied itself. Sputum from that point on failed to show tubercle bacilli. The patient remained free of infectious sputum for 28 months, despite the presence of an open cavity. Her most recent tomogram unexpectedly showed rapid cavity closure. The cavity was present on tomogram six weeks before. It is possible that there has been obliteration of the bronchocavitary junction.

Thus far, no one technique of management appears advisable for all instances of open-healed cavity. First, it is essential that frequent sputum examinations be made to justify the "healed" designation of the cavity. If these examinations persistently fail to reveal tubercle bacilli, it may be safe to continue chemotherapy with further observation of the patient. Pneumothorax may prove to be a suitable treatment for the management of these lesions in some patients. In others, resection of the residual cavity might be advisable. In our series, this was recommended in the case of a young woman with a small child. It was not felt desirable that she resume care of her child with an open cavity, since there was no guarantee of the permanent reversal of her sputum infectivity.

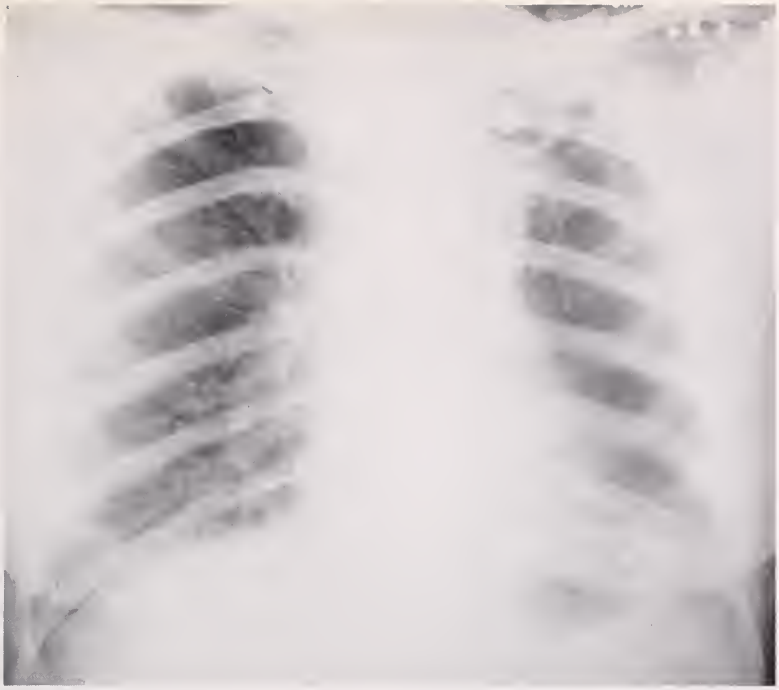
THE USE OF ACCESSORY THERAPY

Surgical Procedures

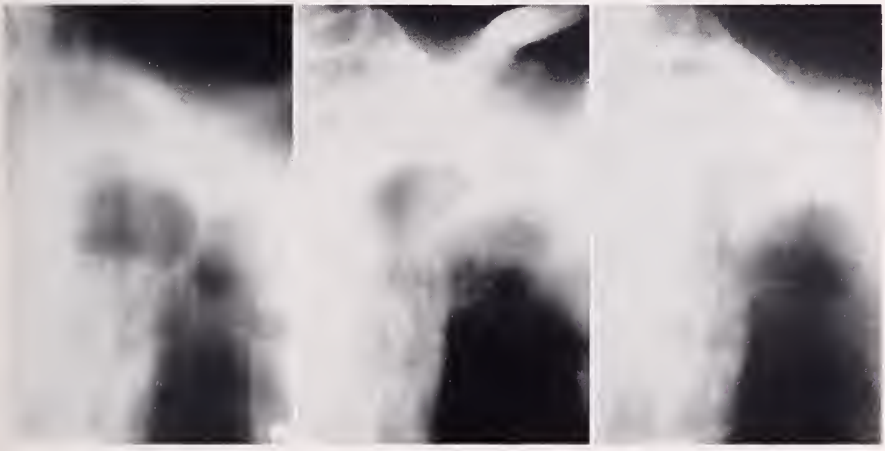
Prior to the introduction of chemotherapy into the management of pulmonary tuberculosis thoracic surgical procedures were the principal forms of active treatment. Since the introduction of chemotherapy a number of these procedures have continued as important accessory measures, and in many instances, surgical treatment plays the major role (66–68). In general, the utilization of the surgery has diminished. Experiences at one institution are detailed in Table XVI (69). Not only has the frequency of surgery changed, but also the indications for its use (50).

Indications for Surgery

A practical clinical analysis of our current indications for surgery for pulmonary tuberculosis is outlined below. It is recognized that this listing is by no



5a. E. W. June 6, 1954.



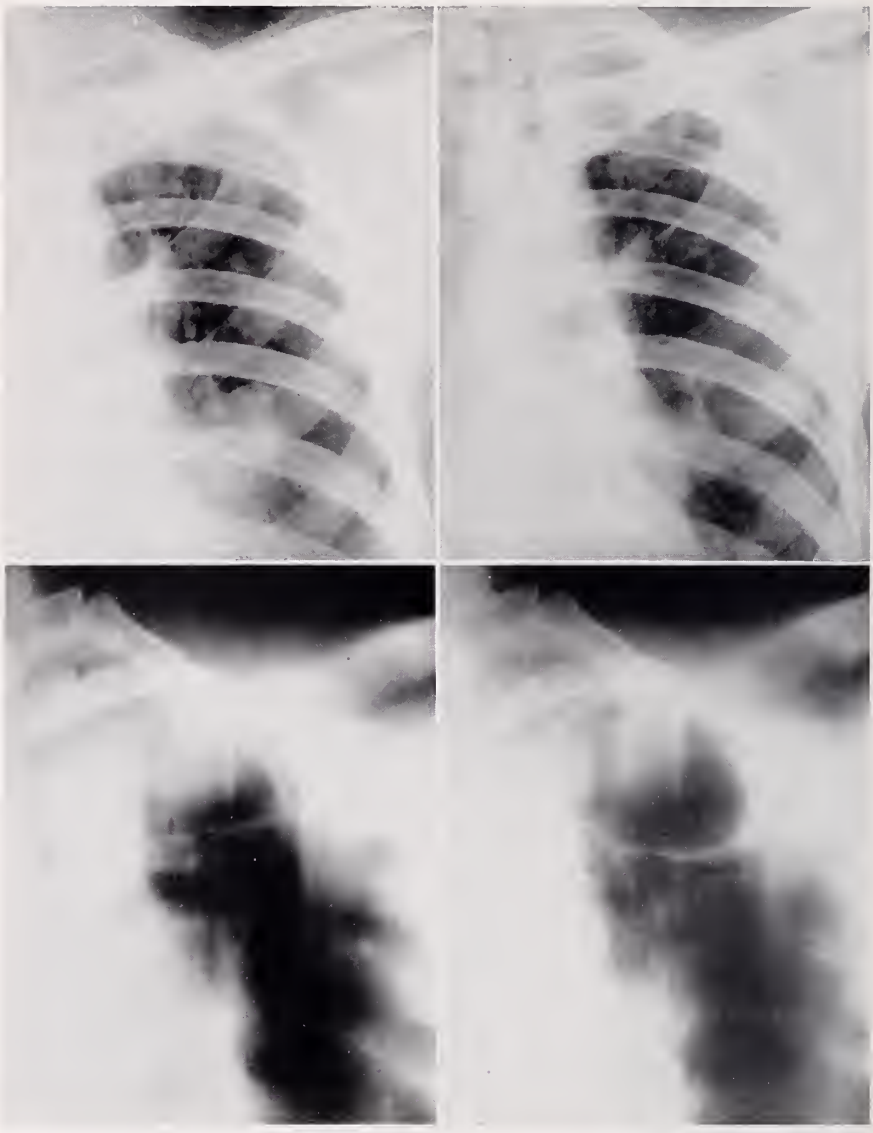
5b. E. W. June 14, 1954 *5c*. E. W. March 20, 1955 *5d*. E. W. Feb. 18, 1956

FIG. 5. OPEN "HEALED" CAVITY. PROLONGED CHEMOTHERAPY

5a. June 6, 1954. Fibrocaseous tuberculosis in the left lung of at least 7 years duration, with dissemination to the right lung. The large cavity at the left apex is the probable source of tubercle bacilli in the sputum. *5b*. June 14, 1954. 8 cm. antero-posterior tomographic section. The cavity is clearly delineated. *5c.–d*. March 20, 1955 and Feb. 18, 1956. Tomographic sections of the same level. Only slight diminution in size. Sputum has been free of tubercle bacilli on 40 smear and culture examinations during the past 18 months.

6a. J. L. Oct. 24, 1953

6b. J. L. Jan. 5, 1956

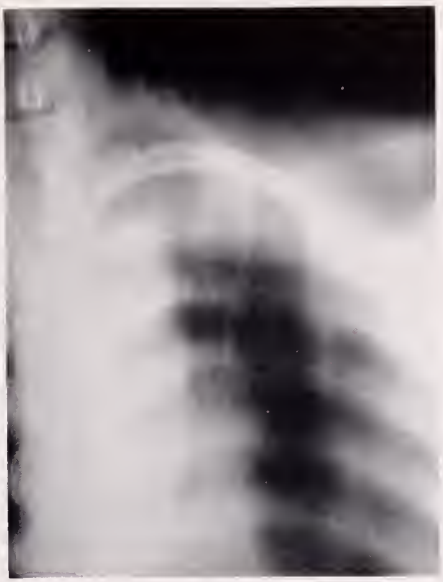


6c. J. L. Dec. 29, 1954. 6 cm. tomographic section

6d. J. L. Feb. 13, 1956. 6 cm. tomographic section

FIG. 6. SUDDEN CLOSURE OF OPEN HEALED CAVITY OF LONG STANDING. PROLONGED CHEMOTHERAPY.

6a. Oct. 24, 1953. Large inspissated cavity is present at apex of left upper lobe. Recent consolidation below left lung root. *6b.* Jan 5, 1956. Persistent cavity at left apex, first noted January 1954. Lesion below left lung root resolved. *6c.–d.* Dec. 29, 1954 and Feb. 13, 1956. 6 cm. antero-posterior tomographic sections. Cavity present on both films. Nevertheless, sputum had been free of tubercle bacilli on over 50 smears and culture examinations, for over two years. This, again, represents the problem of "open-healed cavitation". Chemotherapy was continued.



6e. J. L. April 16, 1956. 6 cm. tomographic section

6e. April 16, 1956. 6 cm. tomographic section. Sudden closure of old persistent cavity. Patient continues under chemotherapy.

TABLE XVI

Sea View Hospital, New York City, Statistical Data (69)

1945–1955

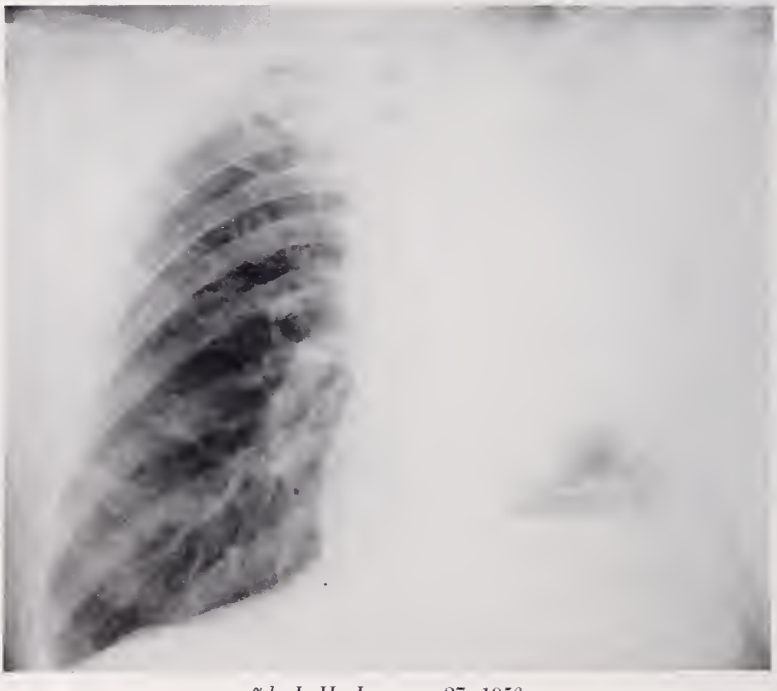
Year	Admissions	Average Daily Census	Deaths	Case Fatality Rate	Major Surgery
1945	968	1422	462	47.8%	538
1950	1988	1521	412	20.7%	834
1955	2004	1391	196	9.8%	305

means complete but it does provide a sound guide for the selection of most cases.

1. ANTICIPATED CHEMOTHERAPEUTIC FAILURE

A) Without trial of chemotherapy.
   a) Destroyed lobe or lung. (Figure 7).
   b) Extensive tuberculous bronchiectasis. (Figure 8).
   c) Pleuro-pulmonary disease.
   d) Emergency resection for bronchopleural fistula and empyema. (Some cases have been successfully treated by chemotherapy without surgery.)
   e) Emergency resection for uncontrollable hemoptysis.
   f) Relative indications. In many cases for which a trial of chemotherapy would otherwise be justified, a long duration of the disease, especially with a previous history of bacterial drug resistance, makes resection

7a. J. H. June 12, 1954.



7 b. J. H. January 27, 1956.

FIG. 7. INDICATION FOR PNEUMONECTOMY-DESTROYED LUNG

7a. June 12, 1954. Extensive destruction throughout the left lung provides an indication for pneumonectomy after a suitable period of preoperative preparatory chemotherapy. *7b.* Jan. 27, 1956. Patient returned to work shortly after the operation and has remained well. Small infiltrates in contralateral lung were stabilized with postoperative chemotherapy.

preferable. Clinical judgment is needed in this group. Other factors in favor of primary resection without extensive trial of chemotherapy, would include very large cavities, multiple cavitation, previous treatment failure, bacterial drug resistance, cavity under thoracoplasty, bronchostenosis, a large, localized caseous area, etc. There is a stronger indication if several of these factors are present in any one case.

g) Occasionally, other factors concerned with the *rehabilitation* and social problems of the patient carry considerable weight. Thus, for example, while an occasional positive gastric culture would not necessarily lead to the advocacy of early surgery, the same finding in a school teacher in contact with young children, might lead to a different recommendation. Similarly, rehabilitation of the breadwinner of a family or of a mother required to resume direction of her household, may demand the increased rapidity of cure with primary surgery plus post-operative chemotherapy.

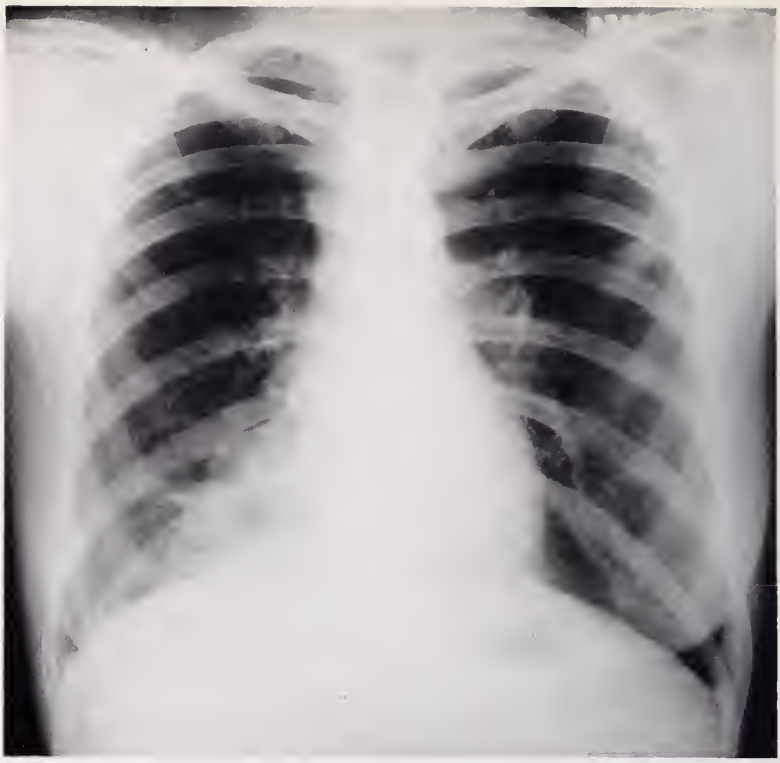
B) With trial of short-term Chemotherapy (Chemotherapy Failure). Patients in whom it is anticipated that a strong possibility of chemotherapy failure exists, should be carefully observed during their trial of chemotherapy. Failure to respond adequately after a short course of treatment should lead to early institution of surgery. Unduly prolonged trial of chemotherapy in patients not responding well increases the possibility of bacterial drug resistance, making the prognosis with surgery somewhat less favorable (70). However, if satisfactory response to chemotherapy continues, especially in patients with extensive disease, the chemotherapy should be continued.

II. RESECTION OF RESIDUAL DISEASE. This has been discussed above.

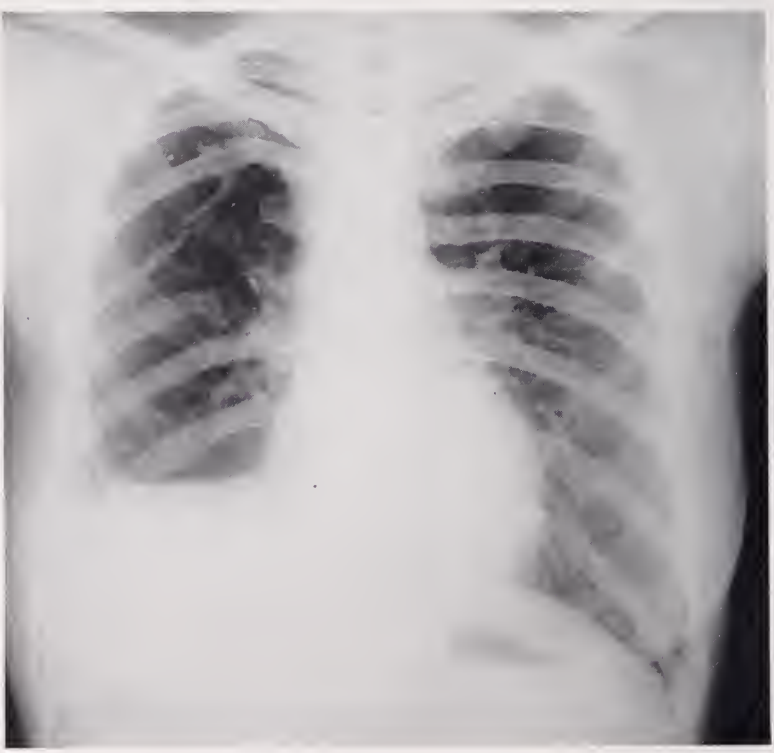
Choice of Surgical Procedure

Resection has become the most popular procedure for pulmonary tuberculosis. Other forms of surgical treatment once thought firmly established, have been uprooted and some are obsolescent. Phrenic nerve operations, extrapleural pneumothorax, pneumonolysis, cavernostomy, are all only infrequently used. A recent jury type review of surgical indications involving 103 thoracic surgeons and internists, found pulmonary resections suggested 10 times as often as thoracoplasty (71).

In some clinics, thoracosplasty is still widely used. Those advocating its use point to the reports of long-term good results. Such statistics, however, should be carefully analyzed. In many instances, it will be found that the type of disease successfully managed by thoracoplasty is also the type of disease now well controlled by chemotherapy. This includes lesions with single thin-walled cavities in the periphery of the lung. On the other hand, lesions less suitable for chemotherapy, such as fibrocaseous disease of long duration with multiple cavitation, thick-walled cavities or large cavities with extensive fibrotic pericavitary infiltration, are also unsuitable for thoracoplasty. Yet it is precisely in such disease, if localized and otherwise suitable, that pulmonary resection is required. Such comparative evaluation is necessary before equating thoracoplasty with pulmonary resection.



8a. C. T. Nov. 7, 1952.



8b. C. T. Nov. 27, 1955.

See opposite page for legend

TABLE XVII

Pneumothorax refills. N. Y. C. hospitals (75)

	1945	1952
Pneumothorax refills	51,400	14,300
Pneumoperitoneum refills	546	34,700

Initial pneumothorax, N. Y. C. hospitals (75)

	1949	1953
Initial pneumothorax	1,200	277
Thoracoplasty	927	317

Pleuropulmonary resection, introduced by Sarot (72, 73) is essential for the successful treatment of pulmonary tuberculosis complicated by tuberculous empyema. Chemotherapy may make its contribution by the control of the toxicity of the patient and by localizing the empyema and the residual underlying parenchymal disease. It cannot substitute for operation.

Even in instances where surgery is decided upon without a trial of chemotherapy, preoperative drug treatment is necessary. The duration of such preparatory treatment is variable and must be individualized. An average of two to three months is generally suitable. The suitability of a patient from a functional point of view should be ascertained by clinical examination and by study of the respiratory function. Prolonged postoperative chemotherapy is required for the "unseen lesions" and to control any spread of the infection that may occur as a result of the operation. The postoperative chemotherapy should be continued for at least one year.

Collapse Treatment: Pneumothorax and Pneumoperitoneum

In some clinics, pneumothorax and pneumoperitoneum have been almost abandoned as therapeutic procedures (74, 20). Table XVII, compiled from data collected by the New York Tuberculosis and Health Association, documents the rapid decline of the use of these procedures (75).

Pneumothorax

The decreased use of pneumothorax in particular has two derivations. First, it is effective principally in those cases in which chemotherapy is also eminently satisfactory. Secondly, complications have not been infrequent, especially when pneumothorax is incorrectly or indiscriminately utilized. Complications include the development of tuberculous empyema, pleural effusion and reactive pleural thickening with loss of pulmonary function.

FIG. 8. INDICATION FOR LOBECTOMY: DESTROYED LOBE. TUBERCULOUS BRONCHIECTASIS.

8a. Nov. 7, 1952. The right middle lobe is the site of extensive destruction with tuberculous bronchiectasis. This is best treated by primary resection after preparatory chemotherapy. *8b.* Nov. 27, 1955. Following lobectomy, patient has remained well for three and a half years to date. Postoperative chemotherapy is essential and was utilized in this case for approximately one year. Note stability of contralateral nodule.

TABLE XVIII

Complications of artificial pneumothorax (78)

	Without antimicrobial therapy	With antimicrobial therapy (SM-PAS)
Patients	116	85
Pleural effusion	15%	5%
Post pneumonolysis effusion	23%	15%
Empyema	3%	0

TABLE XIX

Complications of artificial pneumothorax (1945–1955) (79)

	Without Antimicrobial therapy	With antimicrobial therapy
Patients	36	29
Pneumothoraces	41	34
Effusions (Large)	16	3
Pneumothoraces terminated	37	0
Restriction of lung function by pleural changes	14	1

However, it is possible that pneumothorax is being buried prematurely. Indeed, some have claimed that the reports of its death have been grossly exaggerated (76, 33, 77). In any event, it is quite possible that it may be revived for use in some cases.

Tables XVIII and XIX summarize reports of decreased pleural complications when pneumothorax is combined with chemotherapy (78, 79). If these findings are widely confirmed, it is possible that pneumothorax might still find an important, albeit limited, place in the modern management of pulmonary tuberculosis. Experience in our series has been too limited to warrant comment on this point. Of three cases treated by pneumothorax, one showed pleural thickening upon discontinuance of the treatment. The pulmonary function was impaired despite the absence of any complications during the conduct of the pneumothorax which was maintained for two and a half years.

Pneumothorax should be considered under the following circumstances.

1. *Residual cavitation following chemotherapy*, with positive sputum. This indication, instead of surgery, is strengthened in instances in which the pericavitary infiltration had been largely absorbed during chemotherapy, and in which the residual cavity is peripheral in location, single, and only of moderate size. Even in less suitable cases, pneumothorax might be worth a trial, in preference to excisional surgery, if the latter involves extensive resection. Figure 9 illustrates a patient in which the use of pneumothorax resulted in satisfactory control of the disease.

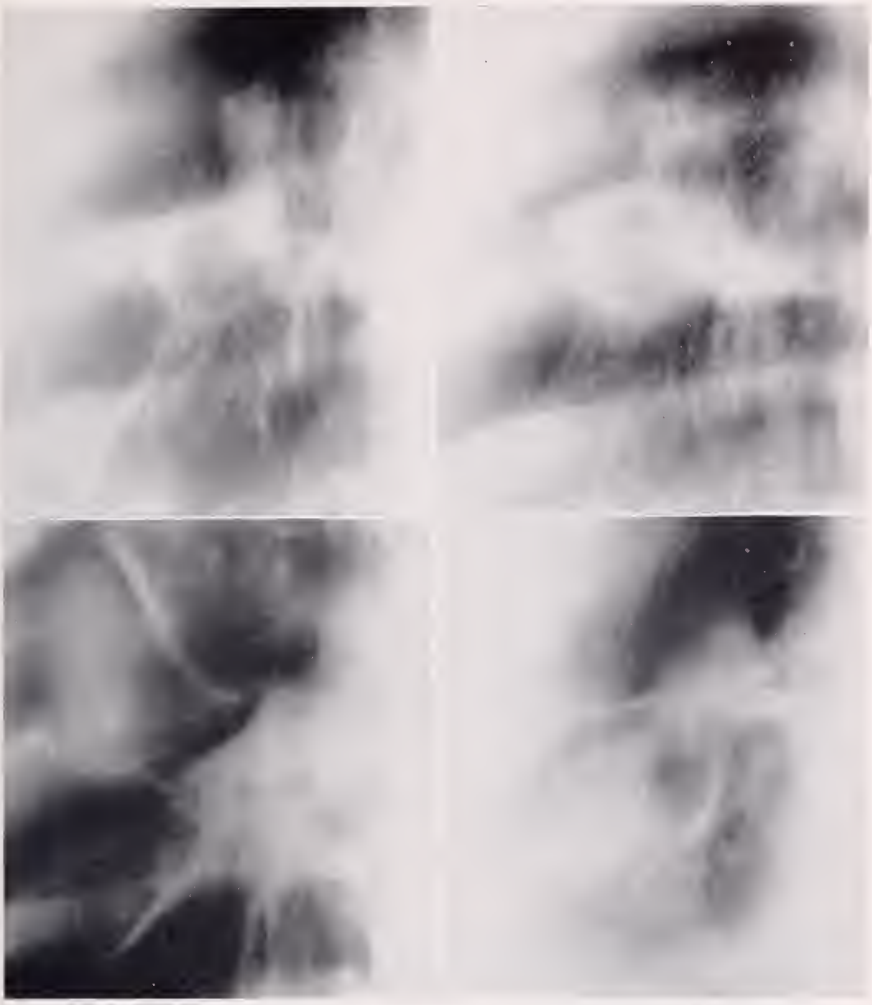
2. As an accessory to trial of chemotherapy in *retreatment*.

3. In selected cases, with *trial of chemotherapy*. This use of pneumothorax deserves wider investigation (13).

4. Treatment of *open-healed cavities*. Figure 10 is an example in which the pneumothorax closed the cavity.

9a. E. C. May 2, 1952.

9b. E. C. Oct. 2, 1952.



9c E. C. Jan. 10, 1953.

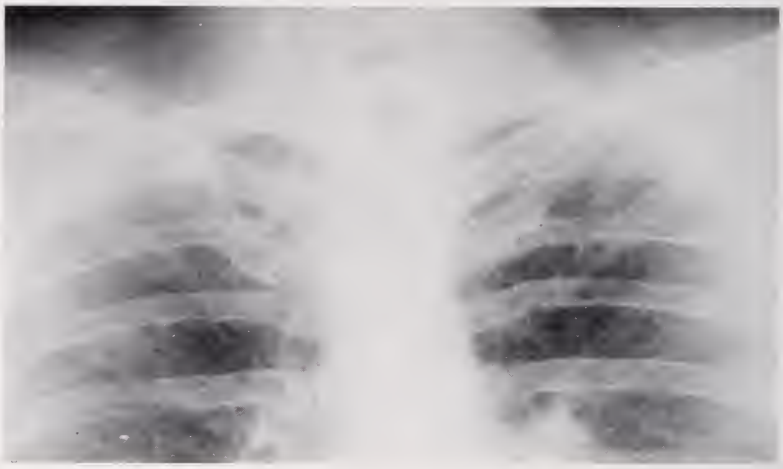
9d. E. C. Dec. 24, 1955.

FIG. 9. RESIDUAL INFECTIVE CAVITY AFTER CHEMOTHERAPY. CLOSURE BY PNEUMOTHORAX.

9a. May 2, 1952. 5 cm. tomographic section. Large cavity in right lower lobe. *9b.* Oct. 2, 1952. Same tomographic level. Cavity enlarged despite combined chemotherapy. *9c.* January 10, 1953. Marked reduction in size of cavity 2 months after induction of artificial pneumotherax. *9d.* Dec. 24, 1955. Tomographic section. Cavity completely closed.

5. In certain instances in which *rapid closure* is desired. Pneumothorax together with chemotherapy may be useful with mothers who have to take care of families, heads of families, etc. We have used successfully pneumothorax in one such case. Sputum conversion may occur sooner with pneumothorax plus chemotherapy than without it, enabling much more rapid rehabilitation. In these cases, pneumothorax can be discontinued much sooner than usual with continuation

10a. G. B. May 26, 1952.



10b. G. B. Oct. 11, 1952.

10c. G. B. Oct. 11, 1952. Tomographic section

10d. G. B. Mar. 4, 1953. Tomographic section.

10e. G. B. Feb. 1, 1956. Tomographic section.

FIG. 10. OPEN-HEALED CAVITY. CLOSURE BY PNEUMOTHORAX

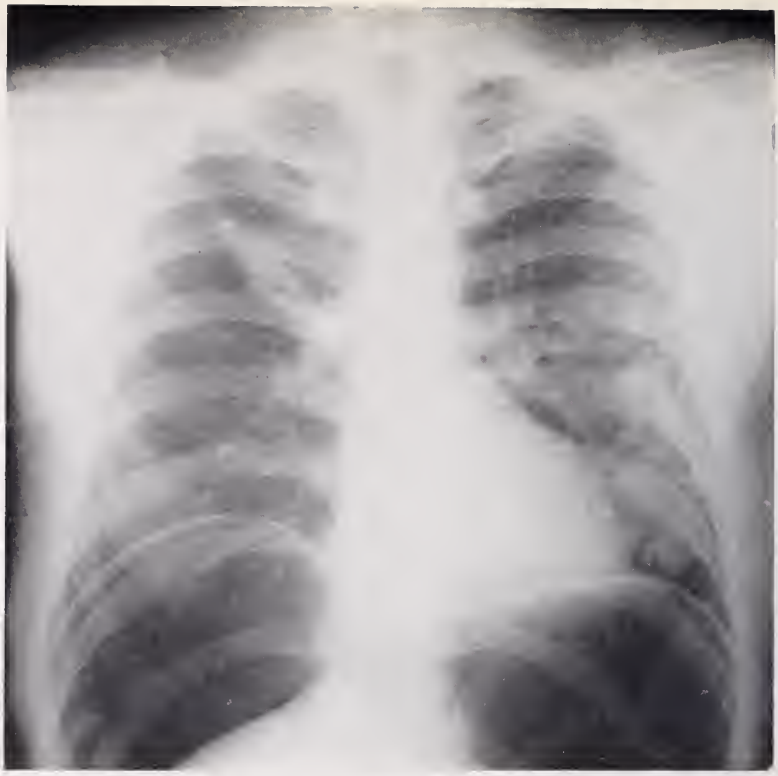
10a. May 26, 1952. 8½ cm. antero-posterior tomographic section. Cavities in both upper lobes. Disease had been present for approximately one year. *10b*. Oct. 11, 1952. Marked clearing of the lesion. The conventional roentgenogram fails to show either cavity. Negative sputum on 26 occasions following iproniazid therapy. *10c*. Oct. 11, 1952. Serial tomograms are required. 8½ cm. section demonstrates cavity on right side on same day as previous film. Tomograms are necessary after chemotherapy because cavities become thin-walled and are easily missed on conventional films.

10d. Mar. 4, 1953. Open-healed cavity closed by pneumothorax. *10e*. Feb. 1, 1956. Similar tomographic section. Cavity remains closed after reexpansion of the lung.

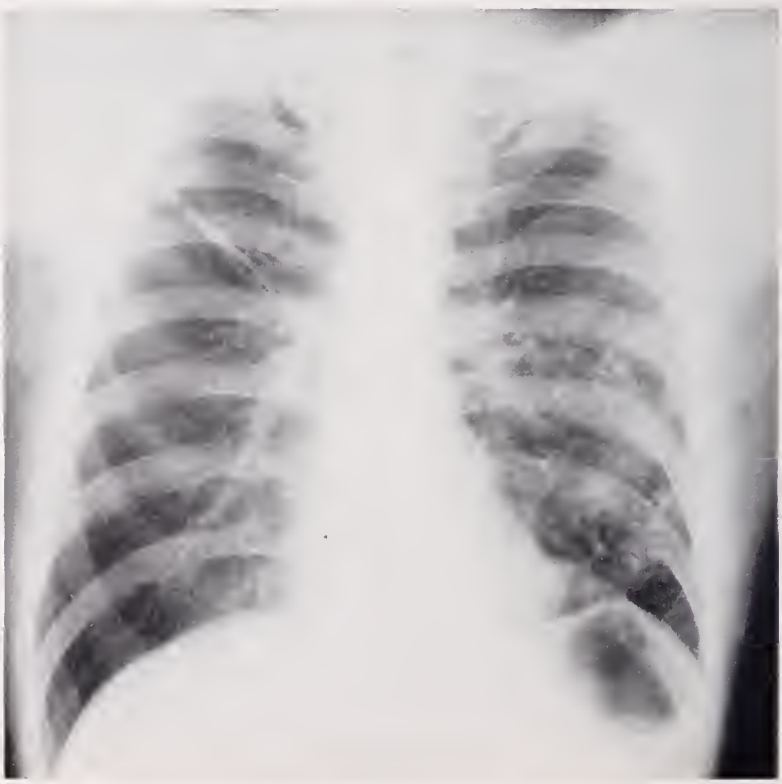
of the chemotherapy. This undoubtedly would diminish the incidence of pleural complications.

Pneumoperitoneum

Indications for pneumoperitoneum are not so clear cut. This procedure, technically less difficult than pneumothorax and relatively free of danger, is more widely used than pneumothorax at present. Its place in therapy is still to be decided, although this will be difficult, since it is rarely used without chemotherapy. Its valuable psychological effect on the patient, however, is not to be lost sight of. It is possible that pneumoperitoneum may prove to be a valuable addition to chemotherapy in the management of the lower lobe disease. Figure 11 is an instance of its use in our series. Pneumoperitoneum may also be advantageous in severe hemoptysis when pneumothorax cannot be induced and surgery is not suitable. In instances of lower lobe spread, pneumoperitoneum may be of use in preparation for later surgery.



11a. W. McK. Jan 11, 1952.



11b. W. McK. Feb. 16, 1956.

BEDREST AND HOSPITALIZATION IN THE MANAGEMENT OF PULMONARY TUBERCULOSIS

Since the advent of chemotherapy as a successful method of treatment in tuberculosis, the need for prolonged bedrest has been questioned. This questioning and the widespread abandonment of intensive use of bedrest are hardly considered in the reported literature. Many practicing physicians no longer use bedrest as an important part of therapy. To the admonition that such abandonment has not yet been indicated on the basis of controlled studies, they are likely to answer that the value of bedrest has similarly not been proved by controlled studies. Moreover, they note that such long term observations as have been recorded have not substantiated the expectation of any prolonged benefit from bedrest, in either minimal (80, 81) or in more extensive (82) disease. These studies seemed to indicate that those patients who had the most bedrest apparently did the poorest. Needless to say, such conclusions are unwarranted since it is likely that longer duration of bedrest was advised for those patients with more serious disease and consequently, with a poorer prognosis. Still, the fact remains that these studies did not demonstrate any long term advantage from bedrest.

Many physicians are reluctant to advocate any significant reduction in the amount of bedrest required in the management of pulmonary tuberculosis (83–87, 74). In addition to bedrest, the value of hospitalization has been emphasized, with particular reference to the education of the patient concerning the handling of his disease (79). The advantage of this aspect of institutionalization has been questioned (88) and it has been pointed out that the educational value of the sanatorium can be replaced by the equally effective action of good clinic organization. Moreover, it is noted that sanatorium admission can break continuity of treatment, quite undesirable where such treatment must be prolonged. If it includes difference of medical opinion, such interruption of therapy may be harmful. It is noted, too, that with clinic or home management, and closer contact with the patient's family, the patient's whole situation may be better managed. This is especially true if the sanatorium is far removed from the patient's home. With elderly patients, this latter situation often leads to irregular discharge from the sanatorium. Stradling notes further (88), that segregation in a sanatorium, in addition to the sense of stigma entailed, often injures morale and undermines a person's sense of social security. Return to work may become a major psychological problem. It is not claimed that sanatoria are not useful in long-term cases and those unsuitable for home care. The latter would include patients unlikely to lose sputum infectivity rapidly, those with poor home circumstances, those in whom sputum infectivity would be a particular risk, especially when there are children in the family.

FIG. 11. PNEUMOPERITONEUM COMBINED WITH CHEMOTHERAPY IN BILATERAL DISEASE

11a. Film of Jan. 11, 1952 shows bilateral active disease, including lower lobe involvement. Although indications for pneumoperitoneum are not yet clarified, it is sometimes useful in such cases, combined with chemotherapy. *11b*. Film of Feb. 16, 1956 shows post chemotherapy and post-pneumoperitoneum status, with good clearing but with residual nodular foci.

The recommendation of short-term hospitalization has been made (89), in place of long-term sanatorium treatment. "It is a mistake to think of the time spent in sanatorium as a holiday, providing physical and mental rest, and to forget what disorganization of family life and the anxiety that separation from home means to many patients. A drug that was capable of causing physical distress of a comparable degree would be used with discretion and the introduction of some less unpleasant but effective medicine be hailed as an advance of treatment. In this light reduction of the time spent in sanatoria may be regarded as an advance in the management of tuberculosis" (89).

All these criticisms of prolonged sanatorium rest would carry little weight if it could be shown that deprivation of such rest worked to the detriment of the patient. There are no data at present which would indicate that this is so. In the series we have studied, all therapy was conducted on an ambulatory basis and bedrest was utilized only in the presence of constitutional symptoms. Otherwise, after a period of graduated rest and activity, full activity was rapidly resumed by the patient, especially where no tubercle bacilli were present in the sputum. More than half the patients began their chemotherapy while on full physical activity. Approximately three-quarters began full activity before the end of six months. An analysis of rest and physical activity of the patients in our series is contained in Table XX.

This problem continues under study. Widespread use of ambulatory therapy has been reported as satisfactory where hospital facilities were either not available or not desired (90–93) and in other investigations in which ambulatory therapy was a deliberate function in the study (94–98). Should such ambulatory therapy, without the inclusion of systematic rest, prove to be an acceptable feature in the management of tuberculosis, the social burden imposed by tuberculosis throughout the world will be minimized. In India, for example, there are today only 20,000 beds for tuberculosis, balanced against approximately 2,000,000 cases of the disease (99). It is our clinical impression that further experience will confirm that bedrest, except for acute disease or in the

TABLE XX

Activity followed in present series

Positive sputum	Activity		Months to reach full activity								Continue on limited activities
	Total	at Onset	1	2	3	4	5–6	7–8	9–11	12–24	
3	4	0	0	0	0	0	0	0	0	2	2
6	8	1+	0	0	1	1	1	1	0	4	0
29	37	2+	0	2	2	11	5	3	1	9	4
21	26	3+	0	4	5	8	4	1	2	1	1
20	30	4+	30	—	—	—	—	—	—	—	—
	105*		30	6	8	20	10	5	3	16	7
					74				24		7

* 3 patients died during therapy and are not included.

presence of constitutional symptoms, adds little to chemotherapy. Should chemotherapy not be available, however, because of toxicity, bacterial drug resistance, etc., bedrest might be utilized advantageously. In the management of the patients in our series, full activity including employment, in many from the date of institution of therapy, did not seem to delay or prevent adequate chemotherapeutic response.

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PULMONARY FUNCTION IN TUBERCULOSIS

Medical and Surgical Considerations

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The voluminous research, clinical experience and writings on the pathological findings, microbiology, x-ray and surgical aspects of tuberculosis have obscured the much smaller body of data on the pulmonary functional disturbances. This is not entirely without reason since certainly the microbiology is of far more importance than the disturbances secondary to the ravages of the inflammatory reaction. Another reason for the limited approach to the physiological understanding of the disease has been the difficulty in evaluating so wide a variety of cases, with varying pathology, and complicated by different therapeutic procedures.

Lung function tests including measurement of lung volumes, maximum breathing capacity, and determination of arterial blood oxygen and carbon dioxide offer considerable information. This has been extended by improved understanding of ventilation-perfusion relationships, including analysis of the alveolar-arterial oxygen gradient with measurement of the diffusing capacity of the lung and the physiological respiratory dead space. Finally, the increased use of bronchospirometry has enabled better evaluation of individual lung function, particularly with reference to surgical intervention.

Advance in the techniques of measurement of pulmonary function has been paralleled by an increased range of effective therapeutic measures (medical and surgical) for the control of pulmonary tuberculosis. The principal value from the medical viewpoint has been the evaluation of the functional status of patients with pulmonary involvement prior to and following treatment with one of the newer antimicrobial agents, as well as the rapidity of response. Secondly, the widespread use of these tests for evaluation of the indications and results of surgical procedures need hardly be emphasized.

Since the extent and type of pulmonary involvement by tuberculosis is so variable, it would be wise to consider individually the functional findings usually encountered in the various degrees or types of the disease.

In minimal tuberculosis, usually there is an exudative lesion involving less than one segment. Pulmonary function tests (1) reveal no significant change in lung volumes, ventilatory mechanics, or in ventilation-perfusion relationships. With involvement greater than a segment or so, an increase in venous admixture may be detected due to perfusion of a hypoventilated area of lung. If this increase in venous admixture is sufficiently large, it may result in a fall

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in arterial oxygen saturation. With effective medical therapy, this finding usually reverts to normal.

In moderately advanced cases of pulmonary tuberculosis, alteration in lung function (1) hinges on the underlying pathological changes. Not only may there be exudation into the alveoli, but the tuberculous inflammatory process may cause an obliterative endarteritis. What results, in effect, is a "pathological resection of the area involved." Lung function may be only slightly compromised. Indeed, in one series of eight patients (1), only two showed impairment in ventilation; one had an increase in the residual volume/total capacity ratio (and could conceivably have had a pre-existing emphysema); six had increase in venous admixture; and three had increase in the physiological dead space. Apparently, the alveolar involvement predominates over the vascular lesion, since the venous admixture abnormality was the most common finding.

In far advanced cases (1), emphysematous changes are more commonly encountered. Approximately half of the patients have impaired ventilatory function and an increase in the ratio of residual volume to total capacity. A majority of the cases have impaired distribution of the inspired gases, an increase in physiological dead space and increase in venous admixture. The diffusing capacity of the lung is often reduced, particularly in cases with an increased residual volume/total capacity ratio. In all cases of moderate or advanced pulmonary tuberculosis where an increase in physiological dead space was encountered, there was also an increase in venous admixture, either alone or associated with a reduced diffusing capacity as well.

With medical therapy improvement in several parameters of lung function takes place. Improvement in ventilatory function, particularly the maximum breathing capacity will occur, often due primarily to improved ability to perform the test compared with performance in the pre-treatment debilitated state. Some improvement in vital capacity may also be attributed to improved performance (and possibly to a training factor). With clearing of exudative lesions, venous admixture would be expected to decrease. Such is indeed the case, particularly dramatically seen in cases with acute lobar involvement. There is usually an improvement in lung volume measurements, due both to anatomical reduction in the size of the lesion, as well as the improved performance noted above. The ultimate fate of lung function, in general, depends on the interplay between destruction and repair of the tuberculous process. No single type of permanent impairment is noted. Residual abnormalities will depend on the relative damage to alveoli compared to the ravages of tuberculous endarteritis. Care in interpretation is required, since improvement in venous admixture measurement may reflect either clearing of the exudate, or reduction in perfusion of the involved area. In advanced cases where emphysema results, irreversible changes may occur and residual findings will be those of emphysema.

Hematogenous (miliary) tuberculosis presents a different picture physiologically. The careful studies of McClement et al. (2) have elucidated the pulmonary function alterations, as well as the hemodynamics in the acute, late and treated stages of this disease. Eleven cases were studied serially. In the acute

stage, lung volumes are, in general, uniformly reduced. Maximum breathing capacity is well maintained at normal or near normal levels. Reduction in this index, may relate occasionally to impaired performance in an acutely ill patient. Marked hyperventilation at rest, exercise, and during recovery from exercise is always present. Diffusing capacity of the lung measured by the method of Riley and Cournand (3, 4), is reduced. The physiological syndrome is one of "alveolar-capillary block" (5).

Antibiotic therapy has altered the ominous prognosis in hematogenous tuberculosis. With clinical improvement, McClement and co-workers (2) noted increase in the diffusing capacity of the lung, i.e., a reduction in the alveolar-capillary block. The less marked physiological disturbances remain. Reduction in lung volumes persist. Maximum breathing capacity is normal or only slightly reduced. Hyperventilation at rest, exercise and on recovery from exercise is only sometimes present, and always mild. The alveolar-arterial oxygen tension gradient (A-a gradient) in this late treated stage is smaller than in the acute phase, and reflects improvement in the diffusing capacity of the lung. Physiological dead space in this stage is still increased. Cardiac catheterization reveals elevation of pulmonary artery pressure on exercise in an occasional instance.

The underlying cause for these changes can be found in examination of the alveolar-capillary septa, which are altered by fibrous and/or granulomatous changes. In acute miliary tuberculosis, inflammatory involvement of the septa is responsible for reduced diffusing capacity. Reduction of the pulmonary vascular bed (hence reduction in diffusing area) also contributes to the reduced diffusing capacity of the lungs. This reduction in the vascular bed is due to presence of pericapillary miliary tubercles, and accounts for the occasional finding of increased pulmonary artery pressure on exercise. Reduction in diffusing capacity apparent in breathing gas with lowered oxygen content, is not incompatible with the finding of normal or only slightly reduced oxygen tensions in arterial blood, found at sea level. Increase in venous admixture when present is due in these cases to the disturbed ventilation-perfusion relationship secondary to aveolar-capillary block, but may also be partially due to perfusion of alveoli with decreased or absent ventilation due to exudative involvement. Improvement following streptomycin therapy for miliary tuberculosis is very rapid. Pathological findings show that the earliest response to streptomycin therapy is resorption of acute inflammatory exudate.

COLLAPSE THERAPY

Pneumothorax (6–11). All but abandoned in the last four years, pneumothorax therapy still must be considered briefly even if only historically, but more particularly since there are many patients who have residual effects of a re-expanded therapeutic pneumothorax (12). Intrapleural pneumothorax is followed by marked reduction in pulmonary function with reduced oxygen uptake in the collapsed lung, and obviously reduced ventilation in the same lung. In contrast, extrapleural pneumothorax causes a less marked effect on function (13, 14). Usually there is a decrease in lung volume at the expense of residual

volume and expiratory reserve volume. This effect is confined to the opposite side. Phrenic interruption in general produces only a small loss in function (14).

Pneumoperitoneum. When pneumoperitoneum is performed as a form of collapse therapy, it produces a marked reduction in the functional residual volume and tidal volume with the patient in the erect position (15). In the recumbent posture, a similar but quantitatively smaller effect is noted. Maximum breathing capacity is only slightly decreased by pneumoperitoneum. When phrenic nerve surgery is performed to establish diaphragmatic paralysis adjuvant to pneumoperitoneum there is a further decrease in the functional residual volume, and a large decrease in the inspiratory capacity, together with a decrease in the function of the homolateral lung.

Thoracoplasty. Surgical collapse by means of thoracoplasty has a variable effect depending on the extent of the thoracoplasty, and on the amount of functioning tissue collapsed along with the diseased areas of lung. Early reports (16, 17) indicated that lung function is reduced by thoracoplasty. Serial studies (14, 18) indicate that function may improve following the initial postoperative loss. This improvement has been noted to take place up to three years following surgery. With the immobilization of the chest wall by thoracoplasty, reduction in both vital capacity and total capacity have been noted. The index of intrapulmonary mixing may be increased suggesting impaired distribution of gas, and the residual volume/total capacity ratio may be increased. Cournand and Richards' detailed study of changes in pulmonary after thoracoplasty (19, 20) revealed that reduction in maximum breathing capacity following a standard seven rib thoracoplasty was as a rule not greater than 15 per cent. When scoliosis supervened, the maximum breathing capacity was further decreased resulting in increased dyspnea on moderate exercise. In general, simple thoracoplasty results in loss of function (19–21) as does thoracoplasty following pneumonectomy (see below).

SURGICAL TREATMENT

Antibiotic therapy has made most of the procedures noted above obsolete or limited in application, since surgical resection has become commonplace. Pulmonary function studies done pre- and post-operatively would offer the following information. First, whether resection improved or impaired lung function. Second, an opportunity to correlate physiological findings with pathological alterations seen in the resected specimen. Third, it permits evaluation of lung tissue *not* to be resected so that any procedure which might make a pulmonary cripple could be avoided.

Conventional pulmonary function tests used preoperatively, in effect offer the same findings as described in medically treated pulmonary tuberculosis. Segmental resection does not incur significant loss of function. Removal of larger amounts of lung tissue may cause small reduction in lung volume, but rarely affects gas exchange unless the material resected is significantly involved with exudative disease.

Of particular importance surgically, is the use of bronchospirometry which

permits evaluation of individual lung function (11, 16, 18). It is limited in usefulness for the study of diffuse pulmonary disease. Conventionally, oxygen consumption, ventilation, and vital capacity are measured in each lung. In normal man, about 55 per cent of function is carried out by the right lung and 45 per cent by the left. Gaensler (22), by means of differential bronchospirometry, also measures expiratory reserve volume, residual volume and total lung volume for each lung. In normal patients, total capacity, expiratory reserve volume, and residual volume were found in the same ratio as the lung volume for both lungs together, but the functional distribution in the two lungs differed in various individuals.

In unilateral parenchymal disease, oxygen uptake on the involved side is usually affected to greater degree than ventilation or vital capacity. Indeed ventilation may be normal or only slightly reduced in lungs with little involvement, and never is decreased as much as the oxygen uptake, no matter how severe the disease (16–18). In localized unilateral parenchymal disease, the vital capacity is usually only slightly decreased. Gaensler's studies in 170 cases of unilateral parenchymal disease revealed a slight reduction in function of the involved lung, with almost equal involvement of the oxygen uptake ventilation and vital capacity (6). The degree of impairment was not as marked as anticipated from the chest x-rays. Bronchospirometry may not be sensitive enough to detect functional loss in early cavitation (18). Pleural involvement unilaterally produces a striking decrease in function on the involved side, particularly reduction in oxygen uptake, with vital capacity and ventilation less affected (6, 18, 23–25). In those cases with pleural involvement, reduction in function was greater than anticipated from the chest roentgenogram (6). Endobronchial disease will result in abnormal distribution of function only when complete or almost complete occlusion of a bronchus is present (6). Bronchospirometry in patients who are to undergo pneumonectomy permits evaluation of function in the lung which is not to be resected. This may permit estimation of how much disability following operation is secondary to surgery or to pre-existing disease. Indeed it has been demonstrated that while overdistension and emphysema occur following pneumonectomy, at times such findings in the residual lung existed prior to surgery on the contralateral lung (11). (The problem of lung function following pneumonectomy will be discussed later.) In cases of subtotal resection of the lung, loss of function is in general equal to a thoracoplasty of similar extent. Pleural complications following resection of any type, make the functional results variable (6).

Vascular involvement may also be assessed bronchospirometrically. If a branch of the pulmonary artery is obstructed, there is practically no effect on the ventilation or vital capacity on the affected side, but oxygen uptake is markedly reduced (6).

Indications for bronchospirometry (11, 26), from the medical point of view, include studies to determine the extent of functional loss in unilateral disease, the function of the lungs in unusual cases of cyanosis or dyspnea, and the results of collapse therapy. From the surgical point of view, bronchospirometry permits evaluation preoperatively of patients who have had previous collapse or resec-

tion, or healed lesions on the contralateral side; preoperative evaluation of patients with dyspnea, lest resection or collapse of one lung leave the patient with inadequate pulmonary reserve on the contralateral side; estimation of the extent of contemplated resection; evaluation of the success of "reconstructive" surgery aimed at improving function, e.g., decortication.

Decortication. As noted previously pleural disease may produce marked reduction in lung function. For many years, decortication of the lung has been practiced in an attempt to restore function to a compromised lung. The effectiveness of the procedure is related to the extent, nature, and duration of the pleural process, and the degree of underlying parenchymal involvement (25). In one series (23) successful clinical results following decortication (especially when combined with thoracoplasty) were not associated with significant improvement in pulmonary function. Furthermore, several studies reveal that results of decortication in cases of tuberculosis, are not as satisfactory as in hemothorax (24, 25).

In the series of Carroll et al. (25), it was stressed that the duration of the process was an important factor affecting results. In three cases of hemothorax, done shortly after the hemothorax, normal function was regained, but this did not occur in a longstanding hemothorax. In five cases of various types of tuberculous pleural disease, those with no demonstrable parenchymal disease, and with pleural disease of the shortest duration had the best functional results. The principal physiological defects noted prior to surgery are decrease in vital capacity and total capacity, occasional increase in residual volume/total capacity ratio, slight decrease in maximum breathing capacity, and a small decrease in effective ventilation as reflected in a decrease in oxygen uptake per liter of ventilation. Bronchospirometry reveals evidence of disturbed ventilation-perfusion relationships. In cases where return of function was incomplete, the improvement in ventilation was greater than in oxygen uptake on the affected side (6, 24, 25). In Gaensler's large series (6), the striking decrease in function in the involved lung is again noted, particularly with regard to reduced oxygen uptake and relatively well maintained ventilation. Marked improvement is seen following decortication providing that pre-existing parenchymal disease is not significant (6). Indeed in patients with parenchymal involvement, not one of five cases showed improvement in pulmonary function (23) and the poorest results in the study of Carroll et al. (25) were in tuberculosis cases with parenchymal involvement and long standing pleural disease.

Pneumonectomy. With pneumonectomy being performed more often for a variety of diseases including tuberculosis, it becomes increasingly important to evaluate the adequacy of function in the contralateral lung prior to surgery, the effect of surgery on the residual lung function, and the effectiveness of various procedures such as thoracoplasty, pneumothorax, oleothorax and plombage in preserving residual lung function. In general, overdistension of the lung following pneumonectomy occurs both in man (27–29) and animals (30) although less marked in the former. Overdistension is not a desirable sequel if it is sufficient to decrease pulmonary function. It is particularly undesirable in pulmonary tuberculosis since an overdistended lung remaining after pneu-

monectomy, may be more susceptible to reactivation of any disease present in that lung (31).

Pneumonectomy is often followed by overdistension of the contralateral lung, as reflected in impaired intrapulmonary mixing of gases in that lung (27, 28) as well as by disturbance in residual volume/total capacity ratio. Maximum breathing capacity is usually well preserved. Gaensler and Strieder (32) have observed also a variable amount of overdistension in the remaining lung, which could not be predicted pre-operatively. To prevent this overdistension, pneumothorax was quite effective, and did not further compromise lung function. Conversion to an oleothorax effected no loss of function. Plombage was similarly effective in preventing overdistension, even correcting pre-operative overdistension, and furthermore was not responsible for further reduction in lung function. Thoracoplasty, on the other hand, has been disappointing in this regard. This procedure may actually reduce the function of remaining lung due to the development of scoliosis (29). This is a particularly dangerous complication in younger individuals (33, 34). In one study (32) an early post-operative thoracoplasty (six weeks to two months following pneumonectomy) did not prevent overdistension of the lung at rest (pulmonary midposition) and caused loss in the maximum breathing capacity, but it did prevent overdistension on deep inspiration by reducing the vital capacity. A late thoracoplasty (two months to two years following resection) only partially corrects overdistension and causes further reduction in vital capacity and maximum breathing capacity. If a thoracoplasty is performed *prior* to pneumonectomy, resection of the collapsed lung will not cause any change in lung function or volumes. In general primary resection of a functionless lung will cause little loss in lung function, but thoracoplasty over a functionless lung causes marked decrease in function of the contralateral lung.

The complication of emphysema in the remaining lung, varies with the age of the patient. In young patients, follow-up studies of lung function for $2\frac{1}{2}$ years after resection, did not indicate that overdistension in this group results in true emphysema with disruption of the pulmonary architecture (32). In older patients progression to true emphysema was noted. In such patients pre-existing emphysema also is a problem and can be demonstrated by overall lung function tests as well as bronchospirometry.

SUMMARY

The nature of the alterations in pulmonary function in tuberculosis of the lungs has been reviewed. Effects of medical therapy have been considered. Utility of function studies in evaluation of patients surgically pre and post operatively has been described.

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THE TREATMENT OF TUBERCULOUS PLEURISY WITH EFFUSION

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INTRODUCTION

The entire problem of tuberculous pleurisy has attained added significance in the past few years since the introduction of chemotherapy for tuberculous infections. Previously the diagnosis of this condition was important chiefly from the standpoint of the evaluation of the prognosis of the patient who was sick, the determination as to how long he should be kept at bedrest, and whether restriction of physical activities for a long period should be advised. A decision as to the diagnosis of tuberculous pleurisy could await a considerable period of observation since the only treatment that could be employed was bedrest, and this was necessary in any event because of the acute manifestations of the infection.

For a long time it has been known in a general way that tuberculous pleurisy has a tendency to be followed by pulmonary tuberculosis and tuberculosis of other organs. Only in recent years have there appeared detailed studies consisting of large numbers of cases which have been followed and observed carefully over a period of years so that a more exact evaluation can be made of the seriousness of the disease. A realization of this is necessary for the appreciation of the need for treatment of tuberculous pleurisy. Furthermore there has developed the concept of the significance of tuberculous pleurisy in relation to lack of resistance of the individual to tuberculous infection, which points the way toward treatment of the disease by the new chemotherapeutic drugs.

The diagnosis of tuberculous pleurisy when the roentgen film discloses a characteristic pulmonary lesion, is quite obvious. In such instances the need for treatment by all the means available is quite clear. However, when only evidence of a pleural effusion is present, some question may remain concerning the diagnosis of tuberculosis, and the necessity for vigorous and prolonged treatment may not be faced squarely unless the importance of the disease is recognized. This paper, therefore, will concern itself with only those cases in which no pulmonary lesion is visible, i.e., the ones which have been termed "idiopathic" pleurisy because of the reservation that the diagnosis of tuberculous pleurisy might be incorrect.

THE DIAGNOSIS OF TUBERCULOUS PLEURISY

If specific therapy is to be the treatment of choice in tuberculous pleurisy, it must be granted that the diagnosis of the condition should be made promptly. Early effective treatment shortens the period of bedrest, diminishes the danger of dissemination of the disease, and may lessen the tendency to thickening of the pleura by exudate and fibrosis. In a patient with a pleural effusion, the following criteria may be depended upon to establish a tuberculous etiology with enough certainty to justify the institution of specific treatment:

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1. An onset with chest pain and fever in a person under the age of 45.
2. The presence of over 90 per cent of lymphocytes in the fluid.
3. A positive Mantoux reaction.
4. The absence of sputum.
5. The exclusion of other diseases by appropriate examinations.

The Mantoux reaction is positive in tuberculous pleurisy except in rare instances of overwhelming tuberculous infection associated with miliary tuberculosis and tuberculous meningitis. However, the test may prove negative if performed with only the higher dilutions of the allergen. The incidence of a negative reaction to the first strength, and of a positive skin test utilizing the second strength, in tuberculous pleurisy, has been found to be 23 per cent in one series and 12 per cent in another (6, 10).

Rarely the fluid is predominantly polynuclear. This occurred in 2 per cent in one series of 190 cases (4). It has been our experience, however, that this occurs only at the onset of the disease, and that the fluid rapidly becomes lymphocytic. If no other cause can be found for a pleurisy with effusion which is not lymphocytic in character, the differential count should be repeated after an interval before excluding tuberculosis as the cause of the effusion.

Because other diseases may simulate tuberculous pleurisy they should be excluded by careful examination. A search should be made for evidences of phlebitis which might be responsible for pulmonary infarction. The gums should be examined for a source of anaerobic infection which might indicate an abscess of the lung which could cause a sympathetic effusion, and an inquiry made as to the occurrence of a recent alveolar abscess or tooth extraction with this condition in mind. Evidences of neoplastic disease, particularly Hodgkin's disease, should be sought for, since this might cause both fever and a lymphocytic fluid.

We have observed a number of cases of tuberculous pleurisy in older persons. Most often the effusion is a complication of known pulmonary tuberculosis quite evident on the roentgen film, but the disease nevertheless occurs at any age with sufficient frequency to warrant its consideration in an idiopathic effusion with fever in a person of any age (11). In older persons especial care should be taken to exclude the possibility of carcinoma by x-ray examination of the chest after removal of the fluid, examination of the fluid for tumor cells and by bronchoscopy. If these examinations prove negative and there is a positive Mantoux reaction and a lymphocytic fluid, the effusion should be considered tuberculous.

It is recommended that the patient be treated as a case of tuberculous pleurisy if the criteria for diagnosis mentioned above are satisfied, and that treatment be started on this basis even though there is no absolute proof of the diagnosis. This recommendation is made because further proof of the diagnosis in the individual case cannot be obtained by examination of the pleural fluid in the majority of cases. In a total of 1382 cases reported by a number of authors, tubercle bacilli were found in the pleural fluid by guinea pig inoculation or culture in about one-third (Table I). The highest incidence of demonstration of the organ-

TABLE I

Incidence of bacteriological proof of tuberculous etiology in "idiopathic effusion" and lack of correlation with the later development of pulmonary and organ tuberculosis

Author	# of Cases	Fluid TB pos.	% Dev. TBC lesions later	Relation of later TBC to Neg. & Pos. Fluids
Kallner (1), 1937	401	43%	28%	No difference
Farber (2), 1943	111	30%	34%	No difference
Jones & Dooley (3), 1946	144	—	25%	—
Thompson (4), 1946	190	17%	27%	—
Purves & Karron (5), 1947	138	33%	12%	—
Kraft (6), 1949	100	35%	22%	More in neg. fluids
Sibley (7), 1950	171	30%	42%	No differenee
Mitchell (8), 1953	88	37%	—	No differenee
Skaggs & Smiley (9), 1955	42	24%	22%	—
Roper & Waring (10), 1955	141	51%	62%	No difference
Total	1,526	Av. 35%	Av. 30%	No differenee in 343 cases

ism in the fluid was 51 per cent (10), and it was as low as 17 per cent in a good clinic (4). It is obvious that if we were to rely upon bacteriological methods for the diagnosis, treatment would be neglected in the majority of the cases.

An analysis of the data relating to the occurrence of later manifestations of tuberculosis in patients with pleurisy considered to be tuberculous on clinical grounds, indicates that the diagnosis must be correct with few exceptions. Those who have made observations concerning the later development of tuberculosis in these patients, have found the same incidence of this complication whether the pleural fluid was negative or positive (Table I). Since the series appertains to 343 cases of tuberculosis developing in 1,012 patients, these figures are significant. Therefore, it is to be concluded that the diagnosis of tuberculous pleurisy was substantially correct even though the diagnosis was made on purely clinical grounds without bacteriological proof.

It is undoubtedly true that reliance on the clinical status for the diagnosis will result in considering occasional patients as tuberculous who in reality are not suffering from this disease. However, in the absence of any more satisfactory diagnostic method in the majority of the cases, it is believed that treatment should not be withheld because the fluid cannot be shown to contain tubercle bacilli.

DISSEMINATION OF TUBERCULOSIS IN THE COURSE OF TUBERCULOUS PLEURISY

The importance of instituting definitive treatment for tuberculous pleurisy is based upon an appreciation of the seriousness of the disease. Of 1,438 cases which were observed for a varying period, fully 30 per cent developed evidences of active tuberculosis of the lung or elsewhere in the body at some time following the absorption of the effusion (Table I). The lowest incidence of the later manifestation of tuberculosis was 12 per cent (5), and an incidence as high as 62 per cent occurred in one series (10). The mortality in the patients who developed active tuberculosis was high in the premicrobial era (3–5) reaching 60 per cent

TABLE II

Incidence of development of extrapulmonary tuberculosis compared to development of pulmonary tuberculosis alone

Author	No. developing Pulmonary TBC alone	No. developing extrapulmonary TB*	% Extrapulmonary among pts. who developed TBC
Farber (2)	28	9	24
Jones & Dooley (3)	11	26	70
Thompson (4)	34	15	31
Purves & Karron (5)	22	16	41
Kraft (6)	19	3	14
Sibley (7)	43	29	40
Skaggs & Smiley (9)	1	7	88
Roper & Waring (10)	49	43	47
Total	207	186	47%

* This includes cases with bilateral pleural effusion.

in one series (1), and even today the disability produced by dissemination of tuberculosis is considerable.

A study of the characteristics of the tuberculosis that occurs in the wake of tuberculous pleurisy yields information that is pertinent to the treatment. Of 393 cases of post-pleurisy tuberculosis, 186 cases or 47 per cent manifested lesions outside the lung (Table II). Simultaneous involvement of both lungs and involvement on the opposite side is common (7). In most of the groups studied, about 50 per cent of the cases became manifest within a year after the effusion, and 25 per cent more within the second year. These observations, taken together with the clinical, roentgenological and pathological findings in the course of tuberculous pleurisy, indicate first, that there is a connection between tuberculous pleurisy and the subsequent tuberculosis in the lungs and other organs, and second, that the spread of the disease takes place by the lymph-hematogenous route.

Tuberculous pleurisy of the type under discussion is the result of a first infection type of tuberculosis. Pleural effusion is rare in the reinfection type, and generally occurs when there is extensive, spreading pulmonary disease. Here the lymphatics are not involved. On the other hand, in primary tuberculosis, there is caseous involvement of the regional lymph nodes and an opportunity for lymph-hematogenous spread of the disease to all parts of the body.

The characteristic of primary tuberculosis is the occurrence of caseation not only within the primary lesion in the lung but in the metastatic foci. Tuberculous pleurisy is a result of the rupture of such a caseous focus into the pleura, practically always from a peripheral focus in the lung (12, 13), although we have observed involvement from caseous subpleural mediastinal nodes. While the tuberculous pleurisy may be caused by a small primary lesion in the lung, invisible on the roentgen film, it appears much more likely that the pulmonary focus is one of several resulting from a sporadic hematogenous dissemination of the disease. The occurrence of such lesions, as well as the fact that they are

caseous, indicates poor resistance to the tubercle bacillus. Thus, the presence of tuberculous pleurisy in itself is an indication of poor patient resistance. It is therefore not surprising that such a patient should later develop other disseminations of the disease, of which pulmonary tuberculosis is but one manifestation.

That diminished resistance to the tubercle bacillus is responsible for the development of tuberculosis after tuberculous pleurisy is exemplified by the increased frequency of this complication among colored people. Thus, the incidence of post-pleurisy tuberculosis has been more than twice as great among the colored as among the white patients (3, 5). An incidence of active tuberculosis lower than the average developed in people of higher financial standing, presumably people with better hygienic standards (8, 10). A frequency double the average has been reported in patients with tuberculosis in the family (1). In any event, whether it is due to general, racial or individual factors, lowered resistance of the patient to the tubercle bacillus must be taken into account in the treatment of tuberculous pleurisy. The diminished natural patient resistance is best augmented by chemotherapy.

GENERAL TREATMENT OF TUBERCULOUS PLEURISY

From the factors that have been presented, it is evident that tuberculous pleurisy is simply one manifestation of a general disease. There may be instances in which the disease is really confined to the chest at the onset of the tuberculous pleurisy. But, even if this is so, the disease later becomes generalized in a considerable percentage of the patients.

Until recently, rest was the only treatment available and it has been recommended to patients with more or less emphasis. However, the value of bedrest after the subsidence of the fever and the absorption of the effusion is open to question (8). In the largest series of cases reported, 401 cases, few patients received significant bedrest (1). The course of these patients was followed for many years, yet active tuberculosis occurred no more frequently than in the remainder of the studies reviewed, although several of the reports emanate from sanatoria where the patients were confined for a considerable length of time.

That rest is of some importance in the treatment of tuberculous pleurisy is suggested by the experience of Roper and Waring (10). Over 90 per cent of their patients who had less than six months of bedrest later developed tuberculosis, while of those who had had an average of ten months rest in bed, only 30 per cent developed this complication. It is notable that the latter figure corresponds with the experience in patients who had little or no bedrest. The unusually high incidence of active tuberculosis in the group under short-term treatment demands some explanation. The cases in this series were collected from an Army hospital. It seems quite probable that the patients were exposed to the difficulties of Army life soon after hospitalization, and that this was the responsible factor. The remaining patients undoubtedly ran a much more benign course because of the delay in returning them to active duty.

The surest way to control the unseen foci in the various organs of the body, as well as in the lungs, in tuberculous pleurisy, is to institute treatment with anti-tuberculosis drugs. The efficacy of this form of treatment in tuberculosis of

any type no longer requires any proof. Certainly in small and recent lesions, such as are represented by the silent disseminated foci in tuberculous pleurisy, these drugs should be curative in practically all instances. In view of the serious sequelae that occur so frequently in the later course, there is no good reason for withholding chemotherapy in any case of tuberculous pleurisy.

The drug treatment should be begun as soon as the diagnosis is made clinically. There is no advantage in waiting for a period of six or eight weeks until reports of the cultures or guinea pigs, inoculated with the pleural fluid, are obtained, for it has been demonstrated that the likelihood of the development of active tuberculosis is just as great whether the tubercle bacilli are demonstrated or not. During the period in which the reports are awaited, the febrile and toxic course of the disease is shortened by chemotherapy and it is unwise to deprive the patient of this benefit. Furthermore, the development of extra-pulmonary foci is cut short by the early institution of treatment, and serious complications, such as tuberculosis meningitis or miliary tuberculosis are prevented.

One may be inclined to withhold treatment because the possibility always remains that the diagnosis of tuberculous pleurisy may be incorrect, and that an occasional patient may be wrongly stamped as tuberculous and treated unnecessarily. However, the facts must be faced. Short of a pleural biopsy or the appearance of a disseminated tuberculosis, a completely certain diagnosis of a tuberculous etiology cannot be made in a majority of instances. However, our studies indicate that there will be very few errors in the diagnosis if the criteria mentioned under the heading of diagnosis are observed. It is better to treat an occasional case unnecessarily than to have the patient run the risk of dissemination of the tuberculosis. Where there is considerable doubt as to the correctness of the diagnosis in an individual case, and the possibility remains that some other important condition may be overlooked, it is best to resort to a pleural biopsy for a definitive diagnosis.

Our plan has been to use both streptomycin and isoniazid together with PAS in the treatment of tuberculous pleurisy. The usual doses of isoniazid and PAS are given. However, we administer a gram of streptomycin daily for ten days to two weeks, and three times a week for a month before continuing with the usual routine of a gram twice a week. It is felt that this modification might be helpful in relieving the toxic manifestations somewhat sooner and perhaps result in less residual thickening of the pleura than if only two drugs are given in the usual dosage.

The chemotherapy is employed primarily for the control of the unseen foci of tuberculosis and the prevention of later dangerous spread of the disease. The tuberculous pleurisy itself is not nearly so important. A tuberculous empyema resulting from a tuberculous pleurisy of the type under discussion is quite unusual, and the thickening of the pleura that results from the pleurisy, is usually not extensive. Nevertheless, we have seen a number of cases in which the function of the lung has been impaired by the residual thickening of the pleura, and this has been observed by others (14). In unusual instances, this may be sufficient to warrant decortication of the lung (13).

There is reason to believe that pleural thickening may be prevented by the

early institution of chemotherapy. It has been shown that high levels of isoniazid surpassing those of the blood, occur in the pleural fluid soon after the administration of this drug (15), and that levels sufficient for the inhibition of the growth of tubercle bacilli occur within the pleural fluid after the administration of streptomycin (16). The increased penetrating power of isoniazid makes this a particularly useful drug in this disease so that one may consider it the drug of choice.

Insufficient data have been compiled for a final evaluation of the drug treatment. However, it is being widely used (13, 17, 18, 19). One well documented series was treated by Emerson (20). Of 19 patients without visible pulmonary lesions, treated with streptomycin, PAS and aspiration of the chest, there was no relapse after two years of follow-up observation, and the length of the febrile course was considerably diminished. None of the patients were left with any significant thickening of the pleura. On the other hand, in a control group of 32 patients, there were 9 who developed active tuberculosis during the same period of observation and one required decortication of the lung for thickening of the pleura.

Exactly how long one should continue the drug treatment remains uncertain. However, it is logical to continue the treatment for as long a period as in any active tuberculosis of moderate extent, since, essentially we are treating latent parenchymal lesions associated with the pleurisy. Experience has shown that a minimum of one year is required for the treatment of such lesions. If further observation shows that there are any relapses in cases treated for only this length of time, a longer course of treatment will become indicated.

It seems reasonable to believe that prolonged bedrest is of little or no importance when chemotherapy is used. Thus far, ordinary physical activity does not seem to have influenced the course of the disease. Moreover, our experience in the ambulatory treatment of pulmonary tuberculosis of minor extent has indicated to us that bedrest is not necessary for cure. The disadvantage of bedrest is forcibly brought to mind by two patients we have observed who died from pulmonary embolization as a result of a phlebothrombosis contracted while they were at bedrest. Certainly enforced rest in bed for a long period has other undesirable consequences, and it should not be ordered lightly.

In tuberculous pleurisy there is an additional disadvantage to the constant recumbent position, namely, the elevation of the diaphragm with resultant contraction of the lung, becoming more or less permanent as adhesions form in the wake of the pleurisy. To prevent this, postural mobilization of the lung has been recommended (21). The plan which we follow is to keep the patient in bed only as long as the fever and toxic manifestations persist. The usual duties of the patient are resumed as soon as he feels generally well enough to accomplish them without fatigue. Strenuous labor or working hours leading to fatigue are, of course, interdicted.

DIRECT TREATMENT OF THE PLEURA

The pleural disease may be treated directly in order to prevent thickening of the pleura or to improve pulmonary function if the pleura has already become markedly thickened. Repeated aspiration of the fluid early in the disease may

prevent a certain amount of deposition of fibrin. Generally, however, if a thick fibrin deposit is to form, this occurs quite early. Aspiration, therefore, is not very helpful unless it is begun at the very onset of the pleural symptoms.

Instillation of antimicrobials, of streptomycin or isoniazid has been practised (21). In the case of isoniazid, this does not seem to be necessary since high concentrations of the drug are to be found in the pleura soon after its administration by mouth. In the case of streptomycin, the instillation may prove useful.

No study has come to our attention concerning the introduction into the pleura of lytic agents to dissolve the dense fibrinous exudate in the early stage of tuberculous pleurisy, and thus permit early complete reexpansion of the lung. At first thought this might appear to be a valuable addition to the treatment. However, one must consider the possibility that the lytic substance might have an adverse effect upon the pulmonary lesion underlying the pleurisy.

Decortication has been performed to improve the function of the lung where there has been marked contraction of the organ from an effusion of long duration. The dense encasement of the lung can be removed without much danger to the patient. It should restore the pulmonary function successfully in the cases under discussion because of the absence of extensive underlying pulmonary disease. However, the indication for decortication arises only rarely, since the pleura, which may be quite thick for several months, almost invariably becomes thin after that time, and good pulmonary function is usually restored spontaneously. Decortication, therefore, should not be resorted to until there has been ample opportunity for the resorption of the exudate. Repeated aspiration of the fluid early in the disease, and the use of antituberculosis drugs will probably make this operation unnecessary in simple tuberculous pleurisy.

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THE TREATMENT OF TUBERCULOSIS IN CHILDHOOD

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The changing pattern of the therapy of tuberculosis in the last decade has affected the management of the disease in children as well as in adults.

Collapse therapy in its various forms, so popular only recently for all age groups, has in the main been abandoned or reserved for certain select indications. Adequate rest, nutrition, the prevention of intercurrent infection, and general medical care, as they contribute to and improve immunity, are still of basic importance in the management of tuberculosis. Emphasis however has been shifting rapidly to reliance on specific therapy with the newer antimicrobial agents. More recently advances in pulmonary surgery have provided techniques for successfully dealing with the sequelae of the initial infection.

Up to the present specific therapy has been concerned mainly with streptomycin, dihydrostreptomycin, promizole, para-aminosalicylic acid (PAS) and the hydrazine derivatives of isonicotinic acid. These agents used singly or in combination are essentially bacteriostatic in nature. Their limitations, and the full scope of their usefulness in the treatment of tuberculosis in childhood are not yet fully delineated. Reports of their effectiveness in childhood tuberculosis though numerous, show a paucity of well-controlled long range studies. This is especially true of isoniazid, which has been available only since 1952.

Despite the gaps in our knowledge of anti-tuberculous therapy, there is an increasing body of evidence that attests the favorable effect of specific antimicrobial therapy on the prognosis of tuberculosis in childhood.

One of the best compilations in this regard is the report of Lincoln (1) which shows the progressive diminution in the mortality from primary tuberculosis on the children's tuberculosis wards of Bellevue Hospital over a period of 20 years. Lincoln points out that in the pre-chemotherapy period between 1930 and 1946, the overall mortality from primary tuberculosis was 21.5 per cent. Between 1947 and 1951 when streptomycin, para-aminosalicylic acid and promizole were given to only 35 per cent of the patients, the mortality dropped to 5 per cent. When isoniazid was added to the regimen, the mortality dropped to 1.5 per cent in 1952–53.

The effect of the specific therapy is even more strikingly apparent in some of the graver forms of tuberculosis in childhood. Tuberculous meningitis has in the last two to three years shown an increase in overall survival rate as high as 85 per cent (2) to 90 per cent (3). It has been noted that results improve and sequelae diminish as the disease is diagnosed earlier and treated promptly. Especially since the introduction of isoniazid, miliary tuberculosis has shown a remarkable susceptibility to specific therapy; and is almost being eliminated as a cause of death. Progressive primary tuberculosis with cavity formation and bronchogenic spread or diffuse tuberculous disease as a result of hematogenous dissemination

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now rarely cause fatality. In tuberculosis of the urinary tract, the G-I tract and the skin, specific treatment has relieved distressing symptoms and accelerated the pace of recovery. In tuberculosis of bone, and tuberculosis of the lymph nodes too, results have improved. Although the response of endobronchial tuberculosis secondary to peribronchial lymphadenopathy has been disappointing, the risk of dissemination has been diminished (4).

The improvement in the prognosis of tuberculosis since the advent of antimicrobial therapy has not been limited to one locality or one age group. Drolet and Lowell (5) recently presented a survey of 15 countries including Puerto Rico, submitting striking data which demonstrate this favorable trend in prognosis.

As data are accumulated, the indications for the use of antimicrobial therapy are broadened and extended. At present specific therapy in the grave complications are considered urgent since this group accounted for 95 per cent (2) of the deaths in childhood tuberculosis in the prechemotherapy period. This group includes tuberculous meningitis, miliary tuberculosis, progressive primary tuberculosis with cavitation, and the complications due to hematogenous dissemination.

When symptoms may be relieved, or the duration of the disease shortened, it is recommended that specific therapy be given. This is indicated in tuberculous disease of the gastrointestinal tract, the skeletal system, the skin, the genito-urinary tract, draining cutaneous sinuses, eye diseases, laryngeal diseases, and diseases of the ear.

Specific therapy too should be used in the preparation for surgery and in the management of tuberculous patients surgically treated.

There remains, in addition to these groups, a group of cases about whom opinions differ sharply as to the indications for therapy. This group includes: (a) patients with asymptomatic primary tuberculosis (b) patients with a recently converted positive tuberculin skin test.

MANAGEMENT OF ASYMPTOMATIC PRIMARY TUBERCULOSIS

Decisive evidence as to the indications for therapy in this group has been difficult to accumulate. In part this has been due to the seemingly benign character of this form of the disease, and in part to the rapid pace of the changes in therapeutic procedure. Notwithstanding the realization that children with primary infection generally recover without complication, it is recognized that there are certain dangers of complications which affect the prognosis. The complications have been characterized as benign when they are manifested by a segmental lesion or a pleural effusion (6). They may however be serious and as has been pointed out by Lincoln (1), may account for the great majority of the deaths (90 per cent) in the first year after the infection is established.

The more serious complications are usually the result of acute or protracted hematogenous dissemination or of progression of the primary disease with cavitation and bronchogenic spread. The time of appearance and the frequency of these complications is of importance. Wallgren (7) and others (8) have indicated

that the most serious complications occur within the first few months after the onset of the initial lesion.

Cammock and Miller (9) estimated that the risk of developing meningitis and miliary tuberculosis among infected children under 5 years of age was 4.1 per cent. Bentley (6) calculated the incidence of hematogenous complications in children less than five years old to be about 10 per cent; above two years of age, it is about 3 per cent.

In addition to these relatively immediate complications, benign and severe, there may be a remote hazard which is attributed to the primary tuberculous infection. It is the increased risk of development of the adult or the reinfection type of tuberculosis in children who have had a primary infection. This risk is very difficult to appraise since it may not manifest itself until many years after the initial infection. Lincoln (10) calculated an 8 per cent incidence of the adult type of tuberculosis, in children followed for 1 to 14 years after the diagnosis of primary tuberculosis. Holmdahl (11) found the total risk of reinfection to be 9.2 per cent after a 20 year follow-up of such children.

The potentially serious risk, both immediate and remote, in children infected with primary tuberculosis would seem to emphasize the importance of treatment for prevention. This has become all the more vital and possible since antimicrobial therapy has been demonstrated to have positive effects on the incidence of complications. And more particularly since isoniazid apparently has been shown to protect against the development of tuberculous meningitis even in the presence of miliary tuberculosis (2, 12, 13).

Unfortunately, there is not yet available sufficient data to give the necessary weight to all the arguments for treatment. Opinions differ sharply (14–16). There are those who would observe the patient and treat the complication as it arises, rather than use a full program of antimicrobial therapy. These observers (2, 6) are not convinced that therapy has any effect on the primary lesion. They call attention to its benign character and point to the early use of therapy as increasing the possibility of drug resistance which may make subsequent treatment or retreatment ineffective. The antagonists of early therapy further emphasize the potentially toxic effects of the drugs, the need for their prolonged use and the possible loss of a positive skin reaction as evidence of loss of immunity. Many of these arguments have some merit; many have yet to be substantiated.

After weighing all the evidence, it has been our policy to treat childhood tuberculosis of the asymptomatic variety in the younger age group. This applies without question to infants under one year of age, and extends with almost equal emphasis to children under three years of age. In addition, treatment has been suggested in certain special groups (8). These include children above the two to three year level where a severe degree of fever and constitutional symptoms of long standing are present; or children with a strong family history of tuberculosis; or where there is considerable enlargement of the paratracheal lymph nodes, as seen on x-ray. It has been suggested too, that recently infected children in the adolescent period over 12 years of age, be included.

Treatment of asymptomatic primary tuberculosis should, in our opinion,

be early and adequate. It may be on an ambulatory basis, although our own experience has been essentially with hospitalized infants and children.

If treatment is given, it should be maintained for about a year. Our practice is to use moderate dosage of a major drug such as isoniazid, and a minor drug such as PAS. Other combinations and even isoniazid alone have been recommended (12).

Therapy in no way diminishes the need for searching out contacts, eliminating the source of infection and for applying frequent and periodic tuberculin tests, as the most important method for detecting the disease.

TREATMENT OF RECENTLY CONVERTED TUBERCULIN REACTORS

The management of the recently converted positive tuberculin skin reactor has aroused considerable controversy. Some observers feel, as does Waring (17), that all recent reactors should be treated. There are others (14) who feel that routine treatment of these children would entail needless therapy in communities where the death rate from tuberculosis is rapidly decreasing. They point to the risk of drug toxicity and bacterial resistance, and especially deprecate the reversion of the tuberculin test as evidence of loss in immunity.

Although the relation of the tuberculin test to immunity is not completely clear, the importance of the tuberculin reaction as a means of detecting tuberculosis is, of course, inestimable. Debré (18) showed the risk of tuberculous complications after conversion of the skin test in childhood. Robinson (19) pointed out that the reversion of the tuberculin reaction is more apt to occur in treated infants, free of demonstrable roentgenographic lesions.

It is our feeling at this time that early detection of tuberculosis in the younger age group should be followed by early treatment. The prime reason is the need to protect against the potentially serious complications. This is emphatically true in the age group under one year, and should extend to the group below three years.

It has been suggested that prophylactic treatment be given to the age group over 12 years (12) when fresh tuberculosis is detected. In the age group immediately above three years, which has been considered a reasonably safe group, it has been considered acceptable that the child be observed at frequent intervals and treatment begun when visible evidence of the disease becomes manifest. Admittedly, age as a criterion is an unsatisfactory one when the predominant aim is the prevention of serious complications. Treatment, when instituted, should include isoniazid and PAS in moderate doses and should be given for about a year to achieve maximum protection.

Specific treatment of the recent reactors in no way obviates the need for removing and treating the source of infection. In the final analysis this plus immunity is the best safeguard against infection and reinfection.

In addition to the two problems discussed, there are many others that await solution. They range from fundamental problems in therapy, to the evaluation of the effectiveness of surgery in the management of the disease. Some of these problems are concerned with the establishment of uniform regimens of therapy,

including the selection of drugs, dosage, and optimum duration of treatment. Others are concerned with strain resistance, drug toxicity, immunity and reinfection tuberculosis. Still others are concerned with the effects of ambulation, relapses, and the possible social implications of antimicrobial therapy.

To these problems may be added other more practical ones which are in need of solution. Not the least important of these is the management of endobronchial tuberculosis in childhood, which has been little if at all influenced by antimicrobial therapy. Perhaps when the present effort of the U. S. Public Health Service to collect and to analyze data on the treatment of tuberculosis and its complications is completed, some final answers to these problems will be forthcoming.

In the meantime physicians must become acquainted with some working plan which should embody the best available practical experience in the management of tuberculosis in children. One of the best of these regimens is that employed by Lincoln at the Bellevue Hospital. Another is that recently recommended by the Committee on Therapy of the American Trudeau Society (20).

The regimen utilized by the author on the Children's Tuberculosis Service of the Willard Parker Hospital in New York between 1951 and 1955 is not unlike that used at many institutions throughout the country. Like the others, the plan of therapy underwent considerable modification as experience accumulated. The measures utilized are general and specific.

General Measures

A high caloric diet, especially rich in protein and fat is recommended. This should include a vitamin supplement containing vitamin A and C in adequate dosage. The additional use of pyridoxine is recommended by some when isoniazid therapy in large doses is utilized. The physical activity permitted the child depends on the character and stage of the disease. When the disease is relatively recent in origin, activity should be limited. This should continue for the first two or three months of the disease even if the child is afebrile. Bed rest, though desirable, is frequently difficult to obtain. Rest in children, can frequently be best achieved by supervised play without excessive stimulation. In suitable weather and in suitable climates play may be outdoors. Pleasant surroundings and an informed solicitous personnel will help assure a proper balance between activity and relaxation. Intercurrent infection should be guarded against (21, 22) and if it occurs, promptly treated. Full protection against measles if exposure occurs is indicated. Children with pertussis should be especially observed and treated. Children of school age who have passed through the acute stage of the disease may attend school classes. Physical activity at school should be somewhat restricted. After the disease has been treated for about six months, activity may be somewhat liberalized. Most restrictions may be dispensed with after about 12 to 15 months. All these measures and modifications of course depend on the extent and character of response of the tuberculous infection. The maximum danger of complications is usually over by the end of the first year.

Specific therapy

When the diagnosis is established, and the decision to use specific measures has been made, therapy must be prompt and uninterrupted. The choice of drug

or drugs used is determined by the nature of the problem. When the most threatening complications of primary tuberculosis present themselves, namely meningitis or miliary tuberculosis, three drugs are usually recommended.

We have used streptomycin, isoniazid and PAS. When progressive primary tuberculosis or evidence of protracted hematogenous or visceral tuberculosis is present, two drugs are usually used. We have recommended isoniazid and PAS or streptomycin and PAS. Although the literature refers to the effectiveness of single drugs, we have made it a policy to use drugs in combination, relying on the evidence that the combination tends to delay and prevent the development of resistance.

Isoniazid is the most popular of the isonicotinic acid derivatives in use. The initial dosage is usually about 8 to 10 milligrams per kilogram per day divided into three or four doses. The higher dosage is used at the onset of treatment of the more serious problems. It may be reduced to a level of 6 to 8 milligrams per kilogram per day in four to six weeks, and thereafter maintained at this level. Its use has made possible a reduction in the high dosage of streptomycin, thus diminishing the risk of eighth nerve impairment.

Although drug resistance is a serious concern, the problem appears to be less troublesome when the drug is given in combination.

That isoniazid readily enters into the serous cavities and the subarachnoid space, may explain its importance in the prophylaxis of tuberculous meningitis. The toxic symptoms of isoniazid are related, in the main, to the central nervous system. They consist of hyperreflexia, constipation, difficulties in urination, dizziness and positional hypotension. Evidence of hepatic and renal irritation have been described, although in our experience these have been uncommon.

Of the major agents, used in treatment, isoniazid presents the least toxic effects. It may be given in average dosage except in fulminating disease. It is easily tolerated and rarely requires interruption of therapy. When necessary, it may be given by injection. When toxic symptoms appear, the dosage may be reduced for a short period and frequently may be resumed without ill effects.

Streptomycin when used, is given intramuscularly. The dosage is usually calculated on a weight basis in amounts ranging from 20 to 60 milligrams per kilogram per day. At the onset of treatment it is usually administered daily for two to four weeks. It is then given twice or three times weekly. It has been demonstrated that the interrupted method of administration is as effective as daily administration, with the advantage of reducing the danger of toxicity.

In the younger age groups, Lincoln (2) recommends 0.5 gram to a child weighing 20 to 40 pounds and 0.3 gram per day to an infant. The dose of streptomycin should not exceed one gram daily. This dose is given to children weighing 90 pounds or more. As with isoniazid, streptomycin should be given in combination with another drug such as PAS or promizole. The combination may help to prevent the development of bacterial resistance, and may provide synergistic bacteriostatic effects.

Streptomycin or its related compound dihydrostreptomycin passes into the spinal fluid less readily than does isoniazid. However concentrations in the subarachnoid space mount readily in the presence of meningeal irritation.

The toxic effects of streptomycin include disturbance of vestibular function, eighth nerve deafness, fever, vomiting, paresthesias, skin eruptions. Dihydrostreptomycin tends to produce eighth nerve deafness in contrast to the vestibular dysfunction induced by streptomycin.

PAS is tuberculostatic in its action and helps prevent the development of drug resistance when given in association with isoniazid and streptomycin. Resistance to PAS however has been known to develop. PAS enters the spinal fluid in the presence of inflammatory reaction and it enters the serous cavities relatively readily.

The dose usually given is 0.3 to 0.5 gram per kilogram per day in divided doses three to four times daily. Dosage does not need to exceed 12 grams daily. There are few symptoms, mainly gastrointestinal.

Promizole, a sulfone, has not been used by us to any significant degree. Lincoln who has had much experience with the drug has emphasized its bacteriostatic qualities in controlling hematogenous spread and miliary tuberculosis.

It is suggested (2) that the drug be given by mouth in divided doses starting from 0.25 to 0.5 grams daily. The drug is increased gradually until a blood level of 1 to 3 milligrams per cent is obtained. Doses up to 8 grams daily may be given. Toxic results at the lower level are not common. At the higher level, one may note development of goiter, cyanosis, leukopenia, and rarely hypertrophy of the breast and nipples. Except for the latter these effects are reversible.

Promizole has generally been used, as has PAS, in combination with one of the major therapeutic agents.

There are a number of newer agents which have been surveyed in the treatment of tuberculosis. Viomycin has been used when there has been intolerance to isoniazid or streptomycin. It has neurotoxic and nephrotoxic properties which give concern. Pyrazinamide, still under study, is used in combination with isoniazid. Its usefulness at this time is apparently limited because of its hepatic toxicity.

Because of its ease of administration, its clinical effectiveness and its importance in prevention, isoniazid is now commonly used especially in childhood. As single drug therapy (23), clinical results have been favorable although it frequently has been pointed out that there is a tendency to the early development of drug resistance. Indications for the use of isoniazid alone are yet to be clearly defined.

We have generally used isoniazid in combination with another drug in initiating treatment. Such combinations as isoniazid and PAS, isoniazid and streptomycin, isoniazid with streptomycin and PAS, and streptomycin with PAS are frequently utilized. We have reserved the use of isoniazid and streptomycin, the two major drugs for the most threatening problems since we have feared the development of intolerance and resistance. When so used, we have generally added PAS although it has been pointed out (24) that the results with the three drugs regimen may not be superior to that with two drugs.

The duration of therapy of tuberculosis in childhood is a subject which has been much discussed. In a general way, treatment should be prolonged rather

than short. Duration varies with the severity of the disease. It should be given for a period of at least one year. The fact that hypersensitivity may develop to all of the antituberculous drugs including PAS must be borne in mind. Sensitivity to PAS may interfere with its complementary tuberculostatic effect. The factor of drug resistance too must be guarded against, although it is known that the clinical status of the patient may not parallel the in vitro alterations in organism susceptibility.

Some of the several complications present special problems in therapy.

In tuberculous meningitis, isoniazid is always given, although there are some (25) who suggest its exclusive use in treatment. It is usually administered as part of combined therapy (3). It is common practice to use a three drug combination including isoniazid, streptomycin and PAS. The total duration of treatment should be a minimum of 18 months to two years. Streptomycin is given daily for about three to four weeks, then intramuscularly twice weekly for about six months. Although spinal taps are performed periodically intrathecal therapy in tuberculous meningitis is being abandoned. There are now many who feel that its use is harmful. Therapy to be most effective must be administered early. The prognosis for cure and elimination of sequelae in survivors is related to a number of factors most important of which is the stage in which treatment is begun.

Block in the subarachnoid space, the result of basal meningitis constitutes a serious problem in the management of the disease. It must be watched for and treated promptly. Cisternal taps, alternating with lumbar punctures are safe and useful therapeutic procedures. The treatment with fibrinolytic enzymes or PPD intrathecally is not without serious hazards, if indeed the results are significant. More recently steroid hormones have been used in the management of this problem, with reported success.

In miliary tuberculosis as in tuberculous meningitis we usually employ three drugs. The duration of therapy is about 18 months although others treat for a shorter period. We usually administer the streptomycin daily for three to four weeks then twice weekly for four to six months.

The duration of therapy for progressive primary tuberculosis is 12 to 15 months or longer, depending on the course of the disease.

In pulmonary disease, the duration of therapy is best determined by the clinical course, the improvement in roentgen findings, and the laboratory tests. Temporary worsening is not unknown. The size of parenchymatous components is frequently difficult to measure and requires long term evaluation. Usually in progressive primary disease or disseminated tuberculosis two drug combination such as isoniazid-PAS or streptomycin-PAS is recommended in the doses previously outlined.

In tuberculous disease due to protracted dissemination the duration of therapy may vary from one to two years or more. The management of bone and joint tuberculosis still presents many problems. Usually two drugs are administered for at least two to three years. The cooperation of a competent and patient orthopoedic surgeon is indispensable. The use of chemotherapy has now made

possible the utilization of indicated surgical procedures before advanced crippling changes can occur.

Tuberculosis of the genito-urinary tract should be searched for in every case of pulmonary disease or tuberculous disease associated with evidence of hematogenous dissemination. Treatment should follow the general principles of therapy for tuberculosis (26), using combined therapeutic regimens for at least one or two years. It has been observed that the triple drug regimen (27), is somewhat more effective than the two drug combination. Close liaison with the urologic surgeon is essential. Good results can be expected even after prolonged therapy where there is no demonstrable evidence of advanced kidney damage.

The management of tuberculous adenitis still presents many problems. In a general way, conservative therapy with antimicrobial drugs is indicated when nodes are discrete or firm. If conservative therapy given over a reasonably long period of time fails, surgery should be considered. Liquefied node masses with or without a draining sinus should be incised and drained. This may be followed by irrigation with streptokinase and streptodornase, as suggested by Hazelhurst (28). Lymph node tuberculosis is frequently associated with tuberculosis in other parts of the body (29), commonly lungs, bones and joints. Management of lymph node tuberculosis as a local disease process without systemic therapy is no longer considered justified (30).

The striking indifference of certain forms of endobronchial tuberculosis seen in childhood tuberculosis to specific therapy has discouraged many from using it. However, the possibility of dissemination and the need for controlling the local spread of the disease in infancy makes specific therapy important. In addition the use of surgical techniques (4) for removal of obliterating lymph nodes or granulomas is best performed in the patient under specific therapy. A combination of drugs such as that recommended for the treatment of primary tuberculosis is indicated.

In the past few years pulmonary resection in children in whom residual sequelae remain after the primary infection has become common practice (31). This is done after prolonged use of chemotherapy has failed to eradicate a lesion that may act as a focus for exacerbation or reinfection. Rubin (32) in summarizing his studies on resection in tuberculosis in children, indicated that children under the age of five years rarely require surgery. In the six to ten year age group, resection is more apt to be used for the shrunken lobe, bronchostenosis, or bronchiectasis. Resection is more often indicated for tuberculosis in the adolescent where, as in the adult, the lesion may not respond to antituberculous therapy.

Notwithstanding the improvement in surgical techniques and the resultant improvement in surgical mortality and morbidity, the final word for the use of excisional pulmonary surgery in childhood remains unsaid. It must certainly await the evaluation of the influence of long term chemotherapy in pulmonary lesions.

SUMMARY

The newer antimicrobial agents have made possible the prevention and the treatment of the serious complications of tuberculosis. Their use has liberalized

the limitations on patients under treatment and has encouraged early ambulation and discharge from the hospital. Management of uncomplicated tuberculosis at home on an ambulatory basis is now common practice (10). Although there is some agreement that active tuberculosis in children should be treated, there remain many problems that will be solved only when controlled data is adequately gathered and analyzed.

The treatment of asymptomatic primary tuberculosis, or the child with a recently acquired positive tuberculin test, is still open to discussion. It is our belief that treatment in these groups is indicated for the prevention of the complication of primary tuberculosis especially in the younger age groups.

As experience increases regimens of therapy are constantly undergoing changes. There is as yet no universally accepted regimen of treatment in the management of childhood tuberculosis.

The regimen we have used, emphasizes the use of isoniazid as a prevention against the serious complications.

The successful use of antimicrobial therapy with its favorable impact on prognosis in all age groups, makes more imperative the need for early detection and diagnosis of tuberculosis in infants and children.

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RESECTIONAL THERAPY FOR PULMONARY TUBERCULOSIS

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It was but thirty years ago that the first book on the subject of surgical therapy of pulmonary tuberculosis was published in this country. This volume, authored by John Alexander (1) and published in 1925, actuated the use of surgical procedures in the treatment of the disease. Virtually none of the methods described by Alexander are in general use at the present time, but it is interesting to note that in this book of approximately 350 pages, less than one printed page was used to discuss pulmonary resection, the procedure on which we, today, depend almost entirely for the surgical treatment of pulmonary tuberculosis. Furthermore, Alexander cited three reasons why this procedure should be excluded from modern surgical therapy. In his enlarged volume of 700 pages published in 1937 (2), pulmonary resection was again accorded but one page of discussion under the heading, "Proposed Operations Which Have Not Been Generally Adopted." He stated, "It is possible, however, that lobectomy, or even pneumonectomy, may prove to be useful for a highly selected group of cases in which prolonged toxic symptoms result from unrelievable bronchial stenosis or in which an open cavity remains after a modern thoracoplasty operation. . . ." and also ". . . lobectomy in tuberculous persons should be restricted to those whose tuberculosis is arrested and in whom there are especially strong indications for lobectomy because of severe bronchiectasis or other nontuberculous disease."

In order to supersede the various collapse methods which were in general use, it was first necessary to prove that excisional therapy had a low morbidity and mortality rate. And it might be pertinent to note here that the discovery of the antituberculosis drugs was not the only factor that made this possible. The great advances in the art of thoracic surgery and anaesthesia, as well as the increased knowledge of pulmonary physiology, the availability of blood for transfusion, and the antibiotics to combat pyogenic bacteria, all have contributed to make pulmonary resection a relatively safe procedure. The radical changeover from the use of the various methods of collapse therapy to excisional procedures occurred much more rapidly and more completely in this country than elsewhere.

The degree to which collapse methods have fallen into disuse is attested by the statistics of operations performed at Montefiore Hospital, in New York City, where 123 thoracoplasties and 134 thoracoscopies and intrapleural pneumonolyses were performed in 1949. By contrast, in 1955, no thoracoplasties were performed for the treatment of pulmonary tuberculosis, and there was only one thoracoscopy, this upon a sixty year old female whose general condition was so poor that artificial pneumothorax had to be induced because no

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other form of therapy could be attempted. The trend in foreign countries is shown by Nuboer (3) who reported 615 resections performed during the past few years. During that same period, he performed only sixty thoracoplasties and thirty-seven extrapleural pneumonolyses.

That resections for pulmonary tuberculosis were performed before the availability of the antituberculosis drugs is adduced by a number of reports in the literature. In 1952, Overholt, Wilson and Gehrig (4) reported on 428 patients upon whom 437 resections were performed from 1934 to 1950. Approximately one half of these operations were performed during the pre-streptomycin era. In this group of patients who received no drug therapy, the combined post-operative and late mortality rate reached 32.2 per cent and, after a three- to eight-year follow up, 60 per cent of the patients had a negative sputum.

From the American literature, Moore, Murphy and Elrod (5) collected the reports of 607 resections for pulmonary tuberculosis which were performed from 1881 to 1948. There was a 26 per cent (over-all) mortality rate in this group of cases. A spread or exacerbation of tuberculosis occurred in 26 per cent of 456 of these patients; 12 per cent developed an empyema; and 6 per cent, bronchopleural fistula. The previously mentioned cases of Overholt were included in this compilation. From these statistics, one can readily understand why, at that time, thoracoplasty was the procedure of choice in the surgical treatment of pulmonary tuberculosis.

THE ANTITUBERCULOSIS DRUGS AND RESECTIONAL THERAPY

Before the discovery of streptomycin, if stabilization of the pathologic process in a localized area were to occur, it took years to accomplish. In some patients, the disease became arrested by bed rest alone or combined with artificial pneumothorax. However, in many, the disease spread to the other lung, making surgical intervention extremely hazardous, if not impossible. Only the "good chronic" with unilateral disease could be treated by thoracoplasty.

The course of pulmonary tuberculosis has been greatly altered by the administration of the antituberculosis drugs. They either arrest the disease or stabilize the process rather rapidly, and almost always tend to localize the disease to those areas affected at the very beginning of therapy. Under drug therapy, spreads and exacerbations are extremely rare. Because of this, the number of patients upon whom surgical intervention is possible has increased greatly.

When first used as an adjuvant to surgery, streptomycin was administered for a few weeks as a pre- and post-operative prophylactic. Even with these short courses of therapy, its marked beneficial effect resulted in a reduction in post-operative complications. Gordon (6) showed that 50 per cent of the patients who did not receive streptomycin developed bronchopleural fistulas after resection, while in those who had three weeks preparation, fistulas occurred in 24 per cent, and with more than three weeks preparation, the incidence was only 6 per cent. And when isoniazid was added to the antituberculosis drugs, the results were even better. Childress et al. (7), reporting on twenty-three patients to whom isoniazid had been administered from forty-eight hours preoperatively

to two months after operation, had no tuberculous complications despite gross pleural contamination in eleven. Two had had no previous therapy. Twenty had had streptomycin and para-aminosalicylic acid, and one had received p-aminosalicylic acid only.

Today, surgery is performed only after a varying period of drug therapy; rarely less than three months, usually from six to twelve months. Of 3,840 patients operated upon in the Veterans Administration Hospitals in the last three years, only 25 per cent had less than three months of drug therapy prior to operation (8). Of the three drugs, streptomycin, p-aminosalicylic acid, and isoniazid, two (usually p-aminosalicylic acid and one of the others) are administered at the beginning of therapy; the third is held in reserve for future use because bacterial resistance to the first two drugs administered may occur.

Surgical therapy for pulmonary tuberculosis is indicated when antituberculosis drug therapy has failed to arrest the disease or when collapse procedures have been unsuccessful. Except for the rare emergency, surgery should be performed for pulmonary tuberculosis only after a planned and adequate course of antituberculosis drug therapy. This is dependent upon the type and severity of the disease, the presence of extrapulmonary tuberculosis, and the general status of the patient. If the tubercle bacillus can be cultured, sensitivity studies should be made. There is an optimal time for operation in every patient requiring surgery. One must watch for it; it should not be missed. Every patient cannot be brought to the "target point," which is closure of cavity, stability of disease as seen on the roentgenogram, and negative cultures of sputum and gastric washings. Although operations at this "point" are accompanied by practically no complications, there are many patients who never reach this stage. They must be operated upon with open cavities, with positive sputum, sometimes with unstable lesions and bilateral disease. If the bacillus remains sensitive to at least one of the drugs, there are few complications, and results are good. When operation must be performed upon a patient in whom the tubercle bacillus is resistant to all three drugs, complications occur more frequently, and the end results worsen. It has also been observed that the results are better in those patients who have been given one continuous course of therapy than in those who have had numerous intermittent courses. A new drug, pyrazinamide, has been used for the operative period in those patients in whom the tubercle bacillus has become resistant to the other drugs. Unfortunately, it is accompanied by toxic reactions in a high percentage of patients and its real value as an antituberculosis drug has not as yet been ascertained.

In analyzing the factors influencing the success of segmental resections, Murphy (9) found that the best results were obtained in patients who had had a first course of drug therapy for at least eight months. Satisfactory results were obtained in 95 per cent of this group. In comparing results in the prestreptomycin era with those in the antituberculosis drug era, Overholt, Wilson and Gehrig (4) found over-all deaths reduced from 32 per cent to 7.7 per cent, and good results (negative sputum) raised from 60 per cent to 82 per cent. These results make it evident that the intelligent planning of the medical ther-

apy is of the utmost importance to the success of the surgical treatment. As soon as the diagnosis has been made, the medical therapy should be planned, for no one can foretell whether or not a surgical procedure for eventual cure will be necessary.

THE INDICATIONS FOR RESECTIONAL THERAPY

Resectional surgery is relatively safe and the results, thus far, have been excellent. Not only does the procedure remove the diseased pulmonary tissue, it affords inspection of the remaining lung on the operated side. It does not cause deformity of the chest cage nor of the vertebral column and, following a lobectomy or segmental resection, there is little interference with pulmonary function. Dijkstra et al. (10) measured the pulmonary function on the operated side before and after lobectomy and segmental resection. They found that the lung that had been operated upon showed a decrease of 4.8 per cent in oxygen absorption after resection of one or more segments in one lobe; 7.9 per cent after removal of segments in two lobes; 9.3 per cent after lobectomy; 14 per cent after lobectomy plus a segmental resection; and 16 per cent after excision of the middle and lower lobes of the right lung.

During the past few years, there has been a radical change in the extent of resection performed. Because of the many destroyed lungs and unsuccessful thoracoplasties persisting from the pre-streptomycin era, the number of pneumonectomies performed in previous years was high; today, segmental resections far outnumber either lobectomies or pneumonectomies. Earlier diagnosis and control of the disease with drug therapy have been the major factors in reducing the extent of pulmonary involvement; thus, well-localized disease processes are presented for surgical excision. The following are the pathologic conditions for which resection is indicated:

1. Residual cavity under a thoracoplasty.
2. Persistent cavity or recurrent cavity.
3. Blocked or filled cavity.
4. Residual nodule.
5. Bronchostenosis.
6. Bronchiectasis.
7. Destroyed lung.
8. Uncontrollable hemoptysis.
9. Giant cavity.
10. Tuberculous empyema with bronchopleural fistula or active pulmonary disease.
11. Tuberculoma.*

A cavity persisting under a previous thoracoplasty is an indication for resectional therapy if the patient has a positive sputum. A persistent positive sputum is a family and public health hazard; therefore, such a patient, though he has had no exacerbation nor spread for years, should be operated upon. Little success has been achieved in attempting to close these cavities with revision operations. Cavernostomy should be performed only if resection is contraindicated.

* See Kirschner, P., Tuberculoma of the Lung, this issue.

As fewer and fewer thoracoplasties are being performed and the backlog of old unsuccessful thoracoplasties is being eliminated, this type of lesion is being seen less and less. Ottosen et al. (11) reported on twelve pneumonectomies and lobectomies performed for cavities persisting under a thoracoplasty. Sixty per cent of the patients had sputum conversion, and there was a 30 per cent mortality rate. All of the large series of resections reported in the literature contain a considerable number of operations performed, during the early years, for thoracoplasty failures.

A cavity remaining after a course of antituberculosis drug therapy is an indication for resection, even though the sputum be negative. Despite the various types of roentgen examinations now available, the presence of a cavity cannot always be determined with certainty. This has been demonstrated by comparing the findings in resected specimens with the diagnosis made from the roentgenograms. Johnsen and Hewitt (12) and Thompson (13) have recently called attention to the "open healing" of cavities. Examination of resected specimens showed that in 9.6 per cent of cavitary lesions, little or no tuberculosis could be found in the walls. In spite of these findings, a cavitary lesion should be excised. When a cavity reappears after it has been considered closed by drug therapy, surgical intervention is definitely indicated.

If a diagnosis of a blocked or filled cavity can be made from the serial roentgenograms of a patient under drug therapy, resection should be performed. Should such a cavity not be removed, there is always the possibility of evacuation of its contents, thereby causing spread and exacerbation of the disease.

The residual nodule is the pathologic condition that has raised the greatest controversy in the therapy of pulmonary tuberculosis. This condition is not infrequently the end result of drug therapy. The acute infiltration has disappeared, and there is roentgenogram stability; the cavity has closed; and the sputum and gastric cultures are negative. This, as has already been mentioned, has been called the "target point." Although the sputum may be persistently negative in this type of lesion, Auerbach et al. (14) have been able to culture tubercle bacilli from a high percentage of these nodules in the surgical specimens. Others have been able to demonstrate the bacilli on smear but have not been able to grow them on media.

There can be no question that the excision of these nodules yields excellent results. Douglass et al. (15) removed this type of residual focus in 397 patients. They divided this series into two groups: those who had had some other residual foci left behind at the time of operation either on the operated side or in the other lung, as seen in the roentgenogram, and those who had no demonstrable foci remaining after operation. Of 256 patients in the first classification, 95 per cent were well. Of the 141 patients in the second group, those in whom all the tuberculous disease had been removed, the entire group was well. In a study of segmental resections, Murphy (9) found that if the "target point" was reached, satisfactory results were obtained in 95.7 per cent of the patients; when not reached, then only 82.3 per cent of the results were satisfactory.

In order to evaluate the advisability of operating upon patients with closed negative lesions (residual nodules), Decker, Raleigh and Welles (16) used a

control group—a series of patients with comparable lesions upon whom operation was not performed. In the group upon whom resection was performed, the disease remained inactive in 98 per cent of the patients; in the control series, 95 per cent of the patients showed no activation of the disease after discontinuance of drug therapy. Should a longer follow-up period not show a greater disparity, then surely the slight difference in these two figures does not warrant an operative procedure.

Occasionally, the size of the nodule will determine the advisability of resection. There are many who believe that a residual nodule larger than two centimeters in diameter should be resected; smaller ones may be left in situ.

Bronchostenosis in pulmonary tuberculosis may be the end result of the healing of endobronchial disease. It may also be caused by pressure from calcified, tuberculous, hilar lymph nodes; however, this occurs long after the initial tuberculous infection and is usually not associated with active pulmonary disease. Bronchostenosis has a deleterious effect upon any parenchymal disease distal to it. Even though this be controlled by antituberculosis therapy, bronchiectasis and pyogenic suppuration may supervene. Resection is the only therapy indicated for this pathologic condition. Gebauer (17, 18) has pioneered in the salvaging of pulmonary tissue distal to bronchial strictures. He has used reenforced dermal transplants after resection of the stenotic area. Jackson et al. (19) and Paulson and Shaw (20) have also reported excisions of bronchial strictures with end to end anastomosis. Fortunately, drug therapy has reduced the incidence of endobronchial tuberculosis; therefore, its sequelae, bronchostenosis and strictures, are seldom seen.

Bronchiectasis may be caused by bronchostenosis or it may be the end result of the healing of parenchymal tuberculosis. If active disease is present in the bronchiectatic areas, resection is definitely indicated. The bronchiectasis which may develop in healed tuberculosis of the upper lobes does not necessarily require any treatment for it usually remains asymptomatic, but when it is complicated by bronchostenosis, suppuration, or hemorrhage, resection is necessary.

A destroyed lung is the end result of long-standing, extensive, unilateral pulmonary tuberculosis. The pathologic condition is one of multiple cavitation, stenosis of the main or lobar bronchi, marked fibrotic and bronchiectatic changes, and fibrothorax. Such a lung may be the seat of frequent intercurrent infections even though no active tuberculosis be present. Not only does it not aid in respiration, it may even be detrimental to the respiratory physiology because of the unoxygenated blood which returns from it to the general circulation. A destroyed lung should be excised if the contralateral lung is not involved and if, by bronchospirometric studies, it is proven to be capable of sufficient pulmonary function. Gaensler and Strieder (21) have shown that resection of a destroyed lung causes less impairment of the respiratory function than does a thoracoplasty. Since the antituberculosis drugs have been available, such extensive pathologic conditions are seen less frequently. This is attested by comparing the number of pneumonectomies with the lobectomies and segmental resections that are performed today.

In former years, severe uncontrollable hemoptysis was treated by artificial pneumothorax, diaphragmatic paralysis, and, occasionally, thoracoplasty. Although this complication of pulmonary tuberculosis is seen less frequently, it does occur at times. If the disease is confined to one lobe or lung and the contralateral lung is free of disease, an emergency resection may have to be performed as a life-saving measure. A number of cases of emergency resection for massive hemoptysis have been reported (22–25).

Unilateral giant cavities should be resected provided there is no contraindication. Unfortunately, they are frequently complicated by cavitary disease in the other lung. If resection is not possible, cavernostomy may be used as a palliative procedure (26, 27).

Tuberculous empyema, when complicated by bronchopleural fistula or cavitary disease, requires a resection of the diseased pulmonary tissue concomitant with the pleurectomy for removal of the empyema sac. With a localized empyema and unilobar disease, the remainder of the lung might be salvaged; however, should the entire lung be involved, then pleuropneumonectomy, as described by Sarot (28), must be performed.

Cavity perforation with tuberculous empyema is no longer a common occurrence as it was when artificial pneumothorax was a popular therapeutic procedure. Should it occur, immediate operation is indicated if the contralateral lung is free of disease. Biancalano (29) considers the emergency to be similar to that of a perforated ulcer and that resection and pleurectomy should be performed.

THE CONTRAINDICATIONS TO RESECTIONAL THERAPY

With the improvement in surgical technique and the development of segmental resection, the contraindications to resectional therapy have lessened. Extensive bilateral disease is definitely a contraindication to resection, but bilateral disease, when well localized to lobes or segments, can be excised. The antituberculosis drugs not only prevent widespread pulmonary dissemination, but they frequently cause a marked clearing of diffuse disease so that only a localized area need be excised.

Insufficient pulmonary reserve is also a contraindication to major resection. One must bear this in mind, particularly in patients who have had previous collapse therapy. If there is any question as to the adequacy of the respiratory function, bronchospirometry should be performed. There is no justification in arresting the tuberculous disease only to have the patient become a respiratory cripple.

Emphysema, especially in the older age group, may be of sufficient severity to preclude any resectional therapy. When respiratory function is so poor that resection cannot be attempted, collapse measures may still be possible.

Active endobronchial tuberculosis of the major bronchi is a contraindication to resection. It is, however, controlled by the antituberculosis drugs and, therefore, occurs less frequently.

Cardiovascular disease of such severity that it precludes any major thoracic

procedure is naturally a contraindication to operation; but a previous coronary thrombosis which has been well compensated for and which no longer causes clinical symptoms is not necessarily a contraindication to pulmonary resection, even to pneumonectomy.

Lastly, any generalized disease which would increase the hazards of a major surgical procedure would be a contraindication to excisional surgery.

THE RESULTS OF RESECTIONAL THERAPY

The results of resectional therapy for pulmonary tuberculosis are being reported in the literature in ever increasing numbers, however, the follow-up periods are not much more than three to five years. In a chronic disease such as tuberculosis, this is too short a time for final evaluation.

Reporting on 589 operations upon 507 patients, Douglass et al. (15) divided the series into 110 "salvage" cases with open cavity and positive sputum, and 397 "elective" cases with closed lesions and negative sputum. The results of the follow up in the first group showed that 70 per cent of these patients were well; 18 per cent had active disease; and 12 per cent had died; but in the second group, more than 96 per cent of the patients were well.

In a series of 512 resections, which included 333 pneumonectomies, Davidson et al. (30) had 97 deaths; after pneumonectomy, the mortality rate was 20.7 per cent; after lobectomy, 17.8 per cent; and following segmental resections, 10.7 per cent. They reported that 90 per cent of the *living* patients had inactive disease. Comparing the results in patients with different types of lesions, Decker et al. (16) showed that after resection of open cavities in patients with positive sputum, the disease became inactive in 78 per cent; in those with open cavities and negative sputum, 97 per cent became inactive; and when resection was performed for closed cavities and negative sputum, satisfactory results were obtained in 98 per cent.

Falk (31) reported a follow up on 93 per cent of 310 patients upon whom resection had been performed. He found that 97 per cent had sputum conversion.

Chamberlain (32), in a series of 300 patients upon whom segmental resection had been performed, reported that 281 patients were well; ten patients had active disease; and there were nine deaths. In 200 consecutive resections, Sze et al. (33) reported that 161 patients were well; eighteen had remained hospitalized; and five had active tuberculosis but were at home. There were seven postoperative deaths and four late deaths. Five were lost to follow up.

Kraan (34) reported 252 good results in 260 segmental resections. Eerland and Seghers (35) performed 300 segmental resections on 285 patients from 1949 to 1953, and they reported six bronchopleural fistulas and empyemas and thirty-three reactivations or spreads; 97.1 per cent had negative sputum and 90 per cent were able to work. Storey and Rothmann (36), in a series of eighty-eight segmental resections, reported three deaths; and 95.2 per cent of the patients were clinically well.

Eerland (37) also reported on a larger series of resections which apparently included the segmental resections cited previously. In a ten-year period, he

performed 790 resections and reported the results in 745 (204 pneumonectomies, 217 lobectomies, and 324 segmental resections). There was a postoperative mortality rate of 2.1 per cent; there were seventeen late deaths. Of 249 patients on whom there was a follow up of two years or more, sputum conversion had occurred in 87.1 per cent; twenty-five had died.

Forsee (38) reported the one- to five-year follow-up results of resections for 221 localized necrotic lesions. Included in this group were fifty-four tuberculomas, ninety-six nodular lesions, two poorly circumscribed lesions, and sixty-nine cavitary processes. Follow-up on 217 patients showed that 207 (93.6 per cent) were well. Good (39) reported excellent results in a group of fifty-one patients who undoubtedly had severe extensive disease, for forty-six required pneumonectomy. There was a 12 per cent mortality rate, but 85 per cent had negative sputum.

Semb and Hjort (40), in a series of 267 patients upon whom resection was performed, reported cures in only 62 per cent; and Efskind et al. (41), in a series of 500 resections, reported that 75 per cent of the patients had negative sputum on follow-up examination.

King (8) has recently reviewed the results of treatment of pulmonary tuberculosis in the Veterans Administration Hospitals. During the past three years, there were 3,840 resections, 1,132 performed within the last year. Since 1953, the incidence of pneumonectomies dropped from 11 to 5 per cent and lobectomies from 41 to 36 per cent, while segmental resections increased from 48 to 59 per cent. Pneumonectomy was followed by sputum conversion in 77 per cent of the patients; after lobectomy, it was 93 per cent; and following segmental resection, it was 92 per cent. The mortality rate over a period of three years was 13 per cent for pneumonectomy and 5 per cent for lobectomy. In the past year, the mortality rate for segmental resection was but one per cent. In the pneumonectomy group, the complications were as follows: fistula in 14 per cent; empyema, 21 per cent; and spread, 3 per cent. In lobectomy there were fistula in 6 per cent; empyema, 5 per cent; and spread, one per cent; and in segmental resection, fistula in 7 per cent; empyema, 4 per cent; and spread, one per cent.

In addition to the immediate and interval results of resection for pulmonary tuberculosis, the relapse rate is of importance in estimating the value of the procedure in relation to other forms of therapy. Various statistics on this phase of follow up are appearing in the literature.

In a series of 101 patients, Geake and Young (42) analyzed the prognosis for the contralateral lung following resection. Of fifty-one patients with no preoperative contralateral disease, two showed unsatisfactory changes postoperatively. Of twenty-two patients who had active contralateral disease during the twelve-month preoperative period, six had unsatisfactory changes; and of twenty-eight patients in whom the contralateral lung was static before operation, three showed postoperative changes.

Schlosser and Jarvis (43) reported on 404 patients upon whom resection had been performed between 1946 and 1951. There were 160 pneumonectomies and

244 lobectomies. There were twenty-one postoperative deaths and thirty-three late deaths. Of twenty-seven patients who were readmitted because of a relapse, sixteen were discharged with negative sputum after another course of drug therapy. Fifteen of these relapses had occurred within the first two postoperative years. Falk and Tucker (31) reported that 3.2 per cent of their series of 310 patients had a relapse following resection.

The Bulletin of the International Union Against Tuberculosis has published ten papers presented at a recent symposium on the "Relapse Rate After Pulmonary Resection" (44). This compilation comprised reports on resections performed in France, Holland, Belgium, and Switzerland between 1948 and 1954. The relapse rates are given in Table I. These figures show that after seemingly good results following resections, relapses occur in approximately 7 per cent of the patients; the relapse rate ranges from 8.7 per cent following lobectomy to 5.5 per cent after segmental resection.

Practically all of the authors who contributed to that symposium agreed that the relapse rate is dependent upon the severity of the disease at the time of operation, the amount of residual disease in the lungs, and the duration of pre- and post-operative treatment. They do not feel that overdistention of the remaining pulmonary tissue is an important factor and, therefore, do not advocate thoracoplasty for the prevention of overdistention.

Patients upon whom bilateral resection has been performed have been included in most of the large series reported in the literature. Almost all of these bilateral procedures have been staged operations but, recently, Shumway et al. (45) reported three simultaneous bilateral resections of the upper lobes. These were performed upon psychotic patients and were deemed indicated to avoid the need for more than one operative procedure. Eerland and Kraan (46) reported twenty bilateral resections, with 100 per cent sputum conversion. Lowell and Conklin (47) reported a series of seventeen patients upon whom bilateral resection had been performed; in 65 per cent the disease was arrested.

Surgical collapse procedures were rarely used in children because of the marked deformities which occurred. Since pulmonary resection for nontuberculous diseases caused little disturbance of pulmonary function or deformity after operation, and the procedure was well tolerated, resection for tuberculosis has been performed by a number of surgeons.

In a recent report by Rubin and Mishkin (48), they cited five pneumonectomies, nineteen lobectomies, and four segmental resections performed upon twenty-eight patients ranging in age from seven to sixteen years. There were two postoperative deaths. Follow up on the remaining twenty-six patients showed that twenty-five were well from six to thirty-six months after operation. Previous to this report, there were a few publications on resectional therapy in children. Ross (49) reported five pneumonectomies and seven lobectomies performed upon twelve patients under fifteen years of age. A follow up of from several months to two years showed that one patient had a late reactivation of contralateral disease, but the other eleven were well and had negative sputum.

TABLE I

Author	Total	Relapse	Pneumonectomy	Relapse	Lobectomy	Relapse	Segmental Resection	Relapse
Kraan	406	40	64	3	138	18	204	17
Berard	1400	101	533	33	731	61	136	7
Rink	563	21	—	—	—	—	—	—
Winter & Pannier	221	23	111	15	92	7	18	1
Nuboer	1051	59	141	7	440	34	470	18
Mathey & Duplay	308	28	51	9	115	12	142	7
Joly & Tobe	399	29	—	—	—	—	—	—
Hirdes	700	50	—	—	—	—	—	—
Gilbert	22	2	—	—	—	—	—	—
Naef & Rodel	236	22	38	2	148	13	50	7
Total	5306	375 (7.0%)	938	69 (7.3%)	1664	145 (8.7%)	1020	57 (5.5%)

Levitin and Zelman (50) reported three good results in four pneumonectomies in children, and Botelho et al. (51) also reported four pneumonectomies in children ranging in age from eight to thirteen years.

Resectional therapy for childhood pulmonary tuberculosis is apparently quite popular in France. Santy and Berard (52) have reported 123 resections upon children of from two months to fifteen years of age. Mathey (53) has reported 112 resections in children, fourteen of whom were under eighteen months of age. The mortality rate in these infants was 36 per cent. In those older than eighteen months, the mortality rate was only 3 per cent. Eleven children upon whom pneumonectomy was performed were well three years after operation.

Pregnancy is not a contraindication to excisional surgery for pulmonary tuberculosis. Wilson et al. (54) states that it may be performed during the first six months. Marmet et al. (55), Madey and Rzepecki (56), and Corner and Nesbitt (57) have all reported successful resections during pregnancy. Lowell and Conklin (47) reported one bilateral resection during pregnancy; both operations were performed in the second trimester. They have also performed a first-stage resection during the second trimester and the contralateral excision shortly after the puerperium.

THE OPERATIVE PERIOD

It is not within the scope of this paper to present a detailed description of the surgical technique used in performing pulmonary resection. There are many excellent text books and articles on the subject (58–63). More germane is a résumé of the salient points in the pre- and post-operative care of the patient and a discussion of the basic principles to be followed in the surgical procedure.

As has been stated, all patients are given antituberculosis drug therapy preoperatively. This, as a rule, causes a regression of the acute symptoms, a lo-

calization of the disease, a diminution in sputum, a notable weight increase, and a marked improvement in the general condition. Nevertheless, we must not lose sight of the fact that we are dealing with a chronically ill individual and it is, therefore, of great import that the status of the patient be carefully evaluated before operation.

Anaemia, when present, must be corrected. Blood volume is sometimes below normal and must, therefore, be measured. Blood proteins should be checked and any possible bleeding tendency corrected.

The sputum volume is usually small under drug therapy, but should it be copious, a short course of antibiotics may lessen it.

It is not necessary to perform bronchospirometry on all patients, but when there is any doubt as to the pulmonary function, especially in the elderly or emphysematous, it is important that adequate pulmonary function tests be made. The function of the contralateral lung must always be tested when pneumonectomy is contemplated.

Bronchoscopy should be performed so that the status of the bronchi is ascertained. The presence of active endobronchial tuberculosis or of healed strictures may determine the operability and the extent of resection required. In selected cases, bronchography may be necessary; it can be performed without fear of complications (64).

Shortly before operation, both lungs should be examined by means of conventional roentgenograms and planigrams to make sure that the extent of the disease has been correctly ascertained.

In the elderly patient, it is necessary to investigate the renal and cardiac status by means of the standard examinations.

It is of the utmost importance that the anaesthetist be one trained in the problems of thoracic surgery. In the majority of cases, inhalation intratracheal anaesthesia is the procedure of choice. The use of the various inhalation anaesthetics, as well as intravenous preparations and the curare drugs, must be left to the good judgment of the anaesthetist who, however, must work as a team with the surgeon during the operation. The combatting of acidosis and hypoxia, as well as the mechanical cleansing of the airways, are problems which should be handled by specifically trained personnel. Should there be secretions within the bronchi at the close of the operation, immediate bronchoscopy must be performed. Various machines have been devised for controlled respiration; these are beneficial.

Blood in sufficient quantity should be at hand to take care of any emergency which might arise during the operative procedure. If the facilities for accurate determination of the blood loss are available, then an equal amount should be replaced during the operation. If measurement is not possible, the amount of loss should be approximated, and replacement made.

The position of the patient on the operating table is not of importance. In the early years, when resections were performed in the presence of a large amount of richly bacillary sputum, the prone position, as advocated by Overholt (65), was a distinct advantage. Many surgeons still prefer this technique, but both the lateral position and the supine position for anterior approach have many proponents.

The postoperative care of the patient is extremely important and may be the determining factor in the success of the operation. When a lobectomy, a segmental resection, or a wedge resection is performed, catheters (usually two) are inserted into the pleural cavity at the close of the operation. They are attached to a standard, underwater, suction drainage system. By this means, the remaining lung tissue is expanded to fill the hemithorax; this will close off alveolar air leaks and approximate the lung to the chest wall. The early, complete reexpansion of the lung is of utmost importance in preventing a postoperative bronchopleural fistula and empyema, two of the most common and serious postoperative complications.

Following pneumonectomy, the thorax is usually closed without drainage. In selected cases, a small catheter is inserted, to be used if equalization of intrapleural fluid or air pressure be necessary.

Postoperatively, the bronchial tree must be kept patent. Deep breathing, forced coughing, and changing the position of the patient are important. Intratracheal aspiration should be performed as often as needed. For this, a catheter is inserted through the nose, as described by Haight (66). Should it not give relief, then bronchoscopy must be performed. If these procedures do not keep the bronchi patent, a tracheotomy is indicated. If paradoxical respiration occurs, it should be controlled by strapping and pressure. Oxygen inhalation should be used whenever cyanosis or dyspnoea is present; and for patients with lowered reserve, it is best to continue its use for a number of days.

Leg exercises and early ambulation are essential as prophylaxis against phlebothrombosis and embolus. Frequent roentgenograms are advisable for they are the only accurate means of determining the intrathoracic status postoperatively.

There are three serious postoperative complications; namely, hemorrhage, bronchopleural fistula, and empyema. In almost every case, there is some postoperative oozing. When drainage tubes have been inserted in the pleural cavity, the amount of drainage which occurs is usually an indication of the extent of blood loss. Blood pressure, pulse, hematocrit, and blood volume determinations should be made until there is stabilization. Blood transfusions may be necessary. Should excessive bleeding continue after operation, the chest should be reopened to secure the bleeding points. Rapid, complete expansion of the remaining lung is the best prophylactic against postoperative bleeding. If blood collects within the pleural cavity, streptokinase and streptodornase should be instilled to liquify the clot (67) but, occasionally, a secondary thoracotomy for treatment of a clotted hemothorax may be necessary.

After a segmental resection or a lobectomy with incomplete fissures, alveolar air leaks occur. As a rule, they close within twenty-four to forty-eight hours, but they may persist longer. Pulmonary expansion aids in sealing them off.

Early bronchopleural fistulas are probably due to poor healing of the bronchial stump. Late occurrences of fistulas may be due to the presence of a postoperative empyema which erodes into the bronchus (68). There are numerous procedures advocated for their treatment. Monod (69) believes in a thoracotomy, and suture of the fistula. Murphy et al. (70) closed sixteen of thirty fistulas by either closed thoracotomy and thoracoplasty or an open thoracotomy with ex-

cision of the remaining part of the lobe or lung. When a fistula occurs, whether after lobectomy or pneumonectomy, a closed thoracotomy must be performed at once. The evacuation of the pleural contents through the bronchus may cause a spread of the disease to other parts of the lung. A large percentage of the postoperative deaths following resection are due to the occurrence of a bronchopleural fistula and empyema.

Empyema occurring after pneumonectomy is a serious complication. If a bronchopleural fistula is present, a closed thoracotomy must be performed at once. A secondary operation in order to resuture the bronchus may be attempted. Cauterization of the fistula with sodium hydroxide has been used. An extensive thoracoplasty is usually required for obliteration of the pleural space.

The question of overdistention of the remaining lung tissue after pulmonary resection has given rise to considerable discussion. There were many who believed that it was a dangerous condition and that this overdistention was a factor in later reactivation. They recommended a tailoring thoracoplasty, concomitant with a lobectomy of the upper lobe, and with a pneumonectomy (71–76). On the other hand, in recent years, the tendency to perform concomitant or later thoracoplasties has lessened.

As has been stated, it is of tremendous advantage to have the remaining lung tissue fill the hemithorax immediately after lobectomy. If, at the time of operation, it is thought that this might not occur, it is advisable to perform a small rib resection to decrease the size of the hemithorax. Miscall (77) has described a pleural tent for this purpose. Cotton and Paulsen (78) have used lucite spheres. Following a pneumonectomy, various methods other than thoracoplasty have been suggested to keep the mediastinum in the midline. Pneumothorax, oleothorax (79), lucite spheres (80), and plastic sponge have all been recommended for this purpose. Gaensler and Strieder (21) have shown that overdistention does not cause emphysema up to two and one-half years postoperatively in the young patient; in the elderly, progression of emphysema does occur.

SUMMARY

Although resectional therapy for pulmonary tuberculosis has very quickly superseded the various forms of collapse therapy, it is still too early to evaluate long-term results. The early results have been excellent; but in a chronic disease such as tuberculosis, a longer period of follow up is necessary. The great variance in the results reported in the literature is undoubtedly due to the type of disease for which operation is performed. When segmental resections are performed for pathologic conditions that have reached the "target point," it is not surprising that the good results uniformly range around 95 per cent. On the other hand, the results of resections for more severe types of disease are not much better than were those obtained with a thoracoplasty in the years before the advent of streptomycin. Many of the patients who today undergo segmental resection would have been discharged from the sanatorium, in previous years, with their disease classified as arrested.

There are surgeons who still perform a thoracoplasty for the same type of cavitary disease of the upper lobe that yielded excellent results when thoracoplasty was the procedure of choice. With the addition of the antituberculosis drugs, present day results would naturally show a marked improvement. The relapse rate after thoracoplasty is known because many large series of cases have been followed over a long period of time (81–85). The early good results have been well maintained over many years of observation. The relapse rate after resectional therapy will have to be observed carefully over the coming years, for it will be an indicator to prove or disprove the long-term value of excision in the various types of pulmonary tuberculosis.

It must not be forgotten that resection, just as collapse therapy was before, is only a part of the entire course of treatment of pulmonary tuberculosis. It is indeed the rare case in which one can feel that the surgeon has removed all of the disease. The very fact that tubercle bacilli can be cultured from resected nodules must mean that there are viable organisms in the diseased areas left behind. There is a growing belief that antituberculosis drug therapy must be continued for much longer periods postoperatively than has been done before. Only with extended postoperative treatment can we hope to combat these potential sources for relapse.

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PRESENT STATUS OF COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS

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In view of the changing concepts in the treatment of pulmonary tuberculosis due to the use of antimicrobial drugs and the introduction of resectional therapy, a re-evaluation of collapse therapy is indicated at this time. All surgical collapse treatment is an adjunct to good medical therapy and can be divided into temporary [pneumothorax; phrenic crush, with or without pneumoperitoneum; extra-pleural pneumothorax; intra-pleural pneumonolysis (open or closed); cavity drainage (open or closed)] and permanent measures [phrenic exeresis; extra- (supra-) periosteal pneumonolysis and plombage; extra-pleural pneumonolysis and plombage; suture constrictions; thoracoplasty; and various combinations of plombage and thoracoplasty]. The indications, general technique and results of some of these procedures will now be discussed.

ARTIFICIAL PNEUMOTHORAX

Combined with antimicrobial drugs, artificial pneumothorax will give better results and fewer pleural complications than when used alone. The indications are (a) pneumonic type of disease with or without cavitation in the upper part of the lungs including the apical segment of the lower lobes where there is a danger of residual or persistent cavitation after drugs and bed rest, (b) extensive disease or an awkwardly placed area of cavitation which has developed in a fairly recent area of pneumonic disease. Scadding (1) reports 457 patients with unilateral cavities treated by pneumothorax with 69 per cent surviving eight years. The closure of the cavity is all important. Crafoord (2) in discussing temporary collapse expresses the idea that it may prevent relapse and recent lesions are an ideal indication for temporary collapse after they are stabilized. A small localized area of destruction (preferably upper lobe), small thin walled cavities, and acute exudative disease after stabilization are all good for temporary collapse. He advises extra-pleural pneumothorax if intra-pleural is inadvisable. Paul (3) suggests evaluation of artificial pneumothorax two to three months after all adhesions are sectioned and to be abandoned in favor of resection if patients are sick, febrile or if there is an elevation in sedimentation rate, positive sputum, effusion on x-ray, or evidence of cavitation, atelectasis, pleural thickening or mediastinal displacement. Tørning (4) uses pneumothorax in fairly recent cases with limited destruction and moderate total volume. In 109 pneumothoraces with drugs but no pneumonolysis one empyema and one clear effusion resulted. In 133 with pneumonolysis there resulted one case with empyema and thirteen with clear effusions. He tries pneumothorax and drugs for a few months for cavity closure. If adhesions or effusions interfere he expands

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the lung and uses extra-pleural pneumothorax. Of 119 extra-pleural pneumothoraces six per cent developed empyema.

PHRENIC CRUSH

Phrenic crush for temporary paralysis of a diaphragm may be used as an adjunct in the medical treatment, at the time of abandonment of pneumothorax, post-thoracoplasty, post-pneumonectomy, post-pleurectomy in post-operative period following lower lobe lobectomy (5) and combined with pneumoperitoneum in lower lobe disease and lower lobe cavity. The chance of the paralysis becoming permanent is always present and greater when combined with pneumoperitoneum. The only indication for permanent paralysis is at the time of pneumonectomy.

PHRENIC CRUSH AND PNEUMOPERITONEUM

Phrenic crush and pneumoperitoneum is useful for relaxation of the lower posterior portion of the lung as an adjunct to antibacterial drugs when the distribution of the disease is such that surgical collapse or resection involving the upper lobe is unlikely. Indications for its use include (a) acute disease of the lower lobes, (b) generalized, predominately unilateral disease to help drugs in the prevention of cavitation. Although pneumoperitoneum and phrenic crush is safer than pneumothorax from the standpoint of pleural complications, its use is fairly limited at the present time.

CLOSED PNEUMONOLYSIS

Closed pneumonolysis (Jacobeus procedure) is being done, but to a lesser degree than previously. Goldberg (6) reports 52 patients with unilateral disease with 47 excellent or good results, and 26 bilateral cases with 23 excellent or good results. Conversion of sputum occurred in 31 of 52 unilateral and 17 of 26 bilateral cases. One patient died of empyema, and one died of spontaneous pneumothorax. When antimicrobial drugs are used with the Jacobeus procedure Beatty (7) reports a 1.4 per cent incidence of effusion whereas without drugs the incidence was 21.6 per cent. In patients with disease in the upper parts of the lungs, including the apical portion of the lower lobe of pneumonic type with or without cavitation or with extensive disease or awkwardly placed cavities in area of pneumonic disease of fairly recent origin, pneumothorax and drugs are of value.

OPEN PNEUMONOLYSIS

Open pneumonolysis is rarely used. If a closed pneumonolysis has failed and other forms of surgery including thoracoplasty are contra-indicated it may be considered. Mortality is five to ten per cent and cavity closure 50 per cent with 70 per cent improved as reported by Allbritten (8).

CAVITY DRAINAGE (Mondaldi)

Where extensive cavity is present in very poor risk patients, cavity drainage is indicated. Following closed cavity drainage, thoracoplasty is done if the con-

dition of patient improves. Where thoracoplasty has already failed, open cavity drainage followed by muscle flap for closure is indicated.

EXTRAPLEURAL PNEUMOTHORAX

LeFoyer (9) reports results of 282 extrapleural pneumothoraces used for (a) unilateral, usually apical, slight cavities, (b) large apical cavities (two to four centimeters in diameter) bi-polar or bi-apical, (c) unilateral opaque lung, massive cavity or bilateral disease with extensive cavitation. There were 47 deaths, favorable results in 213, 195 were cured, 49 per cent lived normal lives and 44 per cent had limited activity. One can by extra-pleural pneumothorax effect a substantial collapse without deformity in a single operation with minimal shock and slight interference with function. Streider and Gaensler (10) consider extra-pleural pneumothorax unsuitable as a permanent collapse measure because of the danger of losing the space, late infection and frequent refills. Sub-pleural or peripheral cavitation is an absolute contraindication. Of 323 primary surgical procedures for cavitary pulmonary tuberculosis 15 per cent had extra-pleural pneumothorax. Their indications are (a) far advanced bilateral tuberculosis in low pulmonary reserve patients, (b) contra-lateral cavitation which may require contra-lateral surgery, (c) active hemorrhage in spite of pulmonary insufficiency and (d) where a good cosmetic result is important. Sixty-eight per cent showed bacterial conversion by extra-pleural pneumothorax alone and 87 per cent with other surgical measures added. One year follow-up showed 84 per cent home and well after extra-pleural pneumothorax alone or after secondary thoracoplasty or resection. Therefore it is ideal for poor risk patients with pulmonary insufficiency. Extra-pleural pneumonolysis may be used as a first stage followed by thoracoplasty omitting the first rib and transverse processes. The extra-pleural lining is used as a flap to hold the lung down. In good risk patients with unilateral disease extra-periosteal plombage or resection is as good or better than extra-pleural pneumothorax, with fewer complications.

PLOMBAGE

Plombage to maintain collapse is an extremely old procedure. Fat, muscle, air, bone chips, paraffin, gauze, rubber balloons, bismuth carbonate and numerous other substances have been employed but were usually abandoned due to infection or severe reactions. In recent years, due to the use of plastic materials, plombage has become very popular and is employed more frequently than most collapse measures. In addition, the loss of function following extra-periosteal plombage as compared with staged thoracoplasty and extra-pleural pneumothorax was studied by Watson and Gaensler (11) who showed that the loss of function was twice as great in staged thoracoplasty as compared with extra-periosteal plombage. Extra-pleural pneumothorax showed minimal loss of function. The loss of function in all three procedures was proportional to the extent of disease and previous collapse on the contra-lateral side. The extent of decostalization was closely related to the loss of function with resection of anterior rib segments contributing more loss than posterior segments. The new materials

include Lucite (methyl methacylate), polystan (spongostan), polythene and polyvinyl. They are used for temporary and permanent collapse, and are also used as extra- or intra-pleural prostheses following resection therapy. Laird (12) favors polystan which is a boilable sponge. If there are pronounced peri-pleural adhesions or superficial apical cavitation the material is placed in an extra-periosteal position without apicolysis. In the other cases an apicolysis is done and the sponge placed in an extra-pleural space. The sponge permits granulation tissue to grow in and fix it in place. If one desires to remove the sponge it must be wrapped in polythene film but this in turn causes fluid. In 74 operations there were no deaths, three positive sputums and one space infection. It is used in bilateral surgery, bilateral apical disease and small apical cavity where thoracoplasty would be too extensive a procedure. Gale (13) reports the use of polyvinyl sponge (ivalon) as an intra- and extra-pleural prosthesis following resection surgery in pulmonary tuberculosis. It can be inserted at operation or as a second procedure instead of thoracoplasty. This material could be tried for extra-pleural plombage as a primary procedure. Adelberger and Serdarusitz (14) advocate pneumonolysis with plastic prosthesis. They do a sub-periosteal resection of one to four ribs and simultaneous extra-pleural pneumonolysis using polystan over the preserved intercostal muscles and periosteum. In 70 cases they report 26 with pneumonolysis and thoracoplasty, 43 pneumonolyses with plastic filling and thoracoplasty, and one extra-pleural pneumonolysis. Nineteen remained positive, one tuberculous infection, one non-tuberculous infection and one broncho-pleural fistula resulted. Two to three years postoperative, 44 were negative, 17 employable and three showed progression of the contra-lateral side.

Late complications from foreign material are to be expected. Hansen (15) advocates polystan instead of Lucite because it is sponge-like and allows ingrowth of fibrous tissue. He used it in extra-pleural, extra-periosteal plombage and for stabilizing the mediastinum after pneumonectomy. In 80 cases of extra-pleural plombage in poorest risk cases, no postoperative mortality or complications occurred. In 12 to 18 months, three of 52 patients followed had staphylococcus aureus space infections and tuberculous infection and bronchopleural fistula occurred in two cases (operative injury). On follow-up 66 per cent were well and sputum negative, 26 per cent had positive sputum and 0.8 per cent died.

In 25 pneumonectomies, prostheses were used to salvage some for later resection or thoracoplasty. Vizcardo (16) also advises apicolysis with plombage in bilateral apical disease even in poor risk patients. In 50 patients, 45 converted sputum and showed improvement, in five sputum was positive, but they were clinically improved. He suggests streptomycin pre-operatively. Infections after plombage were studied by DesForges et al. (17). They took cultures of the subcostal space at the time of conversion thoracoplasty in 32 cases four months after Lucite spheres had been inserted. Nine showed tubercle bacilli on smear and culture and three on culture alone. One patient developed a tuberculous sub-scapular abscess with osteomyelitis of the rib. All these patients had long

courses of streptomycin prior to surgery. Other authors report similar tuberculous space infections in as high as 60 per cent of cases. One should certainly hesitate before leaving prostheses in permanently. Temporary plombage with Lucite prevents re-expansion by stimulating a membrane, prevents adhesions between the scapula and intercostal muscles and keeps the latter approximated to the collapsed lung. These Lucite balls can be removed at the second stage and can be re-inserted at further stages but it is advisable to remove them. Joly (18) reports the use of temporary plombage with Lucite in 52 patients. The effect on the pulmonary lesion was more rapid and more constant, the number of ribs removed less and the deformity due to poor position of scapula avoided. Joly (18) now uses thoracoplasty with temporary plombage in preference to extra-pleural pneumothorax in recent lesions and patients under 45 years of age. Povah (19) reports 43 patients treated by thoracoplasty with temporary extra-periosteal Lucite ball plombage. At the first stage ribs are stripped but not as far anteriorly as for thoracoplasty and balls are inserted and held in place by sutures between the ribs. In three to five months he removes the ribs (not the first) and balls. The scapula does not sink in, transverses proceses and first rib are left intact, and the result is less deformity. In 43 patients, four had bilateral operations, 88 per cent were moderately or far advanced with cavitation, 95 per cent were positive before operation, 60 per cent had contra-lateral disease, 73 per cent had six ribs or less stripped and only five ribs resected, 89 per cent were negative to concentrate and culture following this procedure. There were no deaths, no blocked sputum and no wound infections. In the Overholt Clinic a polyethelene sheet is wrapped around the balls which in nearly all cases are left in. Only two infections have occurred in almost 400 cases. Thoracoplasty combined with subscapular paraffin pack as advocated by Lees (20) is another variation of plombage. He uses a one stage thoracoplasty, removes as many as eight ribs and fills the subscapular space with paraffin. In 235 patients, fluid accumulated three times, the pack was removed in one, there were no spreads. In six months four deaths unrelated to surgery occurred and three died in three months, but only one death was related to tuberculosis (a salvage case). In 116 patients where good results were expected, nine per cent had positive sputum in six months. In 41 patients where only 50 per cent control was expected 63 per cent were negative in six months. In nine far advanced bilateral salvage cases there were five deaths and four positive sputa. This type of pack has merit but a longer follow-up is required. O'Brien et al. (21) consider Lucite plombage thoracoplasty the most useful tool in bilateral surgical problems. They treated 38 patients of which 53 per cent are clinically well and sputum negative, 11 per cent are still salvable, 18 per cent are hopelessly ill and 18 per cent died.

In the type of case being treated by segmental resection, a one stage non-deforming plombage thoracoplasty results in the same conversion rate, less mortality, less morbidity and a lasting cure. Scadding (1) advises extra-periosteal plombage for cavitary disease in the upper third of the lung fields, especially limited disease at the extreme apex. When extensive disease is treated

for three months or more and results in apical cavitation, plombage is indicated. If more extensive disease exists, thoracoplasty is advised and, although there is more deformity, there is less risk from foreign substances. Ten thoracoplasties were done and forty-four plombages. In 58 patients there was one death from plombage, one from thoracoplasty, one late thoracoplasty death from empyema and in one patient disease was still active.

SUTURE CONSTRICTION OF THE UPPER LOBE

Before discussing thoracoplasty I would like to mention briefly the Paulino procedure consisting of suture constriction of the upper lobe. DeCamp et al. (22) used this procedure 34 times in 31 patients, three of whom had bilateral operations. Following a limited rib resection and an extra-facial pneumonolysis concentric purse-string sutures are placed around the upper lobe. It is indicated in bilateral advanced upper lobe disease, unilateral upper lobe disease where contra-lateral side has already had thoracoplasty or resection and in patients with paramediastinal cavities or limited respiratory reserve with unilateral disease. Twenty-five patients were operated upon seven months or more, five are inactive, 13 arrested, with an operative mortality of 5.9 per cent. This procedure may lead to infection and also deformity of the lobe with interference of bronchial drainage resulting in retention of infected bronchial secretion. It needs more study and follow-up.

THORACOPLASTY

In analizing results from thoracoplasty one must always take into consideration the various types of pathological lesions treated, age, type of patient and general condition of patient. The effects of the antimicrobial drugs must be analyzed in reference to the safety of the procedure, extension of indications, especially into older age groups, and changing concepts of when to use resection and when to use thoracoplasty. Thoracoplasty is employed in the treatment of parenchymal disease, pleural disease and the complications of surgery such as empyema and broncho-pleural fistula. Stage thoracoplasty and the Schede type are effective in the treatment of tuberculous empyema, especially of the mixed type. Thoracoplasty is also useful prior to, concomitant with, or subsequent to resectional surgery to reduce the volume of the chest cavity and prevent over distention of the remaining lung tissue. Douglas and Bosworth (23) report 33 patients with pleural problems treated by limited paravertebral, extensive and Schede type thoracoplasty. Fifteen were far advanced, 17 moderately advanced and one minimal. There were no deaths due to progressive pulmonary tuberculosis. Two deaths occurred from cor pulmonale eight and nine years postoperatively. Obrien et al. (21) report on 289 patients operated upon in a five year streptomycin era. In 1947 conventional thoracoplasty was done 23 times, resection eight and plombage thoracoplasty not at all. In 1951, 18 thoracoplasties, 40 resections and 39 plombage thoracoplasties were done. Their results are as follows:

Conventional thoracoplasty	93 cases	83% final conversion to negative sputum
Extra-periosteal plombage thoracoplasty	68 cases	91% final conversion to negative sputum
Extra-pleural plombage thoracoplasty	17 cases	88% final conversion to negative sputum
Extra-pleural pneumothorax	4 cases	100% final conversion to negative sputum
Revision thoracoplasty	1 case	100% final conversion to negative sputum

Of the 93 conventional thoracoplasties, 29 had subsequent resection revisions. The final result of collapse therapy:

Postoperative deaths	1.1%
Late deaths	4.4%
Living	94.5%
Clinically well and sputum negative	90%

Only patients with giant cavity not suitable for resections have conventional thoracoplasty in stages from below up. Lucite plombage thoracoplasty is a most useful tool in bilateral surgical problems. Hughes et al. (24) present results in 111 patients treated by Alexander-type of postapical thoracoplasty from 1947 to 1951 with follow-up to 1952:

Death rate, early	1.8%
Death rate, late	9%
Postoperative spread (after strep)	9% (High)
Late spreads	29.3% (39% now inactive)

(64% of the cases were considered inactive.)

Medical treatment with drugs was carried out for three months, but no drugs were given routinely at the time of thoracoplasty. In 1546 thoracoplasties done between 1948–1953, Bérard (25) reports results in pulmonary and pleural indications. In the first three postoperative weeks total mortality was less than one per cent. He thinks that the danger of fatal postoperative dissemination of tuberculosis is eliminated by the antibiotics. About half of the cases were done in one stage with a maximum of five ribs removed for pulmonary indications, but as high as ten ribs removed in one stage for pleural indications. Pulmonary function studies are not deemed necessary by Bérard (25) and in fact, if done, might deprive certain patients of operation. This is not entirely advisable and pulmonary function tests seem indicated in most, if not all patients prior to surgery. Adie (26) reports results in 334 thoracoplasties from 1932 to 1948. In 1949, 230 were living, 104 dead of all causes, 58 per cent were arrested or apparently cured. Of the 230 living and 12 who died of other causes, 84.3 per cent were arrested or apparently cured of tuberculosis, thus justifying thoracoplasty by late results. Bérard (27) reports a series of 52 patients over 50 years of age prepared with streptomycin and P.A.S. and treated by thoracoplasty. There were 38 complete recoveries, five spreads, eight stabilized with positive sputum and one death. The death occurred among eleven patients in whom Lucite balls were used. In a series of 464 patients between 1938 and 1950, Gontijo (28)

reports 53.1 per cent cured, 21.9 per cent improved, 10.5 per cent unchanged, 11 per cent progressed and 3.5 per cent postoperative deaths. In his latest 200 using antibiotics, 70.5 per cent were cured, 15 per cent improved, 5 per cent unchanged, 7 per cent progressed and 2.5 per cent died (immediate deaths). This author considers thoracoplasty (first rib retained in selected cases) the best procedure for chronic apical tuberculous cavities and finds the results are inversely proportional to the size of the cavity and directly related to location. The Monaldi drainage is used as a supplement for tension cavities. Tørning (4) considers stabilized chronic fibro-cavitary disease in the apico-posterior part of upper lobe including thick walled cavities or extensive necrosis as typical indications for thoracoplasty. He employs drugs preoperatively for two to three months if tissues outside the field of surgery are not severely involved. Laird (29) presents follow-up results (two to eight years) of thoracoplasty in 583 patients with persistent open cavity or active tuberculosis in the upper half of one lung as indications for surgery. He considers thoracoplasty as a stage in the treatment with maximum effort to improve tuberculosis before surgery. Fourteen-hundred-four operations were done and patients were kept in the hospital six months post-thoracoplasty.

After successful thoracoplasty there is a good chance of disease remaining inactive in five out of six patients. One hundred twenty-four were discharged with positive sputum, but lesions improved, 60 per cent became quiescent, 80 per cent could return to work, and mortality was seven per cent. Of the group followed five years 88 per cent were alive, 72 per cent quiescent and 74 per cent working. Of 166 with contra-lateral pneumothorax at the time of surgery 27 had respiratory embarrassment in the early postoperative period and mortality rate was eight per cent. In cases of destroyed lung or stricture of larger bronchi resection is best.

Decision between thoracoplasty and lobectomy or segmental resection in the treatment of upper zone disease is difficult.

Douglas and Bosworth (23, 30) present a ten year follow-up of 238 patients operated upon in the pre-streptomycin and pre-resection era. Thirty-three had pleural problems (negative sputum) including inexpansible lung and empyema of various types. There were no deaths due to progression of pulmonary tuberculosis. In 205 patients with parenchymal disease and positive sputum at or near surgery, there were no cavities in 26, 21 per cent had unilateral disease, 62 per cent had stable contra-lateral disease, 14 had active contra-lateral disease and 70 per cent were arrested at ten years (sputum negative or absent, no cavity on x-ray, reasonable physical activity). Sputum conversion was early, the number arrested was almost constant after the second year and the size of the cavity or age of patient was not significant. Fifteen had relapses mainly in the fourth postoperative year, two died, two were arrested and eleven were active. Fifty per cent of the relapses were due to contra-lateral disease. Thirty-seven patients died in the ten year period; 32 of progressive tuberculosis.

Borrie (31) discusses indications for thoracoplasty in relation to pathological lesions. He recommends it where there is chronic fibro-caseous tuberculosis with

small or medium sized apical cavitation, fibro-sclerotic disease associated with small rigid walled cavities and gross deviation of the mediastinum, to a less degree in cavernous progressive type with thin walled cavities (may require subsequent resection), and bilateral disease, as above, with lesser lesions controlled by pneumothorax. Borrie suggests operation when there is some immunity, normal temperature, normal sedimentation rate and good general condition.

He also suggests thoracoplasty when other treatments fail as manifest by unstable healing with bed rest and drugs and with break-down of the lesions, in apical disease or unsatisfactory pneumothorax (adhesions) and in early primary cases with a thick walled cavity.

Borrie suggests penicillin postoperatively and that streptomycin and P.A.S. be held in reserve even if the patient has been prepared with these drugs. The operative procedure varies according to the pathology. If there is no large apical cavity with marked tracheal deviation, a one stage procedure without apicolysis is done with the removal of seven ribs or less. In the presence of extensive multiple cavitation, a stage procedure with apicolysis and resection of the posterior ribs to the costo-transverse joints is done and in order to keep the lung in place, a polythene bag with Lucite spheres or musculo-osseous flap is used.

Thoracoplasty with apicolysis can close 80 per cent of tuberculous cavities, collapse a tuberculous lesion and put the lobe in a more favorable position for healing but does not cure immediately. Aufses and Harte (32) present results 11 to 16 years after thoracoplasty as final follow-up of 90 patients reported in 1941. Of 64 arrested, 57 remained arrested; of 16 with positive sputum, six had late conversion, one was arrested, nine had active tuberculosis. Early favorable results tend to persist. They conclude that with antibiotics, thoracoplasty on a selected group should give a very high percentage of lasting good results. Of the procedures employed in the surgical treatment of tuberculosis, thoracoplasty is still used frequently (30.3 per cent in 1944–45, 28.7 per cent in 1951–52). Pulmonary resection increased from 2.2 per cent in 1944–45 to 22.4 per cent in 1951–52 and Lucite ball plombage not used in 1944–45, was employed in 24.8 per cent in 1951–52. Phrenic crush and pneumonolysis both were used sparingly in later years. If disease is not too extensive plombage and resection are favored. Solid lesions or major bronchial disease contraindicate collapse therapy. The overall mortality was 4.8 per cent for thoracoplasty with a cure rate of 56.7 per cent. Thoracoplasty is indicated if the patient can stand a major operation and the lesion is suitable for collapse therapy (does not reach the base of the lung), after closed cavity drainage, heroically where resection, etc., is contraindicated.

Disadvantages of thoracoplasty are deformity, necessity of multiple stages, impairment of respiratory function and paradoxical motion in the postoperative phase. Trapp (33) has suggested a one stage thoracoplasty using an adhesive hemi-cast. Elastoplast and plaster are employed, as many ribs as desired are removed, minimal paradoxical motion occurs, no spreads result, and collapse is more complete than by stage procedures. Wilson (34) presents an excellent discussion on collapse therapy which in summary relates that it is contraindicated

when there is inadequate cardiac or respiratory reserve, another uncontrollable or fatal disease, or cavitation other than post-apical, basal disease, a solid lesion, bronchiectasis or destroyed lung. He states that collapse therapy is indicated if there is residual cavitation under four centimeters in size in the apical posterior segments of the upper lobes after medical treatment or if drug resistance or contra-lateral disease may forbid resection.

Staged thoracoplasty including the first rib and transverse processes was practiced prior to 1950. Since 1950 it has been abandoned in favor of extra-periosteal plombage thoracoplasty using Lucite spheres wrapped in polyethylene to prevent migration. After four months, if the sputum is negative, the plombage and de-periostealized ribs are removed, but not the first rib or transverse processes. If the sputum is positive, resection and thoracoplasty are done. In 140 patients, 120 were successful and 20 failures required resection. There were no deaths from surgery or tuberculosis, but two from coronary disease and one from metastatic carcinoma. Of the 137 living, 127 are completely well. Extra-pleural procedures are suggested for young patients (4). Previously extra-pleural pneumothorax was done, but now resection or extra-periosteal plombage and delayed second stage thoracoplasty is advocated. In 19 poor risk patients with marginal respiratory function, extra-periosteal plombage thoracoplasty was done. One can leave the thoracic cage intact and make it reversible by removing the plombe, or remove the plombe and do a thoracoplasty preserving the first rib. Extra-periosteal procedures are replacing the extra-pleural operations. Between 1947 and 1954, 269 cases (64 per cent before chemotherapy) were treated initially by collapse therapy and resulted in:

0.7%	Post-operative deaths
5.5%	Late deaths
93%	Living survivors
88.5%	Well with negative sputum

In 163 cases treated by procedures other than staged thoracoplasty, there were no postoperative deaths, three late deaths, 98 per cent living, and 93 per cent well. A lesion adequately controlled by collapse has an equally good prognosis as those resected.

SURGICAL TREATMENT OF THE OLDER AGE GROUP

Seventy patients over 50 years of age in the O'Brien series (21) were treated by surgery. Results of surgery in patients of 50 years or over are not as good as in younger ones, but surgery is of definite value and not too hazardous (29). Beaconsfield (35) reports 55 patients (1933–1949) over 50 years of age treated by thoracoplasty, 24 of whom had far advanced and 31 moderately advanced disease. Four died within four months as a direct result of surgery, 29 had conversion and cavity closure, ten occasional positive, three improved but cavity open and sputum positive and nine failures. Sixty-seven per cent of those who survived operation resumed useful work. Bérard (27) also reports a series of 108 cases over 50 years of age treated by various measures including thoracoplasty. As a

result of these reports and others, one is led to the conclusion not to accept too readily the "good chronic", but consider more of these older patients for definitive treatment by surgical collapse. Paine (36) shows the changing trends in surgical therapy of pulmonary tuberculosis. Whereas in 1948 thirty-three patients had collapse therapy and three resections, in 1953 nine had collapse therapy and 53 resections. As a result of antibiotics and better anaesthesia, apical or five rib thoracoplasty for residual foci, is now replaced by resection. The results of unilateral collapse in 137 patients were 84 per cent sputum conversions, three per cent post-operative complications, six per cent late relapse, five per cent late deaths (five of seven tuberculosis deaths). Of 95 per cent living, 82 per cent are well with negative sputum, 8.5 per cent positive or unstable, and two per cent hopelessly ill. Results in bilateral surgery were comparable, but not as good. He considers extra-periosteal plombage with paraffin rather than Lucite as the best procedure. However, resection was the most commonly practiced operation in 1953. Fifty-four were performed as compared with nine collapse operations. He advocates the use of collapse early when bronchial drainage is good and the cavity might collapse easily and heal.

DISCUSSION

Although artificial pneumothorax probably can be induced with greater safety in conjunction with antimicrobial drugs, it is being used less and less in this country. It still is being used to a fair degree abroad. Extra-pleural pneumothorax is advocated and practiced if the intra-pleural route is inadvisable or already has failed. Phrenic crush combined with pneumoperitoneum has been abandoned by most workers except for very limited indications. Closed pneumonolysis, although safer with antimicrobial drug protection, is employed rarely. Cavity drainage is limited in its use and usually is followed by a thoracoplasty or other surgical procedure.

Plombage with the newer plastics has become very popular. The extra-pleural placement has been discarded in most cases for an extra-periosteal location of the plombe. There is still a considerable difference of opinion as to whether the plombe should be temporary or permanent. The combination of plombage with delayed modified thoracoplasty is frequently used in various clinics. The specific material to be used in plombage varies with individual preferences and whether the procedure is to be temporary or permanent. Infections following plombage have been reported and long term follow-up of permanent plombage is necessary to accurately evaluate this problem.

The Paulino procedure of suture constriction requires more cases and more long term follow-up before definite conclusions concerning its efficiency can be stated.

Thoracoplasty for pleural indications has a real place in the surgical treatment of tuberculosis. With the more universal use of antimicrobial drugs, and the use of pleurectomy, decortication and pleuro-pneumonectomy, the necessity for thoracoplasty may be decreased in future years. The reports on conventional thoracoplasty for pulmonary indications show that this procedure is being re-

placed by resection or extra-periosteal plombage combined with a modified type of thoracoplasty. Although long term follow-up studies show clearly how effective and permanent thoracoplasty can be, the disadvantages have forced most surgeons to abandon this procedure in favor of other surgical measures. In the next few years after the long term studies of newer methods (resection, plombage with or without thoracoplasty) are compared with the results of thoracoplasty, one will be able to evaluate better the comparative methods.

Definitive collapse measures have been successful in the older age group and one should not withhold surgery merely because of age. A "good chronic" is a constant source of tubercle bacilli and should be converted by surgery if possible.

SUMMARY

A review of the various types of collapse therapy in the new drug era is presented, including indications, general technique and results both short and long term. Definite trends are noted, unsolved problems discussed and suggestions made. A study similar to this should be repeated in five years for re-evaluation of the problem in the light of long follow-up of this newer surgical approach to pulmonary tuberculosis.

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TUBERCULOMA OF THE LUNG

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INTRODUCTION

The term "tuberculoma" of the lung has its origin in the early days of the study of the pathology of tuberculosis. At that time it was used to designate a gross mass of tuberculous tissue resembling a tumor. Involvement of the lung as well as the spleen, brain, choroid of the eye, liver, and other organs has been noted. As with many other early descriptive terms, its euphonious character and its convenience have caused it to become ensconced in everyday usage despite subsequent studies which elucidated its varied pathology and pathogenesis.

With the widespread use of mass radiography of the chest, advances in thoracic surgery, and the advent of effective antituberculous chemotherapy, it has assumed a new clinical significance. It has been the subject of many papers in the past two decades culminating in a detailed and thorough monograph by Hillerdal (1) from which much of the material herein included has been taken.

DEFINITION

With this increasing knowledge have come many attempts to redefine the term; indeed each author begins his discussion with what he believes to be an all-inclusive definition. Since there is no uniformity, it is proper to begin this paper also with a definition to eliminate any prejudicial notions and to allow for the broadest possible concept.

A tuberculoma can be regarded as a sharply circumscribed, dense, rounded mass of tuberculous tissue within the lung, visible radiologically. Without reference to its radiologic appearance, the term would have no clinical significance today as it is only through this modality that such a lesion can be discovered, observed, and studied with a view to future management.

Its minimum size is generally considered to be one centimeter in diameter, but variations in minimum size of from 0.5 to 2.0 centimeters have been mentioned. Its shape is rounded, oval, or irregularly rounded. Its border is sharply defined. This, according to Hillerdal, is an important feature, as it excludes from consideration localized areas of tuberculous infiltrations such as bronchopneumonia, minimal lesions, etc.

PATHOLOGY AND PATHOGENESIS

Pathologically tuberculomas can be divided into three types.

I. Tuberculomas developing from the healing of cavities. This is the so-called inspissated or "blocked" cavity. As has been shown by Coryllos (2) and others, one of the methods of cavity healing is by bronchial occlusion. If such occlusion occurs after a tuberculous cavity has emptied its contents into the bronchial

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tree, the air in the cavity is absorbed, the walls approximate each other, and healing takes place by contraction with the formation of a stellate scar. Such a scar may show characteristic tuberculous tissue but caseation and necrosis are minimal or strikingly absent. If however bronchial occlusion occurs before the cavity has shelled out, the caseous contents remain in situ, the air is absorbed and a characteristic dense circumscribed shadow can be seen on x-ray. The evolution of such a shadow can be traced on serial roentgenograms. It should be emphasized that bronchial occlusion may not necessarily be due to actual tissue growth but rather plugging of the lumen by inspissated caseous contents. This explains the not infrequent re-appearance of cavitation within the previously solid mass. In such instances the characteristic appearance of the cavity on x-ray is small, thick-walled, eccentric, cleft-like, or slit-like. This is the situation which obtains when a tuberculoma is accompanied by a positive sputum. Occasionally, if all the caseous contents are expectorated, a thin-walled cavity results. The clinical significance of this behavior will be discussed below.

II. The second group of tuberculomas develop from more or less diffusely defined caseous bronchopneumonic lesions which have not cavitated, and in which tuberculoma formation represents a form of healing. Such lesions include minimal foci or Assmann's foci. With healing there is limitation of peripheral spread, sharp circumscription of the border, increased density, regression in size from the original areas of bronchopneumonia, and sometimes calcification. Grossly and radiologically this type of tuberculoma may be indistinguishable from that of the first group. Histologic techniques for elastic tissue will show the ghosts of alveolar lung structure within the center of the mass, indicating that cavitation has never occurred.

III. The third group consists of tuberculomas which arise by confluence of small patchy infiltrations occurring in an area previously free of disease. This type has the concentric laminations—at times calcified—around a central necrotic core. The laminated structure is believed to be due to appositional growth in periods of activity followed by remissions with fibrous tissue deposition. This last group presents a clinical and radiological course of progression of disease as contrasted with types I and II which signify healing.

ROENTGEN FEATURES OF TUBERCULOMA (1, 3–9)

1. Calcification. This is generally regarded as a diagnostic hall-mark of a tuberculoma. The presence of any type of calcification rules out a malignant lesion unless by actual growth a cancer has engulfed a pre-existing neighboring area of calcium deposition in the lung; a highly unusual and most unlikely happenstance. Calcification in the tuberculoma may take several forms:

a. It is usually central, distributed as flecks or spicules in small lesions.

b. It may be peripheral in larger masses.

c. It may be scattered throughout the lesion.

d. It may take the form of concentric laminations or rings; an uncommon but specific finding.

Other lesions resembling tuberculomas in which calcification is found are

hamartomas (where it may be stippled), histoplasmosis, silicotic nodules, and rarely in bronchial adenomas. Calcific deposits may be discovered on conventional films, Bucky films, or often only on tomograms. In any event, the discovery of calcification in a circumscribed mass in the lung almost certainly rules out the presence of a malignancy. If serial films are available, the gradual deposition of calcium can sometimes be noted. Clinically the presence of calcification is usually but not necessarily synonymous with inactivity.

2. Cavitation. This feature is generally not regarded as a characteristic of tuberculoma. However, in the literature it is commonly mentioned. It takes the form of a small irregular rounded or slit-like cleft. Thick walls are common. The appearance of a thin-walled cavity at the site of a previously solid mass indicates the excavation of an inspissated or "blocked" cavity. Evidences of cavitation, like calcification, can often only be demonstrated on tomograms. Clinically, the tuberculoma associated with an occasional positive sputum is of this variety (in the absence of active lesions elsewhere in the lungs).

3. Satellite shadows. The presence of small satellite shadows in the vicinity of the mass is another feature strongly indicative of tuberculoma. Again, sectional radiography may be the only way to demonstrate them. Enlargement of the tuberculoma to engulf these shadows is the form of appositional growth referred to in the discussion on pathology.

4. Streaky shadows. Shadows extending from the mass toward the hilum are not uncommon in tuberculomas. When present they are of considerable importance in the distinction between tuberculoma and circumscribed cancer. In the latter condition, streaky shadows when present extend peripherally and represent areas of atelectasis.

TUBERCULOMA AS A CLINICAL PROBLEM. (DIAGNOSIS, PROGNOSIS, TREATMENT)

The manner in which a tuberculoma commonly presents itself in the general population or in a general hospital is by the fortuitous discovery—by x-ray—of an asymptomatic lung nodule (10). The prime clinical problem is to determine whether or not surgical removal of the nodule is necessary. Many papers have appeared in the recent literature describing the so-called "coin" lesion (10, 11). The reason this type of lung nodule has assumed importance is the inability of the physician to differentiate a benign from a malignant lesion in a large proportion of cases. The chief benign lesion in the differential diagnosis is the tuberculoma.

Small circumscribed nodules in the size range of 0.5 to about 1.5 centimeters are usually not primary malignancies. Carcinomas of this size usually appear as faint infiltrations or "smudges". It is only as the lesions enlarge that condensation occurs and the circumscribed density of the "coin" lesion becomes apparent. The border of a tuberculoma tends to be sharper than that of a carcinoma. If the tuberculous lesion is of relatively short duration and is still in an unstable state, its border may not be sharp. The mass may contain areas of calcification. This is almost positive proof that the lesion is not malignant. Satellite lesions may be found around tuberculomas, rarely around carcinomas. However one

must be on the alert for the development of a carcinoma in a lung already infected with tuberculosis. An extremely confusing situation may be present which may not be resolved by the most thorough and astute clinical and radiological work-up and thoracotomy may become necessary. Faint streaky shadows extending toward the hilum from the mass indicate tuberculoma. In cancer if such shadows are present they are located peripherally and represent areas of puckering of lung tissue distal to the tumor (9). Cavitation may occur in both tuberculoma and cancer and the two may be indistinguishable. A positive sputum on the one hand or the discovery of exfoliated cancer cells on the other will establish the diagnosis. Change in size occurs in both cancer and tuberculoma. Enlargement as well as shrinkage may be found in the latter. Usually the type of tuberculoma which changes significantly in size is the "fresh" lesion found in a tuberculous sanatorium population rather than in the general population.

Having decided that the mass in the lung is actually a carcinoma or something indistinguishable from it, is only the first part of the clinical problem. The second aspect concerns the course of action to be taken when a definite diagnosis of tuberculoma has been made. This leads naturally to a discussion of the course and prognosis of tuberculoma itself.

A number of reports in the literature deal with this aspect (5–7). It is apparent that to a certain extent the prognosis of the tuberculoma will depend upon its type. A recently inspissated or blocked cavity has an entirely different potential than a dense lesion with concentric calcified laminations. Often such a sharp differentiation does not exist clinically. Moyes (7) reported that of 34 unresected cases 91 per cent were in good health after three to 15 years. However 17 cases showed some signs of activity during this period. He pointed out that the lesion might excavate, produce a positive sputum, and cause local spreads, but indicated that such spreads were peculiarly benign. He inferred that tuberculoma formation indicated a high degree of resistance to tuberculous infection with a tendency to isolate the lesion in a round form. None of his cases died of tuberculosis.

Mitchell (12) studied tuberculoma from the point of view of its natural history uninfluenced by resection or chemotherapy. He showed that although there is one chance in four of progression of untreated tuberculoma, a fatal outcome is rare. Now, with chemotherapy, activity can be restricted further.

Hillerdal's series of 139 cases (1) paralleled these findings. The results of sanatorium measures or mere observation were uniformly good. In some instances chemotherapy, when used, affected only associated fresh lesions, while the tuberculoma ran its own benign course. In 17 cases with cavitation, closure was accomplished with artificial pneumothorax in 16. Four patients, who also had associated unstable disease, did well with thoracoplasty. Only six of 139 came to resection and all did well.

On the other hand, surgeons in particular have stressed the potential dangers of leaving in situ a mass of caseous tuberculosis in actual or potential communication with a bronchus and have strongly urged and practiced resection (13). This aggressive attitude in this traditionally benign condition is finding support in

the newer knowledge of the pathology of tuberculosis as exemplified by the studies of Medlar (14). This worker has emphasized the omnipresent threat of residual caseous foci in the lung and has been an advocate of their surgical removal.

In the past, with a few exceptions, tuberculomas were treated in a way similar to that of many other tuberculous pulmonary lesions. The cornerstones of therapy included rest and sanatorium care and sometimes collapse therapy. The latter is admittedly an illogical method, since it is impossible to collapse a solid nonaerated focus in the lung. Occasionally, in lesions with cleft-like cavities or those with reversible components (tuberculous bronchopneumonia) in their periphery, some radiological and clinical improvement was noted. When streptomycin became available, it was widely used but it soon became apparent that it could not affect significantly an old lesion with a thick wall and a caseous necrotic center. However many "tuberculomas" of a sort were actually produced by antimicrobial therapy, i.e. the residual caseo-necrotic focus described by Medlar (14), and these in turn have been attacked surgically (by resection) with great zest in some quarters.

Tuberculoma has always been considered one of the standard indications for resection in pulmonary tuberculosis (15). Removal of a blocked cavity, or of a large mass of caseous material in potential communication with the bronchial tree is regarded as excellent prophylaxis against breakdown and spread. The early results have been uniformly good both as regards immediate surgical morbidity and exacerbation of tuberculosis. On the other hand many have argued that tuberculoma is essentially a stable and benign lesion and the risk of uncontrollable spread of tuberculosis is less than the admittedly small risk of surgery. The lack of urgency of surgical treatment is generally accepted and there is much room for the exercise of clinical judgment.

Surgical excision should be seriously considered in the following situations:

1. Large tuberculomas
2. Uncertainty of diagnosis (versus cancer)
3. Unstable lesions
   a. Recent appearance
   b. Variations in size
   c. Cavitation (even if sputum is negative)
4. In association with other lesions in adjacent areas that themselves require surgical therapy.

Techniques in resectional surgery that preserve normal lung tissue are to be preferred. Segmental and wedge resection and occasionally lobectomy are the procedures of choice. Pneumonectomy is practically never indicated. Specific antibiotic coverage is generally not necessary in old lesions but should be employed in short-term fashion in most cases to prevent exacerbations of other more active lesions which may be present.

SUMMARY

A tuberculoma is defined as a localized sharply circumscribed mass of tuberculous tissue in the lung, visible radiologically. There are three pathological

types: (a) blocked cavity, (b) residual of an area of caseous bronchopneumonia, and (c) fusion of multiple adjacent areas of tuberculosis into a single mass. Its roentgen characteristics are described with special reference to differentiation from cancer of the lung. It is considered on its own merits as a unique form of pulmonary tuberculosis with emphasis on its natural history and the indications for surgical treatment.

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TUBERCULOUS MENINGITIS

General Review and Experience at The Mount Sinai Hospital

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The purpose of this report is twofold; first, to document and evaluate the limited experience in the management of tuberculous meningitis at the Mount Sinai Hospital in the light of experiences reported from major tuberculosis centers throughout the world, and secondly, to outline, in retrospect, the successive stages in the development of treatment and the problems that have arisen as a result.

Obviously, the goal of any therapy is to obtain the lowest possible mortality and morbidity rates. In the case of tuberculous meningitis, antimicrobial therapy has gone a long way toward reaching this goal, but still falls short of the mark when compared to antibiotics in other infectious diseases. Morbidity was unknown prior to 1947; the mortality rate being almost 100 per cent. For the first time, with the introduction of streptomycin, observations (clinical and laboratory) were made on patients who survived the heretofore overwhelming, fulminating and fatal course of tuberculous meningitis. Early diagnosis meant little, since its downhill progression to death could not be prevented. The effectiveness of streptomycin in altering this downhill course brought forth many new problems in the management and understanding of the disease process. As Lorber (1) pointed out, first we had to learn how to use this new medication. It soon became apparent after trial and error that intramuscular streptomycin did not provide adequate cerebrospinal fluid concentration to be effective against the organism. And so streptomycin was administered intrathecally as well as intramuscularly. This in turn disclosed other problems such as the development of resistance of the tubercle bacillus to the medication, the development of spinal block due to the formation of fibrinous exudate and the appearance of toxic signs and symptoms. Dosage adjustment, length of treatment time and the introduction of supplemental drugs such as P.A.S., promizole, streptokinase, P.P.D., and cortisone in an attempt to counteract these problems was the next step in management.

When isoniazid was proved to be effective in inhibiting and destroying the tubercle bacillus, when this drug was shown to produce an adequate spinal fluid concentration with oral administration, and when the drug proved not to cause significant toxic side effects, a substantial advance was made in the treatment of this disorder. The intrathecal route of streptomycin was dropped by most treatment centers. Also another tool now was at hand to lessen the chance of early resistance of the organism to either streptomycin and/or isoniazid.

To date the combination of streptomycin, isoniazid, P.A.S., and/or other drugs directed at lessening the inflammatory process produced by the anti-

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microbial medication and the breakdown products of the organism and diseased tissue, has resulted in survival rates as high as 80 to 90 per cent in some series. These glowing statistics are not the rule, since treatment centers from different parts of the world still report survival rates of only 50 to 60 per cent as the follow-up periods become longer.

Complications in the survivors, aside from those directly attributed to the medication, also are relatively new to the medical profession. Mental retardation, convulsive seizures, optic atrophy, hemiplegia and brain stem dysfunction are some of the more common residuals. With early detection and improved therapy these complications have been occurring less frequently.

The limited number of patients upon which our experience is based may be judged as insignificant when compared to the large series from other centers. However, the problems and considerations mentioned and to be discussed remain the same for each case and are therefore no less significant.

MATERIAL AND RESULTS OF TREATMENT AT THE MOUNT SINAI HOSPITAL

From 1933 through 1946 there were seventy cases of tuberculous meningitis at The Mount Sinai Hospital. All but one expired shortly after admission or within a few weeks. The lone survivor was a child with a proved tuberculous lesion in the occipital region of the scalp who developed mild meningeal signs. The spinal fluid revealed a pleocytosis, mostly lymphocytes. No organism could be found in the spinal fluid by smear, culture, or guinea pig inoculation. This child improved without any specific medication and remained well for at least eight years after her discharge according to follow-up letters written by the parents. From 1947 through 1952 four adults diagnosed as having tuberculous meningitis promptly were transferred to another institution for streptomycin therapy. Some expired within a few days after admission before a diagnosis was established or streptomycin was started.

Since 1953 the tendency has been to hold and treat patients highly suspected or proved to have tuberculous meningitis after admission. There were eleven such patients treated during this period. Seven were children and four were adults. Amongst the children, four of the seven were three years of age or less. The age range in the adults was from twenty to forty-two. All the patients were admitted with symptoms referable to the nervous system such as headache, nausea, vomiting, mental confusion, lethargy, convulsive seizures, etc. The duration of the symptoms was three weeks or less. Four of the patients were semicomatose on admission. The outstanding neurologic findings were mental changes and meningeal signs. In addition, three patients had signs referable to the brain stem such as ocular palsies, nystagmus and dystaxia. Three patients had hemiparesis and one had convulsions. Four of the eleven patients had no evidence of pulmonary tuberculosis or tuberculosis in other parts or organs of the body. Three of the children had positive tuberculin reactions.

The diagnosis was established definitely in eight of the eleven patients either by culture, smear, guinea pig inoculation or post mortem examination. No one laboratory method proved best in detecting the organism.

Cerebrospinal fluid findings. A pleocytosis was present in all the cases and ranged from 60 to over 1,000 white cells. The predominant cell was the lymphocyte. However, occasionally polymorphonuclear cells dominated early and later gave way to lymphocytes. Xanthochromia was present in three of the cases. The total protein was elevated in all of the spinal fluids and ranged from 72 to 342 milligrams per cent. Sugar and chloride determinations were done in nine of the eleven cases. In four of the cases the sugar was definitely decreased and ranged from 11 to 33 milligrams per cent. In the remaining five patients the spinal fluid sugar was within normal limits throughout the entire course of the illness. In one proved case where the patient had a downhill course and expired, eight sugar determinations were made and they ranged from 56 to 79 milligrams per cent. The chlorides were generally below the normal range but fluctuated a great deal without any relationship with the clinical course. For example, in one case the chlorides were 102 milliequivalents on admission and prior to death rose as high as 120 milliequivalents.

Treatment. All eleven patients were treated with streptomycin, P.A.S. and isoniazid. Three patients in addition received promizole. The streptomycin or dihydrostreptomycin (three cases) was administered intramuscularly, the dosage being approximately 40 milligrams per kilogram of body weight per day for children and one gram a day for adults. Streptomycin was not given intrathecally. The dosage of P.A.S. was 12 grams a day in divided doses for adults and two to four grams a day in divided doses for children. Isoniazid was given orally in dosage of 100 to 150 milligrams four times daily for adults and approximately eight milligrams per kilogram of body weight per day for children. There was no uniform treatment time but in general the patients received the above dosages for three to four weeks and if improvement was apparent both from the clinical and laboratory standpoint, the dosage of all three medications was cut in half. Those who were discharged home from the hospital were instructed to continue the medication on one-half the dosage for a total of six months. Some were instructed to take this medication only two or three times a week.

Mortality. Four of the eleven patients expired. One of the four was transferred to another institution in a decerebrate state and shortly afterward expired. The remaining seven survivors are well although two of them had continuation of therapy at another hospital. Four of the survivors were children and three were under the age of three years. Post mortem examinations were done on the three patients who died in this hospital. All three showed typical tuberculous meningitis. One case had, in addition, a left cerebral abscess secondary to congenital heart disease and another had tuberculous involvement of the pituitary and a subdural hematoma. The cause of death of these two patients cannot be wholly attributed to the meningitis.

Morbidity and drug toxicity. Of the seven survivors there was no definite evidence of permanent toxic effects from the medication. Several had transient nausea but this could not be attributed wholly to the drug. There was no case of deafness. One patient developed ataxia but this child had other evidence of

brain stem disease, probably tuberculoma. Three patients have residual neurologic deficits. One has become a behavior problem and mentally retarded and two have ocular palsies that have not as yet cleared. Thus far, after twelve to twenty-two months, there have been no recurrences.

The earliest response to treatment was the change for the better of the mental state. The patients usually became more alert and better oriented. This was followed closely by the disappearance of meningeal signs. The spinal fluid was the last to show a full return to normalcy. All of the survivors at dischange still showed white cells in the spinal fluid and at least half of the patients had an elevated protein.

DISCUSSION AND COMMENTS

In general this modest series compares favorably with the mortality statistics of other clinics with obvious reservations. When compared to the mortality rate at The Mount Sinai Hospital prior to 1946, one can appreciate the effectiveness of the present day treatment.

Among the best organized studies of the treatment of tuberculous meningitis since the advent of streptomycin has been that conducted by Lorber (2) in England. In a series of 549 patients gathered from five large centers in Great Britain (under the same unified direction) and treated with intramuscular and intrathecal streptomycin, there was an overall 46.1 per cent two year survival rate. Of the "early" cases, that is those admitted fully conscious and with a relatively short history, 74 per cent survived. Of those classified as intermediate cases, 54 per cent survived, and of the advanced cases, only 24.8 per cent survived. Lorber emphasizes that those admitted unconscious and below the age of three have the poorest prognosis (2). It is of interest to note, however, that three of the seven survivors in the recent Mount Sinai series were three years of age or less. Only one below the age of three (7½ months) expired. Two hundred and forty-five survivors from the group of 549 patients reported by Lorber were followed for a period of two to six years. Nine per cent showed moderate to severe neurologic sequelae amongst the early cases and as much as 55 per cent showed neurologic residuals in the advanced cases. Deafness was the outstanding complication as a result of streptomycin occurring in 14.7 per cent of the survivors. The meningitis was not deemed to be the cause of the deafness. Subsequently an additional eighty-nine cases reported by Lorber (2) were treated with streptomycin and para-amino salicylic acid (P.A.S.), theoretically, to help prevent the resistance of the organism to streptomycin. There was an overall survival rate in this group of 64 per cent. The survival rate of the so-called early cases increased to 88 per cent. However, the survival rate of the advanced cases remained about the same, 26 per cent.

Smith (3) in 1953 reported on a five year follow-up of one hundred cases of miliary and meningeal tuberculosis treated with streptomycin intramuscularly and intrathecally. Of twenty-five cases with miliary and meningeal tuberculosis only one was alive after five years. Of forty-three cases of tuberculous meningitis without miliary involvement, seven were alive after five years. Of thirteen

patients with miliary tuberculosis followed by the development of meningitis, none survived. Cairns, Smith and Vollum (4a) in 1950 reported a 56 per cent survival rate in ninety-three patients treated with streptomycin alone. Flori (5) the same year, reported a similar survival rate in 265 cases treated with streptomycin and promizole. Lincoln and Sifontes (6) in 1953 reported 67 per cent survival rate of fifty-two patients. Riley (7) in 1952 reported an 89 per cent mortality rate in sixty adult patients treated with streptomycin. Oldham, Bower and Carre (8) reported a 38 per cent survival rate in ninety-two cases of tuberculous meningitis in children treated with streptomycin after a follow-up period of two to six years. It is apparent from these figures, as a sampling, that streptomycin alone or in conjunction with P.A.S. can produce no better than an overall 50 per cent survival rate.

Since the introduction of isoniazid the survival rate has increased but a proper evaluation cannot be made until longer and larger follow-up series are reported. There is little question, however, that the use of isoniazid at the expense of streptomycin has reduced the amount of toxic effects from streptomycin. Intrathecal therapy has been dropped by most centers with the notable exception of Lorber's clinic. Smellie (9) reported on a group of fifteen consecutive patients treated with intramuscular streptomycin, oral isoniazid and P.A.S. No intrathecal medication was given. Only one of the fifteen cases expired.

More recently Lorber (10) studied a series of two groups. One group consisting of twelve patients received isoniazid in addition to the streptomycin and P.A.S. and the other group, consisting of ten patients, did not receive isoniazid. Eleven of the twelve survived in the isoniazid group and eight of the ten survived in the group not receiving isoniazid. He found that the patients of the isoniazid group required fewer intrathecal treatments of streptomycin. Although he is still reluctant to give up intrathecal therapy he admits that isoniazid is very beneficial and perhaps can replace intrathecal streptomycin. Appelbaum and Anderson (11) reported the survival of seven patients out of ten after a two-year follow-up treated with oral isoniazid only. Anderson, Kerr and Landsman (12) treated seven cases with isoniazid alone and all survived after a six to twelve month follow-up period. However, he recommended that isoniazid should not be used without streptomycin since there may develop a rapid resistance of the organism to the drug. Spies and his co-workers (13) found in a comparison study that isoniazid alone was as good as streptomycin and isoniazid and much better than streptomycin. Clark et al. (14) also found that isoniazid was superior to streptomycin in the treatment of miliary tuberculosis and tuberculous meningitis. Lawson and Lees (15) found that in a group of patients with miliary tuberculosis without meningitis treated with streptomycin alone, 33 per cent developed meningitis during the course of therapy. In another group of acute miliary tuberculosis patients without meningitis treated with isoniazid alone or in combination with streptomycin none developed meningitis. Wolinsky, Pratt and Steenken (16) in 1954 compared the effects of isoniazid, iproniazid, streptomycin, and streptomycin and isoniazid in guinea pigs injected with cultures of human tuberculosis. They found that all the drugs were about equally effective

if the guinea pigs were treated within eight days after infection. If the treatment began sixteen days after the animals were infected there was a 50 per cent mortality and in those that were treated eighteen to twenty-one days after being infected there was a 100 per cent mortality. Most clinics today are employing both drugs for greater insurance against the development of resistant organisms, and of course, early diagnosis and treatment are stressed.

The addition of isoniazid to the armamentarium of treatment still did not significantly reduce the complications allegedly due to the inflammatory process and subsequent formation of fibrinous exudate. Whether the resultant fibrous exudate is due to the toxic effects of the drugs, particularly streptomycin, or whether it is due to the breakdown products of the tuberle bacilli or the diseased tissue still is subject to debate. Assuming one or both processes take place many attempts have been made to counteract this reaction. Streptokinase was used by many investigators and subsequently discarded as being ineffective. However, in 1954 Fletcher (17) pointed out after an investigation of the plasminogen levels in the spinal fluid of fifteen patients with tuberculous meningitis that streptokinase definitely is "capable of producing useful concentrations of fibrinolytic enzyme". He stated that most investigators did not use large enough doses of streptokinase and recommended dosages three to thirty times higher than previously used. Cairns, Smith and Vollum (4a) introduced the use of intrathecal tuberculin in cases developing spinal block. They reported some dramatic responses in seemingly hopeless situations (4b). Since then intrathecal tuberculin has been used by others in extreme cases and the feelings about its effect have been mixed. Violent reactions such as extremely high fever, convulsions and death have been reported (Robinson and Ro (18)). Intraventicular and intracisternal administration of streptomycin generally has been discarded when spinal block develops. More recently cortisone and ACTH have been used in conjunction with streptomycin and isoniazid in the hope of reducing or preventing excessive inflammatory reaction. Although it has been widely agreed that these drugs are dangerous in active tuberculosis it was deemed by some investigators to be relatively safe when used with isoniazid and streptomycin. Ashby and Grant (19) reported success attributed to the early use of cortisone with full knowledge that it does not have any effect on fibrous tissue once it is formed, but that it may inhibit inflammation and thereby prevent its formation. They claimed also that the spinal fluid cell count fell more rapidly in the patients treated with cortisone. Bulkeley (20) for the same reasons treated patients with ACTH and isoniazid and reported that the mortality rate was lessened by its use. The effect of cortisone and hydrocortisone on piarachnoid adhesions was investigated recently by Feldman, Behar and Samueloff (21). Talcum was introduced via the cisternal route in cats. Some of the cats were treated with cortisone and hydrocortisone intracisternally and others were not. It was found that the cortisone treated cats showed a decrease in the "migration and phagocytic activity of the histiocytes in the subarachnoid space, thus inhibiting the formation of foreign body giant cell granulomata" commonly found in the untreated animals.

The neurologic complications since the beginning of antimicrobial therapy for tuberculous meningitis have varied in number and character depending on the series reported. In general, the complications were more frequent in series dealing with children below the age of three and in series that included a high percentage of advanced cases on admission. The delay in starting therapy because of the patient's neglect in seeking hospital admission and the delay in diagnosis in many cases have contributed to the high complication rate as well as the high mortality rate. Mental retardation, hemiparesis, optic atrophy and seizures are the most common residuals and vary in order of frequency from one series to another. The recurrence rate also varies and here it is in direct proportion to the length of the follow-up study. Thus far, relapse rarely has been more than 10 per cent. Of course, one should define recurrence or relapse as compared to the fluctuations seen in the course of treatment. This is difficult to define.

Before isoniazid therapy was introduced the commonest toxic effect was the development of deafness. It was soon discovered that dihydrostreptomycin was responsible for a greater occurrence of deafness than streptomycin (22, 23). Riley (7), in a series of sixty patients treated with streptomycin, reported that 22 per cent of the patients developed deafness in varying degrees. Lorber (2) reported an incidence of 14.7 per cent. As might be expected in small series the incidence at times was much higher or lower. Vestibular dysfunction did not occur quite as frequently. The elimination of intrathecal streptomycin and the overall reduction of the amount of intramuscular streptomycin, after isoniazid came into use, has resulted in lessening the number of cases of deafness. The outstanding toxic effect attributed to isoniazid has been peripheral neuritis. Oestreicher et al. (24) reported eight patients who developed peripheral neuritis, and stressed the fact that pyridoxine deficiency was the common background in seven of the eight patients. They recommended the administration of pyridoxine when isoniazid is used.

Although early diagnosis of tuberculous meningitis seems to be essential for a successful outcome of therapy it is often difficult to obtain bacteriologic proof. The clinical picture can simulate a variety of other conditions such as viral encephalitis, certain bacterial meningitis, torula meningitis, carcinomatosis of the meninges, etc. Also, it is well known that there are many cases where no etiology can be determined. Some investigators have assumed that a given case is of tuberculous etiology because of the presence of tuberculosis in the lungs or elsewhere, because of a strongly positive tuberculin test and because of the so-called "classical" spinal fluid findings. The literature proves and disproves each of the above assumptions. In series reported by Appelbaum and Anderson (11) and Fitzpatrick (25) only 45 to 50 per cent of the patients gave evidence of tuberculosis of the lungs or other parts of the body. On the other hand, in a series of children reported by Robinson and Ro (18), as high as 99 per cent had evidence of pulmonary or miliary involvement. In our series, seven of the eleven patients had evidence of tuberculosis other than in the nervous system. Robinson and Ro (18) in the same series reported positive tuberculin tests in twenty-

three out of twenty-five children. Waddell et al. (26) reported positive tuberculin tests in twenty-one out of twenty-five children. In adults the tuberculin test generally has not been used and when it has, proved unreliable. As for the "significant" spinal fluid findings such as pellicle formation, decreased sugar and chlorides, there too, a discrepancy exists. In our series a definite pellicle formation was not noted in any of the cases. The sugar content of the spinal fluid was within normal limits in five out of nine patients where the determinations were made. A striking example of the unreliability of the chlorides was described in one of our proved cases. Riley (7) in his series of sixty cases from Bellevue Hospital also has focussed attention to the unreliability of these determinations. The difficulty in recovering organisms from the cerebral spinal fluid by smear, culture and guinea pig inoculation is well known. In a large series of 450 cases (27) bacteriologic proof was possible in not more than 82 per cent of the patients. In our series proof was obtained in eight of eleven patients. This is close to the average of most series. Etiologic proof in some instances has been obtained only after post mortem examination. Although it may be scientifically unsound to include in a series for the literature the patient assumed to have tuberculous meningitis, the judgment of the experienced clinician should prevail so that early treatment can be instituted. Where only guinea pig inoculation tests have turned out positive, six weeks usually have elapsed and if treatment has been held up because of lack of etiologic proof then the chance for survival has been reduced considerably.

SUMMARY

Although this small series from The Mount Sinai Hospital has not touched upon all the aspects concerned with the treatment of tuberculous meningitis, it has reflected many of the advances and the problems discussed in the review of the recent literature. When one has become accustomed to the initial dramatic drop in the mortality rate after 1947 and when one has evaluated the results of long term follow-up studies with streptomycin, he realizes more soberly that there still is much to be done. The information gained through clinical and laboratory studies since specific therapy began had given us but clues and a general direction for the future. The explanations for the relatively high mortality obviously are incomplete.

A survey of most of the important literature when boiled down merely makes recommendations that are applicable to all diseases namely early diagnosis and prompt treatment. In the case of tuberculous meningitis the best treatment to date is a combination of streptomycin and isoniazid.

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RENAL TUBERCULOSIS

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Immediately following the discovery of the tubercle bacillus at the end of the 19th century, its role in the etiology of renal tuberculosis was accepted (1). Nevertheless, although tubercle bacilli were found to be present in the urine in many cases, tubercle bacilluria was not uniformly accepted as an indication of genito-urinary tuberculosis (2). It was stated that excretion of bacilli could occur through the "renal filter", and the presence of tubercle bacilli in the urine was therefore not necessarily an indication of kidney tuberculosis. Increased glomerular permeability, demonstrated by Rusznyak and Nemeth (3), was offered as an explanation for bacilluria in the absence of grossly demonstrable renal tuberculosis.

In contrast to the theory of "excretory bacilluria", Israel and Casper maintained that bacilluria, if obtained directly from the kidney, definitely indicated tuberculosis of that organ (4, 4a). This early observation was later confirmed by Medlar and Sasano in 1924–25 (5), and by the work of Lieberthal and Huth in 1933 (6). The former workers examined serial sections of the removed kidney from which bacilluria had been present and in each case they were able to find at least minute, sometimes only microscopic, tuberculous lesions. These observations, and those of Huber (7), indicated that most of the early lesions are localized in the cortex and cortico-medullary areas. In Medlar's series 75 per cent of the lesions were in the cortex, 11 per cent in the medulla and 14 per cent in the corticomedullary area. This localization of renal involvement, as noted later, is important from the point of view of diagnosis.

Tuberculous infection of the kidney is hematogenous in almost every case. Not only does this explain the frequency of cortical and cortico-medullary localization, but it also predicts the observation that renal tuberculosis is almost always bilateral at its inception. In a series of 1,028 consecutive autopsies in patients with tuberculosis, in at least 322 cases microscopic tuberculous lesions were present in the kidney (8). Of these 322 cases, there were 284 in which the disease was bilateral. In 9 cases nephrectomy had previously been performed for renal tuberculosis and of these 9 cases, 8 were found to have tuberculous lesions in the remaining kidney. Furthermore, in 6 of these 8 cases, "organ tuberculosis" (surgical kidney) was present (Table I). Similar findings have been reported elsewhere.

It was observed rather early that cortical and cortico-medullary miliary foci can heal. Auerbach showed that not only do non-disintegrating lesions heal, but small cortical or cortico-medullary cavities can heal with resulting connective

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TABLE I

Renal tuberculosis in 1028 consecutive autopsies (8)

Total number of cases with renal tuberculous lesions	322
Bilateral involvement	284 (88.2%)
Unilateral involvement	38 (11.8%)
Total minimal lesions	279
Total organ tuberculosis	43
Bilateral organ tuberculosis	18
Remaining kidney organ tuberculosis after nephrectomy	6
Unilateral organ tuberculosis, contralateral uninvolved	5
Unilateral organ tuberculosis, contralateral miliary foci	14

tissue defect (9). Small microscopic scars, often difficult to detect, mark the site of an orginal miliary or small nodular lesion, with hardly any pathognomic evidence present to indicate the etiology of the findings. This healing process may be marked by calcification both in small nodular lesions or in larger caseous foci. This process may in some cases even include the whole kidney, producing the so-called "cement kidney".

There is evidence that ulcerative tuberculous foci can also heal. Beach and Schulz reported 8 cases with tubercle bacilluria, where patients became and remained symptomless from 2 to 15 years (10). A series of seventeen cases with tubercle bacilluria has been reported that showed no evidence of genital or renal tuberculosis on pyelographic or cystoscopic studies (8). In each of these seventeen cases, the urine became negative for periods of observation ranging from two to four years. The above data indicate that, at least in its inception, renal tuberculosis is bilateral and that there is a tendency to spontaneous healing.

Before the era of the antituberculous drugs, the treatment of unilateral renal tuberculosis was nephrectomy. However small the renal lesion, it was considered "surgical tuberculosis", if the disease was visualized by x-ray and confirmed by a positve smear and/or positive guinea pig or culture examination of the urine. Early nephrectomy or ureteronephrectomy was advised in these cases. The result of this type of therapy was considered satisfactory, if the remaining kidney showed no subsequent involvement. Wildbolz reported 60 per cent of his cases alive after 10 years (11). Emmett reported five year cures in 43.5 to 50.3 per cent of his cases, while of 863 cases operated upon at the Mayo Clinic, 58.1 per cent were clinically cured four years post-operatively (12). Nesbit had 50.3 per cent of his patients alive 11 years post-operatively (13). Oppenheimer and Narins studied 117 cases of renal tuberculosis admitted to the ward service of The Mount Sinai Hospital from 1928 through 1945. 106 cases were treated surgically. The follow-up studies are summarized in Table II. It is seen that even including the number of cases lost to follow-up, the survival rate fo · a 5 to 10 year period was 55 patients alive out of 96.

The average 10 year survival rate reported from various clinics is over 50 per cent. This was, however, not true if surgical treatment was withheld. Parsons in 1925 showed that 85 per cent of conservatively treated patients with unilateral organ renal tuberculosis were dead in five years (14). Wildbolz in 316 non-

TABLE II

Follow-Up Period	Pts. traced during this period	Pts. lost to Follow-Up for this pd.	Patients alive		Patients dead		Cause	
			No.	%	No.	%		
Yrs.								
0–3	96	0	89	92.5	7	7.5	Extra renal tbc.	4
							Renal tbc.	2
							Peritonitis (non tbc.)	1
3–5	77	12	72	93.5	5	6.5	Renal and Pulmonary tbc.	5
5–10	62	10	55	89	7	11	Adrenal tbc.	1
							Renal tbc.	5
							Cause?	1
10–15	39	16	35	90	4	10	Renal tbc.	4
15 plus	15	20	12	80	3	20	Hypertension	1
							Coronary	1
							Cause?	1

operated cases showed a 58 per cent five year mortality and only six per cent alive in 10 years. Of course, the condition of the contralateral kidney greatly influences the mortality rate. Emmett and Kibler found that if the remaining kidney urine was negative after nephrectomy, the 5 year mortality rate was 20.3 per cent and for 10 years, 34 per cent (15). If pus cells were present, the mortality rate was 40 per cent and if bacilluria was found in addition to pus cells, the five years mortality was 60 per cent.

To diagnose tuberculosis in an apparently uninvolved kidney is a very difficult task. In a study of 57 cases, where nephrectomy was done for apparent renal tuberculosis, the disease in the remaining kidney became apparent in 39 cases within six months, in 53 cases within twelve months, in 56 cases within 18 months, and in 57 cases within 24 months (8). This data does not indicate the probable percentage of patients who will have contralateral involvement, since the cases were in a select group, but it should serve as a constant reminder of the danger of subsequent contralateral infection and should impress us with the necessity of thorough preoperative investigation of each side.

With regard to bilateral renal tuberculosis, conservative therapy was advised by most urologists. Nevertheless, one school advised the removal of the worse kidney, stating that this removal helps the healing in the remaining one. Their attitude was supported by Uffredazzi's experiments published in 1918 (16). He produced bilateral renal tuberculosis by injecting one drop of a suspension of bacilli into each kidney. After the infection was established, he performed nephrectomies at various intervals. Some of the animals with bilateral involvement were kept as controls. Uffredazzi stated that animals in which one kidney was removed had longer survival periods than the control animals, and he found that when nephrectomies were performed at an early stage, almost complete healing occurred on the opposite side. Nephrectomy did not help the contralateral kidney when performed later or if the post infection period was along. No mention was made of the type of bacilli used in these experiments. This experiment was repeated by Sporer using bovine and human tubercle bacilli in

two series of rabbits and Uffredazzi's results could not be confirmed (17). No evidence of healing in the remaining kidney could be found after nephrectomy when bovine bacilli were used, although spontaneous healing occurred with human bacilli. Moreover, within the limits of the infecting doses used in these studies, the number of injected bacilli was not found to play an important role in the pathogenesis of the disease.

In a study of 69 clinical cases with bilateral renal tuberculosis treated conservatively without chemotherapy, the duration of life was as follows (8):

9 dead within 6 months after diagnosis was made
16 " " 12 " " " " "
39 " " 24 " " " " "
56 " " 38 " " " " "
60 " " 42 " " " " "
9 alive 4 years post diagnosis.

Eight cases were reported where nephrectomy was performed in the presence of bilateral renal tuberculosis. Seven patients died within three years, and one survived three years with an essentially unchanged kidney. This data indicates in bilateral renal tuberculosis nephrectomy should be performed only as an emergency procedure and then with the understanding that the procedure per se, will not improve the condition of the remaining kidney.

CHEMOTHERAPY OF RENAL TUBERCULOSIS

Since the advent of chemotherapy, treatment of renal tuberculosis has undergone considerable change. Final criteria for therapy have not yet been established, since much longer experience and post therapy observations will be necessary before definite conclusions can be drawn.

An analysis of 219 consecutive autopsies in patients with tuberculosis since the introduction of modern chemotherapy reveals a striking contrast (18) with the pre-chemotherapy findings, noted above. Almost all of these patients had prolonged antituberculosis therapy with alternating courses of several drugs. A number of observations in this series are worthy of note. In comparison to Table I, there is a relative diminution of instances of organ tuberculosis. *The real surprise, however, is the very low percentage of minimal tuberculous involvement.* While in 1028 autopsied cases without chemotherapy there were 279 with minimal lesions, in those with prolonged treatment with antituberculous drugs there were only 7 instances of miliary foci in 219 cases. *This point alone should prove the effectiveness of antituberculous chemotherapy in curing minimal lesions or preventing them at the end stage of hematogenous dissemination.* In this latter series, the patients with minimal renal foci and tuberculous involvement of the prostate were symptomless. Of five cases with organ tuberculosis, four were symptomless, though all had intermittent pyuria. There seems to be little doubt, that minimal renal tuberculosis should be treated with chemotherapy. However, a practical difficulty lies in the determination of the extent of the tuberculous lesion in the kidney. The usual diagnostic procedures sometimes inaccurately

TABLE III

Autopsy findings in a series of 219 patients treated with antituberculous chemotherapy

Total No. of Autopsies	219
Tbc. within the G U tract	17
Organ Renal tbc	
Bilateral	3
Unilateral	2
Tbc. of prostate	5
Tbc. of epididymis	1
Minimal foci in kidneys	
Bilateral	3
Unilateral	4

delineate the extent of the disease. Pyelograms may appear relatively normal in cases of advanced destruction and conversely, may indicate more extensive lesions than found in the removed specimen. Often, retrograde ureteropyelography may be more diagnostic than excretory urography and vice versa. Tomograms (laminograms) in association with pyelography can be very helpful in establishing the normality of the contralateral kidney in unilateral renal tuberculosis. It is obvious that all patients should have urines obtained from each kidney, collected only after the bladder has been emptied to prevent reflux. Such urines are routinely cultured for tubercle bacilli, injected into guinea pigs and the sediments stained for tubercle bacilli. As mentioned previously the absence of bacilluria does not rule out tuberculosis. Oppenheimer reported a case without bacilluria in which tuberculin used at the suggestion of Dr. Edwin Beer, assisted in the diagnosis of renal tuberculosis (19). Aortography has been advised to assist in the diagnosis of cortical or cortico-medullary lesions. In a small series of personal cases it did not exclude or affirm the diagnosis and this has been the experience of several investigators. Microscopic pyuria, especially in presence of pulmonary tuberculosis calls for thorough study of the genito-urinary tract to exclude tuberculosis of this system. Significant proteinuria, on the other hand, is not common in renal tuberculosis and its presence often is a sign of renal amyloidosis complicating renal tuberculosis.

Chemotherapy is indicated in every case of renal tuberculosis, although its effectiveness may be limited by the nature of the disease present. Overall effectiveness has been marked and has been reported in several large series.

Nesbit in 1954 reported a series of 21 cases in which in 47.6 per cent of cases after prolonged therapy, the urine became negative (20). Of 12 cases with bilateral renal tuberculosis, the urine became negative in 8 cases and of a total of 90 cases treated medically and surgically, the urine became negative in 65 cases. Latimer and his associates reported 253 cases treated with streptomycin in which bacilluria disappeared in 26 per cent of the cases, when two grams of streptomycin daily were used for periods up to 120 days (21). Objection to prolonged use of streptomycin is the emergence of streptomycin-resistant tubercle bacilli.

Huffines and Weber stated that in their series of cases, resistance to streptomycin occurred on the 45th day of therapy. Therefore, as early as 1949 they

were already advocating the use of streptomycin alone for only 42 days. Lattimer, who has had the opportunity of studying and following probably the largest series of cases, in 1952 advised a combination of drugs for the treatment of genito-urinary tuberculosis and reported a series of 458 cases treated with combination therapy (23). Ross, Gow and Hill reported a review of 85 cases where after combined medical and surgical therapy they achieved negativity of urine in 80 cases (24).

However small the lesion in the kidney, therapy should be prolonged. The necessity of the prolonged therapy is clearly indicated in the report by Hobby (25). She was able to grow tubercle bacilli from kidney lesions as late as at the end of seven months utilizing special culture technique. In some cases the disappearance of characteristic histological lesions were reported by Dick (26). Auerbach also noted a tendency toward healing in advanced lesions, and stipulated that even further use of chemotherapy might cause complete healing in these advanced cases (25).

While there is a unanimous agreement in so far as the therapy of early renal tuberculosis is concerned, the treatment of moderately and far advanced lesions is still in an experimental stage. Lattimer was so satisfied with the result of combined drug therapy that he has not removed any kidney during the last three years (27). He expects to perform nephrectomies only in those cases where relapses will occur.

However, if the destruction is advanced and progressive and if it is localized in one kidney, nephrectomy is still the recommended therapy in many clinics. Nevertheless, before surgery, prolonged medical therapy should be tried. In a number of cases the disease can be arrested or cured, and in a small number of cases it may become localized to a circumscribed area, where segmental resection of the diseased segment can be curative.

Segmental resection of a diseased kidney has been reported by several workers. Probably the largest series of cases was reported by Semb from Oslo who performed this procedure in 87 of his patients with 90 per cent urinary conversion at the end of two years (28). Lattimer has reported 5 cases with segmental resections with at least a two year follow-up and all are well with negative urine (29). An unanswered question at present is the advisability of segmental resection where a minute lesion or lesions are present in the remaining part of the kidney. We believe that a minute non-cavitary lesion in the remaining segment might not be a contra-indication for the contemplated resection, under prolonged chemotherapy.

An interesting procedure called cavernostomy in renal tuberculosis has been suggested by Staehler (30). He suggested this method for cavities which do not communicate with the renal pelvis. He treated cavities whose size varied from that of a cherry to that of a pigeon or chicken egg. He incised the cavity, curetted the wall with a sharp spoon and installed streptomycin powder in the cavity. He stated that in seven cases the procedure was tolerated better than segmental resection and primary healing of the wound occurred after removal of the drain. Neither urinary nor tuberculous fistulae were observed. This pro-

cedure is contraindicated where the cavity communicates with the renal pelvis. As yet we have had no personal experience with this technique.

When is surgery indicated in unilateral renal tuberculosis? We believe that if resistance to all available antituberculous drugs develop, when the pathological changes in the kidney progress despite prolonged therapy, or where intercurrent uncontrollable bleeding or infection occurs, nephrectomy is indicated. Nephrectomy is more easily decided upon if in addition to renal pathology, obstructive ureteral pathology is present. This can cause further severe non-specific damage to the kidney. Obstructive stasis and recurrent non-specific renal infection certainly can hasten indication for nephrectomy in a case where otherwise prolonged therapy would have been tried.

Pre- and post-operatively, anti-tuberculous therapy should be used, and the post operative therapy should be maintained for at least 12–18 months, preferably much longer.

The therapeutic management of bilateral renal tuberculosis should be conservative. All available data stress the necessity of avoiding surgery in these cases. Lattimer states that the five year mortality of patients with bilateral renal tuberculosis who were treated with chemotherapy was only 8 per cent (31). Recommended therapy is 100 mgm. isoniazid three times daily, plus 4 grams PAS three times daily, plus 1 gram streptomycin twice weekly, for at least 12 to 18 months. Therapy is usually associated with rest for at least 3 to 6 months, with urine cultures and pyelograms done at regular intervals.

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THE CHEMOTHERAPY OF PERIPHERAL TUBERCULOUS LYMPHADENITIS

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Chemotherapy is indicated in every instance of active tuberculous lymphadenitis. This is true not only as a derivation of the dictum that all active tuberculosis should have antimicrobial therapy, but also because of pathogenetic considerations.

Peripheral tuberculous lymphadenitis is almost always part of generalized tuberculosis. Although local therapy may have been justified in the past, the use of radiotherapy, cold quartz treatment, local surgical excision or local injection therapy are inadequate at present without systemic therapy. The generalized nature of tuberculous lymphadenitis must be appreciated, whether the local lesion is the result of a primary tuberculous infection or the result of lymphohematogenous post-primary dissemination.

In the former case, recent studies indicate that disseminated organ tuberculosis (pulmonary, meningeal, pleural, osseous) not infrequently follows the appearance of primary infection with local lymphadenitis. Miller studied 40 cases of peripheral tuberculous lymphadenitis in children with visible primary lesions of the skin, tonsil or mouth. The lymph nodes involved were the regional groups. Observation of these patients showed instances of miliary tuberculosis, tuberculous meningitis, erythema nodosum and phylectenular conjunctivis (1). In the so-called "Iwagasaki accident", nature provided a clinical experiment. When whooping cough vaccine was given to 209 infants, 60 developed swelling and suppuration of the injected site with draining axillary nodes about one and a half months later. Tuberculin conversion occurred and human type tubercle bacilli were found on culture of the draining nodes. Five-year observation of these infants showed three instances of tuberculous meningitis, one of miliary tuberculosis and one child with osseous tuberculosis (2).

When peripheral tuberculous lymphadenitis is part of post-primary lymphohematogenous dissemination, evidence of disseminated tuberculosis is often found in other organs and if not obvious, at least microscopic presence must be suspected. Haex and van Beek performed aspiration liver biopsies on 189 proven cases of tuberculosis (and 150 controls). Careful study of these aspiration biopsies, with each specimen having approximately 100 sections cut and examined, showed that disseminated tuberculosis was very common in almost every form of tuberculosis, including peripheral tuberculous lymphadenitis (3). In a clinical study, Roper and Waring followed 141 patients with acute primary serofibrinous pleural effusion, presumably tuberculous. During five years observation of

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these patients, all previously healthy young army personnel, 10 developed lymphadenitis (4). The frequency with which peripheral tuberculous lymphadenitis is associated with tuberculosis elsewhere in the body is evidenced further by Gale's experience (5), in which review of 210 cases of peripheral tuberculous lymphadenitis showed that 88 per cent of the patients had associated tuberculosis in other parts of the body, most commonly in the lungs and in the bones and joints. Although this series was selected, coming as it did from a tuberculosis hospital, such data should nevertheless emphasize the disseminated nature of peripheral tuberculous lymphadenopathy.

The post-primary dissemination to peripheral lymphnodes gives evidence of its presence at varying times after the primary dissemination. Thus, following the Iwagasaki accident, in two cases the nodes first became enlarged five years after the contaminated vaccination. Grzybowski similarly comments that, unlike tuberculous meningitis and miliary tuberculosis which usually occur early after primary infection, tuberculosis of lymphnodes is scattered over a wide period of time following such infection (6).

It is because of such irregularity and unpredictability of appearance of peripheral tuberculous nodes that no one period in the natural history of tuberculosis is immune from their appearance. Moreover, because of the increased incidence of primary infections in older age groups in the past two decades, there is further reason to anticipate tuberculous lymphadenitis in all age groups (Table I).

PRESENT STUDY

During the past four years 44 patients with peripheral tuberculous lymphadenitis have been treated by us at the Mount Sinai Hospital. Although all were treated in the out-patient department, a number were admitted as in-patients

TABLE I

Peripheral tuberculous lymphadenitis

The Mount Sinai Hospital, 1952–1956 (44 cases)

Female (35)	Race	Male (9)
3	White (5)	2
9	Negro (9)	0
23	Puerto Rican (30)	7
	Age	
7	10–20 years	0
10	21–30 years	2
10	31–40 years	6
8	41–50 years	1

	Location of nodes		
	Right	Left	Bilateral
Cervical	18	14	5
Axillary	1	3	2
Inguinal	0	1	0

for node biopsy. This series is characterized in Table I: it will be noted that more females than males are included, and that the cases are almost evenly divided among the various age groups from 10 to 50 years of age.

There are a number of features in this study which are perhaps worthy of note.

1. *All patients were treated by chemotherapy.* Tentative observations on the efficacy of isoniazid in peripheral tuberculous lymphadenitis during early clinical studies (7), coupled with previous experience on the effect of streptomycin and PAS, prompted the study of the use of chemotherapy as a definitive treatment for peripheral tuberculous lymphadenitis. Early results were encouraging and have been reported (8). Our studies began in March 1952 and have continued to the present.

Several drug regimens have been utilized and are being evaluated (Table IV). Results of this comparative evaluation will be reported in the future, with more extended post-therapy observation. All regimens have contained isoniazid. In some cases it has been used as single drug treatment, in others, PAS has been added. In others still, usually patients with more extensive disease, or with other evidence of disseminated tuberculosis, triple drug therapy with isoniazid-dihydrostreptomycin-PAS has been utilized. In a number of instances, especially those with fluctuant glands, there has been direct instillation of dihydrostreptomycin into the fluctuant massive nodes.

It is essential that isoniazid be included in the chemotherapy of tuberculous lymphadenitis. Firstly, pharmacologically, isoniazid is eminently suitable for such use. Studies with C^{14} tagged isoniazid indicate that this small molecular substance penetrates well into caseous nodes (9). Secondly, isoniazid is more effective than streptomycin in disseminated disease. In miliary tuberculosis, for example, development of meningitis is almost never seen during isoniazid therapy whereas it is not uncommon with streptomycin and PAS (10). This deficiency of streptomycin-PAS therapy has been documented recently by Haex and van Beek. They found, using serial liver biopsies, that dissemination continued for several months despite apparently adequate streptomycin-PAS therapy (3). Finally, it has been our experience that isoniazid therapy is more effective than other drug treatment.

2. *Diagnosis was confirmed histologically and/or bacteriologically in almost all cases.* It is highly desirable to establish a definite diagnosis of tuberculosis in patients with diseased peripheral nodes. From a purely diagnostic point of view, other significant diseases, some amenable to therapy, may resemble tuberculous lymphadenitis and differential diagnosis is therefore important. Secondly, as will be noted below, chemotherapeutic management of peripheral tuberculous lymphadenitis includes the necessity for prolonged treatment. Before embarking upon such a course it is obviously desirable that its necessity be established, especially since drugs with minimal but nevertheless definite toxicity are employed. In 40 of the 44 patients we were able to establish a definite diagnosis (Table II). In 4, clinical diagnosis was obvious and confirmed by the response to therapy. We are sometimes reluctant to require incisional biopsy of cervical

TABLE II

Diagnosis of peripheral tuberculosis lymphadenitis. 44 cases

1. Aspiration of node: tubercle bacilli on guinea pig inoculation		10
2. Excision biopsy		30
Acid fast bacteria found	13	
Typical tuberculous histology	17	
3. Clinical diagnosis		4
		44

TABLE III

Peripheral tuberculous lymphadenitis: response to chemotherapy (44 cases)

Month of Therapy	Initial Response	Maximum Response
1	32	1
2	9	6
3	1	12
4	2	15
5–12	0	10
Total number of patients	44	44

nodes for cosmetic reasons, especially in young women. We do not, however, hesitate to recommend this procedure, or that of aspiration biopsy, because of the possibility of persistent sinus tract formation; this has not occurred in our series since post-biopsy chemotherapy has been employed.

3. *All patients in this series were treated as ambulatory, non-institutionalized patients.* Although there is still discussion with regard to necessity for bedrest as an accessory in the treatment of various forms of tuberculosis, we would simply state that were it not for ambulatory chemotherapy almost none of the patients in this series would have been treated. Few had any constitutional symptomatology and these few became asymptomatic soon after the onset of chemotherapy (Table III). Most were employed or were engaged in full-time household duties.

4. *Accessory therapy.* With the exception of local injection in several cases no accessory therapy was employed in this series. Fourteen of the 44 cases had had tuberculous lymphadenitis previously. Six had been treated with bedrest alone, one had had excisional surgery and seven had been treated with radiotherapy. Neither radiotherapy nor excisional surgery was utilized in our group. Nevertheless, it is likely that circumstances may arise in which such accessory therapy may be advisable. It is possible that in the presence of a huge mass of caseous nodes local excision of this mass, preceded and followed by chemotherapy might accelerate resolution. Similarly, radiotherapy, which has been an effective method of local treatment might be used (11), and this has indeed been advocated (12).

The use of drugs other than isoniazid, streptomycin and PAS has been considered. Pyrazinamide, for example, has been found to give rapid regression in peripheral tuberculous lymphadenitis (13) but is too toxic for general use (14). It is unlikely that viomycin, oxytetracycline, or tetracycline could find wide use in this condition. It has been claimed that sodium salicylate has a satisfactory effect on the local lesion. Nevertheless, in one series in which this medication has been used, five of 75 patients treated developed generalized tuberculosis (15).

5. *Chemotherapy must be prolonged.* Experience with other forms of tuberculosis are confirmed in the chemotherapy of peripheral tuberculous lymphadenitis. Short-term treatment carries a definite risk of recurrence and inadequate resolution. We consider that one year of chemotherapy is the minimal acceptable duration of treatment. No hard and fast rule can be made, however. Chemotherapy should be prolonged much beyond one year in instances in which continued regression is observed. Just as in pulmonary tuberculosis, in which caseous lesions of long duration heal more slowly and require more prolonged therapy (16), so do some cases of peripheral tuberculous lymphadenitis require similarly prolonged treatment before maximum reabsorption takes place (Table III). We would suggest that complete stability and absence of symptoms in any lesion for at least four months be required before therapy is discontinued, with the proviso that no course of therapy be shorter than one year.

Where other tuberculosis exists concomitantly, the duration of therapy must be evaluated differently. Thus, management of pulmonary or renal tuberculosis would take precedence, in estimation of the nature and duration of chemotherapy, over the lymphadenitis.

Occasionally, clinical stability of the lymphadenitis may be difficult to judge, as when intercurrent upper respiratory infections are accompanied by the appearance of pain and tenderness in the involved nodes. We have seen this on a number of occasions and this has been noted by others in instances of lymphadenitis secondary to Vole bacillus vaccination (17). It is difficult to be sure whether one is dealing with a non-specific lymphadenitis in glands whose architecture has been altered by healing following tuberculosis, or recrudescence of tuberculous lymphadenitis consequent upon such non-specific lymphadenitis. Where we have been in doubt, we have continued antituberculous chemotherapy for periods longer than otherwise planned, or we have restarted chemotherapy in recently discontinued cases.

RESULTS OF THERAPY

Although final evaluation of results of therapy in our series has not yet been made (almost one-third of our cases are still under treatment) tentative conclusions based on observations to date seem warranted. First, and most important, it is apparent that chemotherapy is a highly effective method of treatment of peripheral tuberculous lymphadenitis, at least insofar as short term results are concerned. Final conclusions in this regard are not justified in a disease noted for

its chronic, relapsing nature. Nevertheless, no other method of therapy so far available gives such rapid therapeutic response.

This response is seen in all types of peripheral tuberculous lymphadenitis. It was seen in patients with simple uncomplicated enlarged nodes, as well as in those with fluctuation, local abscess formation, discharging sinuses, matting, pain and tenderness. This frequency and breadth of response has been observed by others (12, 18, 19). This has been seen with each of the drug regimens we have employed. Present observations are still inadequate to indicate a preferential regimen. Single drug isoniazid therapy has proven effective (8, 18), but other factors such as stability of results on long term observation, may indicate that combined chemotherapy is preferable. Where streptomycin therapy is not feasible, certainly isoniazid with PAS is a perfectly satisfactory regimen and if the PAS is not tolerated, isoniazid alone should be used.

Response to chemotherapy is usually rapid. In every case in our series such response was noted before the end of the fourth month. Indeed, in 41 of the 44 cases it was seen within the first two months. We would suggest that where response is not seen in the first few months of therapy the diagnosis of tuberculous lymphadenitis should be questioned. *In this sense, chemotherapy with isoniazid can serve as a "therapeutic test" for the diagnosis of peripheral tuberculous lymphadenitis* (*Table III*). The overall results of treatment to date are summarized in Table IV. It will be noted that in almost 15 per cent of our patients who have completed a course of therapy, recurrence of the lymphadenitis has been noted. Analysis of these cases indicated that in each, therapy had been inadequate insofar as duration was concerned. Each had had four months or less of chemotherapy. Upon reinstitution of chemotherapy, renewed regression of the tuberculous lymphadenitis has been noted. The retreatment continues in most cases. It has been noted elsewhere (18) that relapse may occur even after more extended treatment. Observation continues in our patients to study this possibility.

Drug toxicity has not been a limiting factor in this series although in one instance tinnitus and vertigo occurred during dihydrostreptomycin therapy. There was no evidence of isoniazid toxicity, and PAS intolerance because of gastrointestinal symptoms was easily controlled.

TABLE IV

Peripheral tuberculous lymphadenitis: results of therapy (44 cases)

Chemotherapy	No.	Good Response		Recurrence
		Therapy Completed	Under Treatment	
INH	17	5	9	3
INH-DHSM-PAS	21	16	4	1
INH-DHSM-PAS plus local injection of DHSM	4	3	1	0
	42*	24	14	4

* Two patients lost to observation

SUMMARY

1. Tuberculous peripheral lymphadenitis is a local manifestation of generalized tuberculosis. This is true whether the tuberculous lymphadenitis is part of the primary infection or a manifestation of post-primary lymphohematogenous dissemination.

2. This pathogenetic concept indicates that local therapy is inadequate.

3. Chemotherapy is necessary for every patient with active tuberculous peripheral lymphadenitis. Local therapy (excision, radiotherapy, antimicrobial injections) may be useful as accessory treatments for the local lesion.

4. Isoniazid alone or in combination with other antituberculous drugs is the treatment of choice. Data are still inadequate for the selection of an optimum regimen. Any chemotherapeutic regimen containing isoniazid will yield a high percentage of satisfactory results.

5. Chemotherapy must be prolonged; a minimum of one year is required. Short term chemotherapy carries a greater risk of inadequate response and/or recurrence of disease.

6. Should recurrence occur, in our experience it has been in the same area as the original lesion. Response to retreatment in each of our cases has been excellent.

7. Response to chemotherapy is noted rapidly following its institution. Should no effect on the local lesions be noted in four months, the diagnosis of peripheral tuberculous lymphadenitis should be reviewed. Maximum response, however, requires a much longer period and chemotherapy should be continued until it has been obtained and has remained stable for at least four months.

8. Peripheral tuberculous lymphadenitis is, however, a chronic and relapsing disease in its natural history. Therefore, long term post-therapy observation would be required before final evaluation is made of chemotherapy as the definitive treatment for this disease.

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CHANGING THERAPY IN CUTANEOUS TUBERCULOSIS

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A discussion of tuberculosis of the skin from the practical viewpoint can be divided into its clinical features, methods of treatment, and prognosis. It is not within the scope of this paper to consider differential diagnosis or the basis of classification by various authors. To do this one would have to discuss bacteriology, histology, immunity, and allergic mechanisms for each category. This is easily found in many textbooks and articles.

For our purpose it is best to divide tuberculosis of the skin into three groups: (a) primary tuberculoses, in which tubercle bacilli can be readily demonstrated by direct examination culturally and/or by animal inoculation, (b) tuberculids, in which organisms are rarely if ever demonstrated and which are of an allergic nature, and which have foci of active tuberculosis elsewhere, and (c) the fringe group, among which are sarcoid and possibly the rosacea-like tuberculid of Lewandowski. In this paper we will discuss only the first two groups.

Table I briefly classifies the various types of cutaneous tuberculoses.

The treatment of cutaneous tuberculosis has been changed significantly by the newer chemotherapeutic agents recently introduced. Prior to 1943, therapy consisted of phototherapy (Finsen Lamp), caustics, surgery, tuberculin injections, salt-free diets, cryotherapy, heliotherapy, radiation therapy and others. These methods produced many good results, but will not be discussed because of recent advances with newer medications.

The chemotherapeutic agents to be discussed include calciferol, streptomycin thiosemicarbazone, isoniazid, and combination therapies.

CALCIFEROL (VITAMIN D_2)

Charpy (1a) was the first to use calciferol in 1943, followed by others whose final observations and techniques were recently summarized at the Tenth International Congress of Dermatology in London in 1952 (1). A few papers reported since the above have added nothing new; merely substantiating previous findings.

It was found that the best average dose was approximately 150,000 units daily for about one month, followed by 100,000 units daily for one year and longer (considered as one course).

Marcussen et al (1b) had an overall 83.5 per cent cure rate (clinical and histological) in 280 cases of lupus vulgaris, including retreatment of relapses in those observed from two to three years. Relapses, however, were common, with 33 per cent recurrence after one course. Therapy beyond 34 months produced no further benefits. His latest report (2) of the treatment of 284 lupus vulgaris resulted in 78.5 per cent cures; 16.5 per cent did not become symptom-free,

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TABLE I

Type of Skin Tuberculosis	Clinical Picture	Histology	Demonstration of Organism	Tuberculin Test
I. Tuberculoses				
A. Primary complex	Ulcer at site of inoculation with lymphangitis and lymphadenitis, mostly on face and buttocks	At first inflammatory reaction which develops into tuberculoid structure	Very frequently	+ + +
B. Lupus vulgaris (T.B. lupus)	"Apple jelly" nodules which coalesce to various sizes to form placques, mostly on face, and causing scarring	Tuberculoid—occasional caseation	Frequently	+ + +
C. Tuberculosis verrucosa cutis	Wart-like papules which coalesce to form placques—especially on fingers. Produces scarring	Tuberculoid—no caseation. Occasional inflammatory reaction. Marked epithelial hyperplasia	Frequently	+ + +
D. Tuberculosis colliquativa (scrofuloderma)	Ulcers surrounding sinuses from underlying infected bones or lymph nodes—scarring	Tuberculoid plus considerable inflammatory reaction	Frequently	+ + + +
II. Tuberculids				
A. Tuberculosis cutis lichenoides (lichen scrofulosorum)	Follicular lichenoic papules in groups. No scarring	Tuberculoid	Rarely	+ + + +
B. Papulonecrotic tuberculids	Many papules, especially on extremities, some of which ulcerate	Tuberculoid, plus ulceration	Rarely if at all	May or may not show reaction
C. Lupus miliaris disseminating faciei	"Apple jelly" nodules usually on face—may case scarring	Tubercules	Rarely	May be positive but most often no reaction
D. Erythema induratum (Bazin's disease)	Deep nodules which may ulcerate, especially in women. Mostly on posterior leg. Heal with scarring	Tuberculoid with deep inflammatory reaction, plus necrosis	Rarely	May or may not show reaction

chiefly because of drug intolerance, and 5 per cent of those had relapsed. His five year observations indicated that 29.2 per cent of the patients first treated and 37.2 per cent of those who became free of symptoms had relapsed. Calciferol was contraindicated in erythema induratum and pulmonary tuberculosis. His comparison with reports of Finsen light therapy in other clinics indicated that the latter produced 70 per cent symptom-free cases over a longer observation period. Finsen-treated cases, however have a tendency to recur after being exposed to local injury (e.g., cold or trauma) or when the body resistance was lowered. This explains the poor results of plastic surgery in Finsen Lamp treated cases. Since Finsen therapy requires hospitalization, it is an expensive procedure and has never become popular in this country. On the other hand, calciferol therapy is easily carried out and we have treated many cases on the Dermatologic service with this drug. Our results parallel those reported above.

Riehl (1c) notes that of 488 cases treated with calciferol in younger age groups, 295 were apparently cured at the end of one year; 70 had a good clinical result; 54 had little or no benefit; 24 had recurrences; 45 were labeled as insufficiently treated. Of 165 cases of lupus vulgaris treated in older age groups using a maximum of 200,000 units D_2 per week, he cured only 12 cases. Others improved in the latter group, but required much longer treatment.

Charpy (1a) has had the greatest experience with calciferol. His results in 1115 cases of lupus vulgaris show a cure rate of over 75 per cent with the rest showing improvement and in only nine cases proving absolutely refractory. He concludes that 2,000 units per kilogram of body weight daily is the maximum dose and 1333 units per kilogram of body weight is the safe dose. His cases were followed by biopsies every four to six months. Milk is prescribed in amounts of 500 to 750 cubic centimeters daily, together with $1\frac{1}{2}$ grams of magnesium chloride, and in most cases supplemented by vitamin C. With his regime he has had no cases intolerant to the remedies used. He feels calciferol is valueless in ulcerated lesions, and should not be used if there is pulmonary tuberculoses. It is of no value in erythema induratum, ulcerative tuberculoses, or in the tuberculids. He advises no local therapy.

Toxic symptoms due to large doses in order of frequency and severity are malaise, headache, indigestion, anorexia, thirst, polyuria, constipation, loss of weight, nausea, vomiting, photophobia, and coma.

Dowling, et al (1d) report that calciferol may produce clinical toxicity, hypercalcemia, and impairment of renal function. There were 13 cases of renal impairment in children and 32 in adults. Of 47 children and 49 adults treated there was evidence of renal impairment in 45, which on final analysis left residually two very slightly impaired children and 15 adults, as evidenced by urea clearance tests. The damage is evidently due to deposits of calcium in the renal tubules. Routine testing, done monthly, should consist of examinations for renal efficiency and blood calcium.

Ehring (1e), after observing 1,000 cases, states that if the total dose is no greater than 3.5 grams given in 10 to 15 milligram doses per week, there will be no kidney complications. If the above dose is doubled, evidence of damage to the kidneys occurs often.

Wetherley-Mein (1f) concludes that calciferol has no direct bacteriostatic or bactericidal effect on the tubercle bacillus, nor does it modify its virulence. Its value lies in its stimulation of cellular reaction of the host to the chemical constituents of the bacillus.

Polano (1g) had a 74 per cent histological cure rate in 70 cases treated with calciferol.

Craps (1h) treated 104 cases of lupus vulgaris, of which 44 per cent were cured over a two year observation period, with improvement up to 90.5 per cent with one course of therapy.

Marcussen and Nielsen (1b) noted that their experiences, as well as others, corroborated the fact that during calciferol therapy tuberculous processes may flare up and fresh tuberculous processes develop in other organs. This occurred in 15.4 per cent of their cases.

Jaksa (1i) agreed with the findings obtained in other clinics and had good clinical results with large doses of D_2 which were documented by histological findings. He feels that lupus vulgaris is best treated with calciferol in combination with salt-poor diets and the use of chemicals locally, or electro-surgical methods when indicated.

Proppe (1j) had no reactions in his cases with total dosages of two milligrams daily. His results were very good if the patients were treated long enough. Of 356 patients, 146 were cured, of which two had recurrences; 146 were improved; 37 had no improvement. One-half of his cases were asymptomatic after nine months of therapy and another 20 per cent after one year of continued treatment. Ten per cent required therapy for two years or longer. He noted side effects in 32 patients in this group, consisting of nausea, vertigo, cardiac symptoms, anorexia and abdominal pain.

THIOSEMICARBAZONE (CONTEBEN, TB_1)

Craps (1h) does not feel that this drug has much value. Sainz de Aja (1k), however, felt it was useful. He improved lupus vulgaris with doses of 200 milligrams per kilogram of body weight per day. Two cases of Bazin's disease were cured. According to him, best results were obtained in muco-cutaneous open lesions.

Riehl (1c) treated 97 cases, chiefly those involving mucous surface, or where calciferol was contraindicated (such as pulmonary tuberculosis). There was great improvement in a short time in 80 per cent of his cases with many going on to cure. His recurrence was larger than with calciferol. He noted menstrual difficulties in many of his patients.

Polano (1g) treats his cases by determining the patient's tolerance to the drug and found it to be between 100 to 200 milligrams per day. He cured eight out of ten with Bazin's disease and had marked improvement in two cases. Two cases each of papulo-necrotic tuberculids and tuberculous erythema nodosum were cured. He feels that this drug is the best for tuberculids.

Ehring (1e) noted in 700 patients treated that it acted better on mucous membrane tuberculosis than calciferol. The latter, however. is superior in other

types of skin lesions. This drug causes frequent side effects relating to the blood and digestive systems.

Martinez (1l) treated 13 cases orally and 12 intramuscularly, plus local application of thiosemicarbazone powder. His results show that the injection route produced more favorable results than when given orally.

STREPTOMYCIN

Sainz de Aja (1k) treated 47 cases for one to three months with one gram daily. Resistance was noted after three months and no further results were obtained after this length of time. He feels it is superior to D_2 in papulo-necrotic tuberculids and tuberculosis lichenoides.

Riehl (1c) treated 25 cases, with the drug benefitting occasionally, but there were many recurrences. Adoni (33) had good results in scrofuloderma and tuberculosis verrucosis cutis with intramuscular injections, as well as by injection of the drug into the lesions. He feels calciferol is better than streptomycin in lupus vulgaris. The best indications were for ulcerated and tumidus lupus vulgaris, scrofuloderma and tuberculosis verrucosa. It is ineffective in the tuberculids.

On the other hand, Hamilton (3) treated two cases of erythema induratum and had dramatic improvement within 42 days in one case and 24 days in another. Foster (4) injected about one gram daily into the lesions of one case of tuberculosis verrucosis and two cases of lupus vulgaris with complete healing in three to nine weeks.

Zeller (5) injected one gram daily of dihydrostreptomycin. This was often followed by cure and sometimes by complete cure with from 10 to 40 grams of the drug. Exacerbations as occur occasionally with calciferol and P.A.S. was not seen. Hypertrophic forms of tuberculosis healed or improved in a shorter time than ulcerative forms.

Sabry (1m) treated 61 cases and feels its benefits were too evident to be overlooked. Van der Meulen (1t) treated 27 cases with 0.5 to 1 gram daily up to 30 to 40 grams total dose, resulting in clinical cures, with only two relapses within a year.

PARA-AMINO SALICYLIC ACID (P.A.S.)

Linnros (6) gave 8 to 12 grams daily, together with ten per cent sodium PAS wet dressing or ointment without any result in two cases of lupus of the nasal cavity. He had good results with this method in three cases of scrofuloderma and had improvement in two cases of Bazin's disease. Appel (7) treated one case of lupus vulgaris locally with a 20 per cent solution of PAS which apparently healed, relapsed, and was cured after prolonged use of this drug. He cured a case of Bazin's with injections of a five per cent solution daily, plus PAS compresses, within three weeks.

Bory (1n) felt it was of value injected into the lesions, plus curettage. Craps (1h) states that used alone it has no value. Riehl (1c) treated 28 cases of scrofuloderma, but did not think it very effective. Holsinger (8) felt PAS was of no value. Ehring (1e) had no results in 35 cases with this drug.

COMBINED THERAPY

Zeller (5) feels a combination of streptomycin, PAS and calciferol is often effective. Pasieczny (9) had excellent initial responses in nine cases by combining streptomycin and isoniazid, and moderate improvement in one case.

Huriez (10) treated 230 cases, of which 67 per cent were lupus vulgaris, by giving streptomycin (one gram) and 15 to 20 grams of P.A.S. daily for two months, after which he gave a 15 milligram ampoule of Sterogyl (D_2) every week for six months. This resulted in 55 per cent cures and 10 per cent failures. He feels the alternating method gives the highest cure rate. Adoni (33) feels a combination of streptomycin, PAS, and calciferol, helps resistant cases. Sainz de Aja (1k), in reviewing his cases, feels the use of various combinations of previous drugs mentioned, plus heliotherapy, with occasional use of curettage when indicated, gave him the best results. Charpy (1a), on the other hand, has no use for combined therapy.

Craps (1h) concludes that the best method is to prepare the patient by PAS and dihydrostreptomycin, followed by calciferol and concomitant use of actinotherapy. He states that mucous membrane tuberculosis responds best with this combination, together with electrocoagulation, if indicated.

Huriez (10) feels that combination therapy, plus local destruction of the lesions, produced best results in 250 cases he treated. Schmid (1p) also preferred combination therapy. Ehring (1e) concludes that combinations of drugs, plus Finsen therapy, cause quicker healing. His results with local application of PAS, calciferol, and thiosemicarbazone indicated no effect. Graul (1q) concludes that combinations of these drugs, plus local therapy, is best because the time of treatment is shortened and primary and secondary resistance to drugs used may be decreased.

Granroth (1r) treated 350 cases of skin tuberculosis and states that none of the drugs can replace calciferol as a single method of therapy. He feels that combined therapy, starting with 0.5 to 1 gram of streptomycin and PAS, 5 to 15 grams daily, for 30 to 60 days, followed by calciferol, will produce better results.

Panja's (1s) experience with 200 treated cases indicates a combination of calciferol, plus streptomycin, produced the best results.

Jaksa (1j) used D_2, streptomycin, and PAS in the hematogenous forms of skin tuberculosis, plus a salt-free diet. Even with this combination he had a high number of recurrences. He felt that PAS was not tolerated in large doses, but in combination with streptomycin there was less tendency to recurrence. His dosage of streptomycin was continued until he gave 20 to 30 grams. However, he felt, in order to get lasting results, doses of 60 to 100 grams were necessary.

ISONIAZID (INH, RIMIFON, NYDRAZID)

This new drug gave a marked impetus to the treatment of skin tuberculosis following the original report of Robitzek et al (11) of its effects on systemic tuberculosis.

It is impossible to summarize the results of the many reports in tabular

form because of the great variation in classification and indices of improvement. For this reason it is felt that the results in each type of skin tuberculosis should be discussed separately.

A. Lupus Vulgaris

Goldberg and Simon (12) treated two cases of lupus vulgaris with dramatic results, so that after four months it was practically impossible to see any activity. Their dose was four milligrams per kilogram of body weight daily. They had no side reactions.

Roof (13) had an excellent result in a case of lupus vulgaris who had received 150 milligrams daily for two years.

The above three cases had a great deal of other therapy with no response, including calciferol in the last case mentioned.

Cormia et al (14) had decided beneficial effect in seven cases with doses ranging from 0.2 to 1.2 grams daily, and felt that the higher doses did not accelerate improvement. Doses of 0.2 to 0.6 grams daily are well tolerated.

Marchionini et al (15) treated 113 cases in which there was excellent immediate response in 111, especially in those with ulcerated lesions. One-half of these were cured within 10 to 14 weeks. He begins with 0.2 gram daily for one week, increasing this dosage until 8 to 12 milligrams per kilogram is given, divided into four doses, after meals, with milk. After 50 to 70 grams (12 to 14 weeks) total dosage, with still no response, treatment was continued for three additional months with a maintenance dose of 5 to 6 milligrams per kilogram. Side effects noted by him were gastrointestinal disturbances, initial leukopenia, paresthesia, drug manifestations, headaches, and dizziness, which are seen early but disappear.

Riehl (16) treated 67 cases with doses of 5 to 15 milligrams per kilogram and observed them for six months. Of these, seven were cured. He felt it was too soon to form an opinion about the others. Ten cases in the group who were refractory to all other methods of therapy had a good response after a short observation period.

Bravo et al (17) used INH in six cases (3 to 10 milligrams per kilogram) over a period of 18 to 58 days. All showed immediate improvement. Lesions disappeared in two cases, only to recur within one month.

Russell et al (18) treated 15 cases, some orally, some by local injections of INH, and some with the combined method. The average oral dose was 300 milligrams daily. The injected material contained 50 to 250 milligrams INH in 2 to 5 cubic centimeters of fluid. Observation from ten weeks to nine months revealed that of those treated orally, one was cured, two had decided improvement, one each had moderate and slight improvement. Of those treated with local injections only, one each had decided and moderate improvement, and four had none. Of four having local and oral therapy, one was decidedly improved, two moderately so, and one only slightly. Improvement was continuous and indicates there was no resistance to therapy. He felt that combinations with calciferol would be better because INH is bacteriostatic and calciferol stimulates the host's resistance.

Leider and Sawicky (19) treated 12 cases of lupus vulgaris with 150 to 250 milligrams daily doses with few reactions. Their results over a period of 7½ months show a 95 per cent healing rate in four cases. Five had a good response and there was no change in three.

Sobel (20) reports a case which did not improve with calciferol and streptomycin, but which almost cleared up with 150 milligrams of INH daily for a period of 2½ months.

Latapi (21) et al, using 3 to 8 milligrams per kilogram per body weight daily on four cases, had one clinical cure, two with remarkable improvement, and one improved observed over a period of two to seven months.

In a symposium (22) on INH therapy of lupus vulgaris, Dowling, et al (22), Sommerville and Milne (22), and Hodgson (22) report that, of 40 cases treated only with INH, with doses averaging 2 to 300 milligrams daily, ten were cured (three in four months), 11 almost cured, 19 improved.

Blumenthal (23) treated 28 cases with average doses of 6 to 8 milligrams per kilogram over a period averaging six months, with four cases cured, nine nearly cured, 12 with appreciable benefit, and three unimproved. He feels that therapy over six months will not result in further improvement. Reactions are rare, mild as well as transient, and consist of nausea, vomiting, vertigo, urticaria, petechiae, and occasionally paresthesia, neuritis, and psychosis only in high dosages.

Wehnert (24), reporting on the first 30 cases of a series of 115 cases (positive cultures being obtained in 22), gave 4 to 5 milligrams per kilogram daily, using two months of therapy as a course. Fourteen of 30 cases were healed, but six have relapsed after one to two courses of therapy; 16 have not cleared yet, but treatment is continuing. In an addendum later (1954), he states he treated 160 patients, of which 136 were lupus vulgaris. His total dose was 100 milligrams three times daily for 200 days without rest. This seemed necessary to obtain 90 per cent results in this form of tuberculosis. He found no resistance developing to isoniazid when cultures of tubercle bacilli obtained from biopsy specimens were exposed to the drug. His emphasis that a resistance does not develop is important because of previous reports with contrary findings. He feels, however, that combination therapy will probably be the method of the future.

El-Mofty (25) treated 13 cases, of which 11 were completely cured, one greatly improved, and one slightly better. He suggests that combination therapy with streptomycin produces a more vigorous improvement.

Granroth (1r) used INH in ten cases of lupus vulgaris, all of whom responded well. He feels best results in the future will be obtained by combining INH with calciferol, inasmuch as the former has bactericidal properties and the latter cellular stimulating ones.

Tchou and Kao (26) treated 22 cases with INH. Nine of these were lupus vulgaris, two tuberculosis verrucosis cutis, two ulcerated tuberculosis, and nine Bazin's disease. In this group there were ten clinical cures, eight showed marked improvement, and four, who were under a short period of observation, improved.

Vivarelli and Hoffman (27) report that they give 3 to 4 milligrams INH per kilogram daily for a variable length of time. They interrupt therapy every

month for eight to ten days. Some of their cases had INH injected intralesionally and a few applied INH ointment. Treatment was continued for several months after apparent cure. In 23 cases of lupus vulgaris, there were 17 clinical cures; three had very good improvement; one was intolerant to the drug; and two were failures. The presence of the tubercle bacillus was proved in the above cases. Vivarelli and Hoffman (27) thought INH the best drug for treatment of cutaneous tuberculosis because of rapid results obtained and because no resistance to therapy was noted, as has happened with D_2. Early toxic manifestations were constipation, diarrhea, vertigo, headaches, loss of appetite, nausea, difficulty in urination; and, in two cases urticaria developed.

Steinhoff's (28) preliminary experiences with INH in 82 cases gave him a thoroughly favorable impression. The majority of his patients were clinically cured. There were no side effects with a dosage of 0.01 grams per kilogram daily and only one case in this series was unable to continue therapy.

Jaeger and Koenig (29) treated 18 cases with INH after relapse under calciferol therapy. They had excellent immediate results, but feel that the end-result of definite healing must await proof obtained by negative animal experiments.

Wortman's (30) results in 19 cases of lupus vulgaris lead him to say that INH is a first-class therapeutic agent; that this drug makes it easy to treat skin tuberculosis; that there are no unpleasant side effects; and, results are faster and, in many cases, cures are effected.

Local applications of INH as five per cent Nydrazid in an emulsifying base applied to six lupus vulgaris (biopsy proved) cases, healed three new cases in eight to ten weeks (31). In three old cases, two were quiescent and one improved. Five of these cases showed no fresh activity after a 9 to 12 month observation. The results of Russell et al (18) have been discussed earlier.

B. Tuberculosis Verrucosis Cutis

Harvey and Leslie (31), using topical applications of INH healed three cases of verruca necrogenica within seven days. Marchionini's three cases responded well (15). Bravo et al treated two cases with total dosage of 10 to 15 grams in 22 to 23 days with considerable improvement (17). Riehl's one case improved quickly (16). Latapi, et al (21) in four cases had three which were clinically cured and one with remarkable improvement.

C. Scrofuloderma

Cormia (14) had decided beneficial results in two cases and Marchionini's six cases responded well (15). Bravo et al (17) treated five cases of tuberculosis adenitis (2 to 10 milligrams per kilogram daily) for a total dose of 2.25 to 12.9 grams). He found immediate improvement in three, cure in one, and one failure. One case of scrofuloderma on a total dosage of six grams was cured in 46 days. Riehl's three cases responded well (16) and Leider and Sawicky (19) healed one case in two months. Latapi et al (21) treated four cases, with one clinically cured, two remarkably improved, and one improved. El-Mofty (25) treated

four cases; two were cured; one had great improvement, and one, slight. Vivarelli and Hoffman (27), using INH, had two clinical cures and one very good result in their three cases.

D. Erythema Induratum

Cormia et al (14) had poor results in nine cases, good in two instances while Harvey and Leslie (31) treated three cases with local applications of INH All became worse and two so badly that treatment was terminated. However Marchionini's five cases responded well (15) while Bravo et al (17) treated six cases (5 to 16.75 grams in 17 to 45 days) and had two with complete disappearance of lesions. Riehl (16) treated 17 cases, most of whom were clinically cured in a comparatively brief period and Leider and Sawicky (19) had five excellent and two good results with seven cases. Latapi (21) had one case with improvement, El-Mofty (25) cured one case and Vivarelli and Hoffman (27) treated three cases, all of whom were clinically cured.

E. Papulo-Necrotic Tuberculid

Marchionini (15) treated five cases which responded satisfactorily. However, therapy was difficult to evaluate because lesions came in crops and tended to heal rapidly and spontaneously. Bravo et al (17) treated three cases (5 to 13 grams in 18 to 45 days) and had complete cicatrization in one case, with improvement in the other two. Cormia (14) treated three cases; had two good results and one poor one. Latapi et al (21) treated two cases with remarkable improvement. El-Mofty (25) cured one case, markedly improved one, and greatly improved the third.

F. Lupus Miliaris Disseminatus

Riehl (16) used 12 grams in one case, which did not respond to therapy.

G. Tuberculids

A few authors reported on tuberculids without specifying the type. Riehl (16) could not determine the effects of INH in this group. Leider and Sawicky (19) had no improvement in one case while Holsinger and Dalton (32) treated two cases with slow response, but they showed definite signs of improvement.

COMBINATION THERAPY OF INH WITH OTHER AGENTS

Pasieczny (9) treated ten females with Bazin's disease by giving one gram streptomycin intramuscularly daily and 200 milligrams of INH. All but one had an excellent immediate response. His final observation indicates that seven had a very good response, one case had fair response, and two were therapeutic failures. Holsinger and Dalton (32) reported no resistance of the organism if alternating schedules were used, such as INH for one month, streptomycin and PAS for one month, and repetition of the same schedule. He cured one case of lupus vulgaris and remarkably improved another. In one case of scrofuloderma he had an excellent result. Of two cases of papulo-necrotic tuber-

culides, one case treated with INH plus dihydrostreptomycin, completely cleared, and the other became worse when these two were combined with PAS He felt that true tuberculoderms did better than tuberculides.

Vivarelli and Hoffman (27) do not believe that combination therapy of INH PAS, D_2, and streptomycin is necessary. They would use it only if INH therapy itself would not cause their cases to respond.

SUMMARY

Prior to isoniazid, calciferol was the best single agent for the treatment of cutaneous tuberculosis.

Calciferol produces clinical cures in possibly fifty to seventy-five per cent of the cases in which it is used. It does produce toxic symptoms, one of which may be permanent, such as impairment of renal function. It seems to be contraindicated in erythema induratum.

Thiosemicarbazone seems to be of value in erythema induratum and in tuberculosis of muco-cutaneous surfaces. It produces many toxic symptoms, and only few investigators recommend its use.

Streptomycin is very useful as a single remedy, but resistance of the bacillus to the drug can develop.

PAS has little value when used alone.

Many investigators feel that various combinations of the above agents produce better results than any single one.

Isoniazid has been in use for only a few years. Its final evaluation will take some time. However, those who have used all previous drugs, feel that INH is possibly the best single drug presently available. This drug has fewer side-effects, produces faster results, and does not cause the tubercle bacillus to become resistant.

The consensus seems to be that combination therapy using the above agents will become the method of choice.

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THE ACTIVE MANAGEMENT OF PULMONARY TUBERCULOSIS IN PREGNANCY

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Approximately three of every one hundred young women who are admitted to the Obstetrical Division of The Mount Sinai Hospital have evidence of pulmonary tuberculosis. This would indicate that the complication of tuberculosis in pregnancy continues to be a serious one.

It is difficult to know whether the extent of the problem has changed in recent years. Comparison with the results of studies made even so recently as ten years ago would hardly be profitable since it must be suspected that the incidence of tuberculosis in pregnant women would have declined simultaneously with the overall decline in the general population. There are no data on this point, except by inference. It is even difficult to ascertain whether the incidence in our institution is approximated elsewhere, because of the paucity of reported investigations.

Those data which have been reported would indicate that our own experiences are not unusual. Freeth examined by routine x-ray 541 consecutive admissions to an ante-natal clinic in Glasgow (1). Although all these women were apparently well, without history of tuberculosis, seventeen (3.1 %) showed evidence of active or inactive pulmonary tuberculosis. Reginster examined 3,290 obstetrical clinic admissions by routine x-ray in Liège and reported that 3.19 per cent of these apparently well young women had x-ray evidence of tuberculosis (2). Both of these surveys were conducted with full scale radiography, as has been our practice at The Mount Sinai Hospital (3). Utilizing a photo-roentgen survey, an incidence of 1.85 per cent was recently reported from the New York Lying-In Hospital (4).

It is of interest in each of these studies, as in our own, the majority of patients found to have pulmonary tuberculosis were unaware of their disease. In Reginster's series more than two-thirds of the pregnant women found to have tuberculosis, had considered themselves perfectly well until the x-ray findings were available. This has been our experience as well. Four thousand seven hundred thirty-nine pregnant women were registered at the ante-natal clinic of the Obstetrical Division from April 1, 1953, to January 31, 1956. Each patient was examined by routine chest x-ray examination, a full size 14″ x 17″ chest film being taken. Evidence of pulmonary tuberculosis was found in 161, and another patient was found to have tuberculosis on clinical examination. Eighty-

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TABLE I

Incidence of pulmonary tuberculosis

The Mount Sinai Hospital Antenatal Clinic (April 1, 1953–January 31, 1956)

A. Total clinic admissions		4740	
B. Patients with pulmonary tuberculosis		162	(3.4%)
Diagnosis by x-ray survey	161		
X-ray alone	86		
X-ray plus history	75		
Diagnosis by clinical examination	1		

TABLE II

Analysis of patients with pulmonary tuberculosis

The Mount Sinai Hospital Antenatal Clinic, 1953–1956

	Active Pulmonary Tuberculosis	Inactive Pulmonary Tuberculosis	Total
Diagnosis			
X-ray alone	28	58	86
X-ray plus history	12	63	75
Clinical examination	1	0	1
Racial origin			
Porto Rican	27	70	97
Negro	12	26	38
White	2	23	25
Oriental	0	2	2

six of the 161 had no inkling of any pulmonary disease before the x-ray was taken (Table I). Parenthetically, it would appear that obstetrical management which does not include routine chest x-ray examination will overlook a significant number of cases with this important complication of pregnancy.

The importance of routine x-ray survey in the diagnosis of pulmonary tuberculosis in pregnant women is emphasized by the fact that it was precisely in patients with active disease that a larger proportion of cases were found by routine x-ray than among patients with inactive disease. This, of course, was to be expected. Patients with inactive disease were likely to have had some previous history of pulmonary infection while those with known disease which was active would tend to be under treatment elsewhere or to have avoided pregnancy. Of 121 patients with inactive pulmonary tuberculosis in our series, in 63 the diagnosis could have been suspected from the history, although in each case there was also x-ray evidence of inactive tuberculosis. In contrast, of 41 patients with active pulmonary tuberculosis, in 28 the diagnosis was completely unsuspected and made only by routine x-ray (Table II).

PROBLEMS AND PRINCIPLES IN THE MANAGEMENT OF PULMONARY TUBERCULOSIS IN PREGNANCY

The first general rule, with which few would argue, would seem to be that all patients with active tuberculosis in pregnancy should be treated. This could be

derived from the dictum in tuberculosis in general, that all patients with active tuberculosis should be treated. However, this is not a simple derivation since the presence of pregnancy raises a number of problems.

First, there is the question of urgency. Usually, though not invariably, when a patient with tuberculosis is seen who is not pregnant there is a certain amount of temporal leeway. A period of observation may often be utilized to determine the exact nature of the disease, its activity and the necessity for therapy. Often, a period of observation with serial films may be utilized before a definite decision is made. Similarly, there are many instances in which it is perfectly safe and even desirable to wait eight weeks or longer for sputum culture reports to assist in evaluation of activity of the disease, and the desirability of treatment.

When the patient with tuberculosis is pregnant, however, we cannot procrastinate. Decision with regard to activity of disease, and consequent absolute necessity for treatment, cannot ordinarily be delayed until we have the comfort of reviewing serial films at intervals of several months. Similarly, although a clear-cut, positive sputum resolves the question when it is present, in many cases such a guide is not available and we are forced to wait several weeks before an answer is obtained and, very often, even then it is an insecure one. In many instances the patient would have delivered before the awaited studies are reported; a highly susceptible infant would then be in contact with a patient of whose disease status we may have doubts.

Moreover, should active disease coexist with our investigative delay, the patient stands the risk of progression of that disease under the influences of the stresses of pregnancy and the puerperium, whether these be social, economic, mechanical, or hormonal, or just working too hard and not getting enough sleep. When to these factors is added the problem of hospitalization of a patient with uncertain disease on an obstetrical ward, it can be appreciated that determination of activity of the tuberculosis in a pregnant woman is of the utmost importance.

Unfortunately, there is no pat nor ready answer to this question. Determination of activity of tuberculosis in a pregnant patient is no easier than in a nonpregnant one. Indeed, it may be more difficult, since the raised diaphragm as well as the prominent vascular markings, are often disturbing factors on the x-ray film, and the sedimentation rate is usually elevated as a concomitant of pregnancy.

The difficulties in x-ray evaluations of activity of tuberculous disease are well known and have been carefully documented in recent years (5, 6). It is unfortunate that this difficulty in evaluation of activity should extend even to the most careful x-ray studies because, especially in pregnancy, the roentgen film is the most suitable and reliable index for such evaluation.

In the present group of patients, since there was great awareness of the importance and urgency of correct evaluation of activity once a lesion was found on the routine survey film, the greatest care was given to this problem. All diagnostic techniques were fully utilized including tomography, apical kyphotic and apical lordotic films, frequent serial films, review of previous films and multi-

TABLE III

Accuracy of evaluation of activity in tuberculosis associated with pregnancy

Extent of Disease Initial Evaluation Final Evaluation	Inactive Inactive	Inactive Active	Active Active	Active Inactive	Total
Minimal	71	4	13	4	92
Moderately advanced	15	4	13	0	32
Far advanced	11	0	4	0	15
	97	8	30	4	139
Inadequate observation	20		3		23
Total					162

ple bacteriological studies. *Despite this, it has been the experience in this study that a certain amount of error is almost unavoidable and should therefore be anticipated and any possible penalty insured against.*

Perhaps a recounting of the experiences in this study will serve to emphasize the difficulties inherent in evaluation of activity of tuberculosis associated with pregnancy. At present writing, of the 162 patients in the series, 139 have been observed for a sufficient period of time (a minimum of three months post-partum and a longer period post-onset of chemotherapy) to give a reasonably good idea of whether evaluation of activity of disease, made after careful study, was correct or incorrect. *In 12 cases of the 139 evaluation of activity was incorrect* (see Table III).

It will be seen from table III that 105 cases were evaluated as having inactive tuberculosis. Subsequent observation showed that this was incorrect in eight cases. Similarly, of 34 cases evaluated as having active disease, the advantage of later observation indicated that four of these cases were, in truth, inactive. Analysis of these cases was undertaken to see where the major pitfalls lay, so that these might be avoided in the future. Even in retrospect, the difficulties remained very real. For example, in 63 of the 139 cases, there was an adequate history of known tuberculosis, with periodic observation in most cases, and yet in five of the 63 cases, evaluation of activity was incorrect.

CASE REPORT

A young woman first presented herself to the obstetrical chest clinic on Sept. 20, 1953 with the history of having had a left segmental resection for tuberculosis two years before. Although a tiny infiltrate was present in the right apex no change had been observed in this in the post-operative period. She was delivered of a live infant on Dec. 6, 1953 with no change in her x-ray status. She had been regarded as inactive and this serial observation indicated that it was so. She became pregnant again and when readmitted to the Obstetrical Clinic another x-ray showed the tiny contralateral infiltrate to be stable. She was delivered of her second baby successfully and again post-partum x-ray showed the right apex to be stable. Thus, on the basis of history, and our knowledge of her previous course, there was every reason to believe that our roentgenographic interpretation of an inactive lesion was accurate. Yet, when this young woman presented herself on November 10, 1955, with her

TABLE IV

Accuracy of evaluation of activity of tuberculosis associated with pregnancy, as related to nature of infiltration

X-ray Interpretation of Pathological nature of infiltrate*	No.	Correct Evaluation of activity	Incorrect Evaluation of activity	Inadequate observation
Exudative	26	23	1	2
Fibrocaseous nodular	51	36	6	9
Productive	117	96	5	16
	194	155	12	27

* Some lesions were "mixed".

third pregnancy, a routine chest x-ray showed fresh disease in the right apex. This reactivation while under observation hardly coincided with our original x-ray interpretation or with the history of stable lesion, thus indicating that stability cannot always be predicted on the basis of history and x-ray in what is an apparently inactive lesion.

Analysis of the data included in table III also indicates that as expected—most difficulty was encountered with small lesions. In 15 far advanced cases, evaluation was correct in each one. Of 32 moderately advanced cases, however, evaluation was incorrect in four and in 92 minimal cases, it was incorrect in eight, an error of over 10 per cent in patients with minimal or moderate disease. Noteworthy also is the fact that evaluation was potentially incorrect both ways, that is, some patients evaluated as inactive were active and vice versa. Thus, eight of 105 evaluated as inactive were actually active and four of 34 evaluated as active were inactive.

The greatest difficulty occurred in evaluation of fibrocaseous nodular disease (Table IV). Figure 1*a–b* shows a sharply circumscribed nodular lesion found on routine x-ray in a young woman completely asymptomatic and with negative sputum. She was placed on prophylactic (vide infra) therapy during her pregnancy and within eight weeks x-ray showed that this nodule was becoming smaller. This indicated that this was an active lesion rather than inactive as provisionally evaluated and therapy therefore was prolonged for 18 months. At one year, the lesion was no longer visible on x-ray. This regression has continued so that on the most recent film of February 1, 1956, only a thin, fine scar is seen in the area of the previous fibrocaseous nodular infiltration. Yet a very similar nodule seen shortly afterwards, in a young woman also with no past history, asymptomatic and with negative sputum, under the same prophylactic isoniazid therapy, has not changed at all. And comparison of films of 11–12–54 and 1–31–56 shows that this lesion, at least at the present, can be considered stable (Figure 2*a–b*).

The above data have been presented, and the three cases briefly mentioned, in order to emphasize and illustrate the difficulties inherent in the evaluation of activity. Although this is not new, or esoteric in the experience of phthisiologists, this problem has not been mentioned in previous studies of tuberculosis and

pregnancy. This is probably because such studies in the past have almost always been retrospective in nature, a review of records of treated patients. At the time of such review, the situation with regard to activity of disease was usually abundantly clear. Such post hoc evaluations are perhaps adequate for academic studies, but they are hardly sufficient for active therapeutic management now that such therapy is feasible.

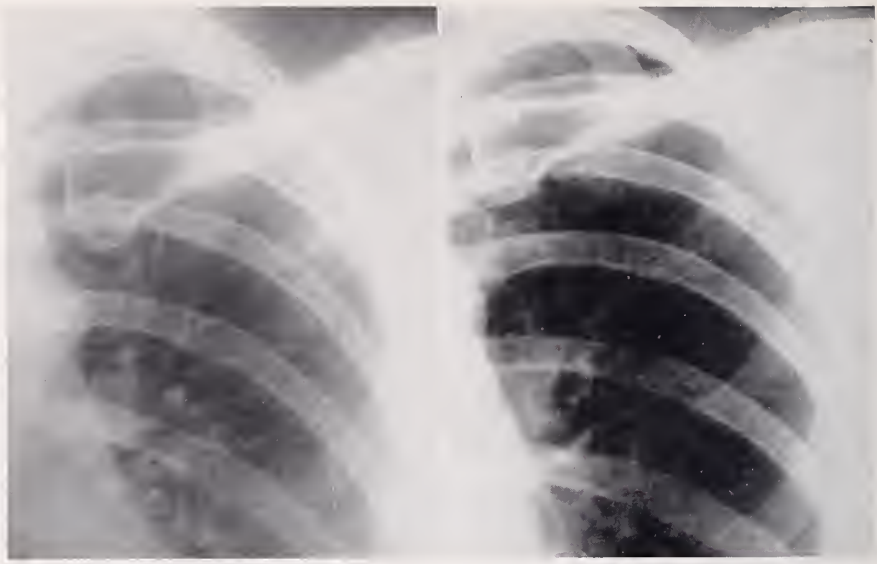
Therefore, even disregarding any tendency for truly inactive and stable disease to reactivate under the stress of pregnancy and merely cognizant of the inherent difficulties of evaluation of activity, it would seem prudent to regard most patients with tuberculosis in pregnancy as potentially active. The therapeutic conclusion which would follow from this premise is that prophylactic therapy for lesions regarded as inactive during pregnancy is a logical and desirable routine. Since it can be shown that such prophylactic therapy carries no significant risk to either mother or child and is without burden socially or economically, prophylactic therapy of tuberculosis in pregnancy appears valid. First on an experimental basis, and later as an essential component, it has been incorporated in the management of patients with tuberculosis in the Obstetrical Chest Clinic at The Mount Sinai Hospital and forms a keystone of the therapy in this clinic.

MANAGEMENT OF PULMONARY TUBERCULOSIS EVALUATED AS ACTIVE DISEASE

Whether the diagnosis of pulmonary tuberculosis is made on routine survey x-ray or on the basis of known disease, the estimation of the activity of the lesion is primarily radiological. Accessory data are welcomed: sputum examinations by smear and culture, review of serial films and evaluation of clinical symptomatology are all valuable but our experience indicates that the main burden, especially with the pregnant patient, must rest on roentgenographic interpretation, even with its acknowledged limitations.

When such roentgenographic interpretation indicates an active lesion (and if interpretation is in doubt, for purposes of management the patient is regarded as having active disease) chemotherapy should be begun at once. There are almost no exceptions to this rule, except perhaps drug intolerance. Those considerations which apply to the management of pulmonary tuberculosis in general are of equal validity in the presence of pregnancy (7). Thus, not only is chemotherapy the mainstay of treatment, but accessory procedures are utilized when indicated. Pneumothorax may be induced or maintained, resectional surgery is possible, as is thoracoplasty collapse. Pneumoperitoneum is not commonly used during pregnancy. Plombage, cavernostomy, pneumonolysis, have also no forbidding contraindications, but are very infrequently used.

Since most patients are seen for the first time during the second trimester of pregnancy, there is usually a period of four to five months of ante-natal chemotherapy. This is of considerable practical importance. Almost all of the patients with active disease treated by us during these past three years, have responded rapidly to chemotherapy, both with regression of the disease on the roentgenogram and reversal of sputum infectivity. These observations are undoubtedly

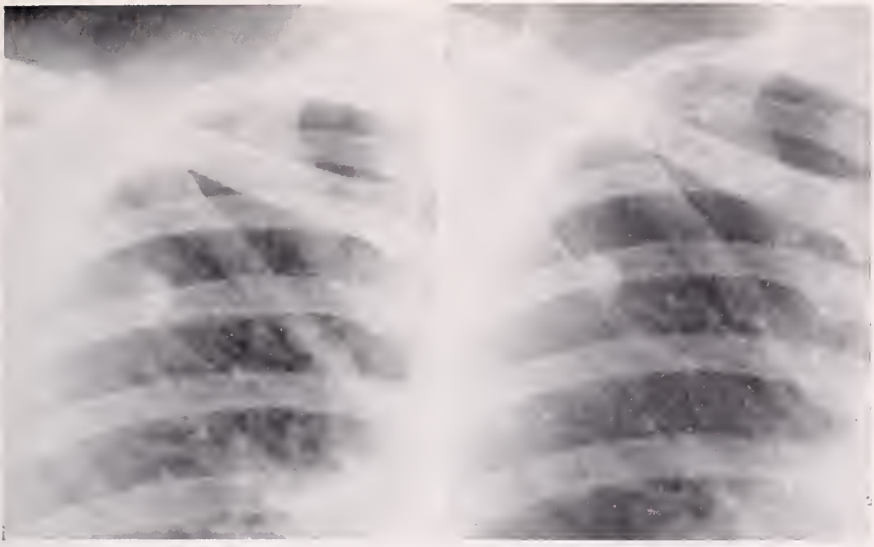


1a M. D., March 26, 1954 *1b* M. D., February 1, 1956

FIG. 1. *a*) Circumscribed nodular infiltrate found on routine prenatal survey film. Considered probably stable. *b*) Placed on prophylactic isoniazid therapy, the nodule regressed, indicating it had been an unstable (active) lesion.

influenced by the fact that the active disease present was presumably of recent origin (8). The rapid therapeutic response observed in our patients is exemplified by the data on sputum infectivity. Examination of sputum showed tubercle bacilli present in 13 cases. Three were transferred to other institutions and one has been observed only recently. Of the remaining nine, eight no longer had tubercle bacilli in their sputum after the first month of chemotherapy and the ninth was similarly free from infectivity after two months of therapy. All nine have been followed for 10 to 34 months and remain non-infectious, with an average period of observation of 20 months at the present time. This rapid reversal of sputum infectivity has resulted in most patients reaching the obstetrical wards in a non-infectious state, an advantage in the practical management of these patients.

With few exceptions, the provisional diagnosis of active tuberculosis is an indication for the use of combined therapy. While we recognize that the selection of a suitable regimen for combined chemotherapy may be subject to variation, it is our practice at the present time to utilize triple drug therapy in most cases. Isoniazid is administered at a level of approximately 4 to 7 mgs/kilo of body weight (9), dihydrostreptomycin is given 1 gm daily for at least several weeks and then one gram twice weekly for a prolonged period. PAS is given to a level of 10 to 15 grams per day if tolerated, with every effort made to give at least 8 grams per day. In a few instances, isoniazid alone was used, especially in those cases in which the initial provisional diagnosis was that of inactive disease with prophylactic isoniazid therapy given. This single drug regimen was then con-



2a C. R., Nov. 12, 1954. *2b* C. R., Jan. 31, 1956.

FIG. 2. *a*) Circumscribed nodule found on routine prenatal survey film. *b*) No change after five months of prophylactic isoniazid therapy. Presumably inactive.

tinued once serial observation showed roentgenographic regression and revision of the diagnosis to that of active disease.

Our experiences indicate that therapy must be prolonged. At least a year of chemotherapy is given and if the disease has been at all extensive, a period of 18 to 24 months has been preferred.

Where serial observation under chemotherapy shows no radiological change, the question of accuracy of the original evaluation as active disease should be reviewed. If it is then determined that the roentgenological abnormality more properly be evaluated as inactive disease, chemotherapy could be discontinued after two months of the postpartum period. Nevertheless, if the roentgenological appearance is uncertain or suggestive of active disease, lack of early regression should not lead to the abandonment of the "active" diagnosis and consequent chemotherapy. This is especially true in the presence of caseous or fibrocaseous disease which requires prolonged chemotherapy for regression (8). Interpretation is especially difficult when the disease is minimal or moderate in extent. In these cases, radiological change is less marked than in more extensive disease (10). Little harm can be done by unnecessarily prolonged chemotherapy, especially since most drug toxicity occurs in the early weeks of chemotherapy. Much harm may result from premature discontinuance of therapy, if the lesion be active, especially with initimate contact with a newborn baby.

All patients in our clinic were treated as ambulatory clinic patients. Rest was advised but we hesitate to estimate the degree to which such advice was heeded. The problem of ambulatory or non-institutional chemotherapeutic management of pulmonary tuberculosis is unresolved at present. Our own ex-

perience indicates that such ambulatory management is both feasible and, indeed, desirable, at least for the patients treated in our clinic. Moreover, it is even more realistic to observe that were it not for such non-institutional chemotherapy, the large majority of our patients would simply not have been treated. Those with disease evaluated as inactive could certainly not have been institutionalized and most of those with minimal but active disease, without abnormal symptoms, would have refused hospitalization.

Nevertheless, for public health reasons, it was recognized that no patient with a positive sputum who, in our judgment would not rapidly become non-infectious, could be treated as an ambulatory clinic patient. This applied to four cases in the group. Each of the four was transferred to a tuberculosis institution, three after delivery and one ante-natal. Yet three of the four left the institution to which they were sent, received no further treatment, and have been lost to observation. On the other hand, nine patients with positive sputum, who it was anticipated would respond rapidly with conversion to a non-infectious state, were treated (all by combined chemotherapy) on an ambulatory basis. Each of the nine converted her sputum, eight within the first month of therapy and the ninth by the end of the second month. Each of these nine patients continued under therapy and in each there is radiological, clinical, and bacteriological evidence of stable regression of the disease. Follow-up in these nine cases has been from 10 to 34 months with an average of 20 months. *These experiences, plus others detailed below, indicate that from the practical point of view, ambulatory therapy is an essential feature of any program for the care of tuberculosis during pregnancy.* It is certainly true that there will be occasional patients who would be better treated in a hospital devoted to the care of tuberculosis. This would include those with very far-advanced disease, persistently positive sputum, with complicated disease, or with constitutional activity. However, if the experiences at our hospital are an index of those observed in other institutions, such cases will be the exception. Moreover, since such cases promise to be few in number, it has been recognized that this would not warrant the establishment of special obstetrical facilities attached to tuberculosis institutions.

Special precautions are taken with those patients whose disease is diagnosed as active. It is our practice to separate such patients upon admission to the obstetrical wards, and they are treated with full isolation technique. This is true even though these patients are non-infectious in most cases upon admission to the hospital. Rationale for this aspect of management lies in the knowledge that an unstable lesion, even while showing regression, may reactivate and progress, especially in the postpartum period. Should this occur, it would be undesirable for contact with others to have occurred, both patients and staff. This possible re-exacerbation has not been observed in any active case in our group treated in the ante-natal period but it seems wise, at least until further experience accumulates, to err on the side of safety.

As a corollary, no mother with active disease, even though her sputum be non-infectious, is permitted to have contact with her baby after delivery until a suitable postpartum observation period indicates that her lesion continues to

regress and re-exacerbation becomes a remote possibility. Several cultures of gastric contents are examined in the postpartum period as are serial roentgenograms. When these prove satisfactory, the infant, which has been separated from its mother either with other members of the family or in a receiving institution, is allowed to return to the mother's care. This usually occurs at approximately the eighth to twelfth week, postpartum. Further precautionary measures taken with the infant are detailed later. Utilizing these precautions, all live infants have remained well so far in the experience of our clinic.

MANAGEMENT OF PULMONARY TUBERCULOSIS EVALUATED AS INACTIVE

As with patients having active disease, the provisional evaluation of inactive disease is primarily radiological. Such evaluation is made after careful consideration, since it means withholding all chemotherapy until two months before the expected date of confinement. At that time, isoniazid therapy is instituted.

This prophylactic use of isoniazid in inactive tuberculosis associated with pregnancy constitutes a new departure in the management of this complication. Discussion of its rationale and effectiveness is detailed below. Here, it should be noted that this regimen has worked well in practice in the Obstetrical Chest Clinic.

The several months between the first observation of the patient in the antenatal clinic and the planned institution of prophylactic isoniazid therapy two months before the expected date of confinement are utilized in investigational procedures. Serial films are examined, bacteriological examination of the sputum and/or gastric contents is undertaken and close clinical observation is maintained. Should any of these investigations indicate that the initial evaluation of inactivity be in error, chemotherapy is started at once.

Combined therapy is not utilized in inactive cases in our clinic. Isoniazid alone is used. There is theoretical justification for this practical manoeuver, in addition to the knowledge that isoniazid alone is an effective anti-tuberculous chemotherapeutic regimen (11). First, the use of combined chemotherapy is derived from the observation that such treatment delays or prevents occurrence of bacterial resistance. Such drug resistance appears to be a product of mutations occurring during bacterial multiplication. In inactive lesions such bacterial multiplication is at a minimum and the opportunity for the development of bacterial drug resistance is thus very small. Secondly, combined therapy has an additive effect under certain circumstances and is thus preferable in the presence of significant disease. However, such enhanced therapeutic effect is not essential in inactive disease, while the disadvantages of possible increased drug toxicity coupled with the inconvenience of parenteral therapy, militate against the use of streptomycin and PAS. These theoretical considerations appear valid: but they would count for little if experience should indicate that such prophylactic therapy with isoniazid were to be ineffective in preventing exacerbation of inactive disease. In our experience so far, recounted below, this has not been the case. But should future experience at our clinic or elsewhere give other results, combined drug therapy even for prophylactic treatment might be preferable.

The duration of therapy has also been an arbitrarily selected one. It has been our practice to maintain prophylactic isoniazid administration for approximately two to three months postpartum. With the ante-natal treatment, this would total a period of four to five months of prophylactic therapy and serial roentgenographic observation. It is recognized that this duration of therapy may not be an ideal one, since there is no evidence that regression may not occur, especially in caseous lesions, after *more* than five months of chemotherapy, indicating an active rather than an inactive lesion. Also, while isoniazid therapy can be depended upon to prevent any reactivation of the lesion in most cases during its administration, there is good evidence that short term therapy will not render inactive even small active lesions (12). Not only is it theoretically possible for reactivation to occur after five months of isoniazid therapy but we have seen one such case in our clinic. This young woman had an apparently stable lesion, which continued so under prophylactic chemotherapy and for several months afterwards and yet showed x-ray reactivation after the isoniazid was halted. Therefore, further experience may suggest that prophylactic isoniazid therapy should be continued for periods longer than five months; perhaps one year of prophylactic chemotherapy might be more suitable. Nevertheless, experiences to date do not indicate that this will be generally necessary.

When, in lesions evaluated as inactive, prophylactic isoniazid therapy results in roentgenographic regressions, this evaluation is corrected and combined therapy with dihydrostreptomycin and PAS is usually added to the isoniazid. Thus, in our clinic, of 102 patients regarded as having inactive disease and treated prophylactically, 7 patients had regression on x-ray with this regimen, indicating that their lesions were active. *Thus, the prophylactic isoniazid therapy served as a therapeutic trial of stability of the tuberculous lesion. This "therapeutic trial" is potentially a valuable diagnostic method in the evaluation of tuberculosis generally and its use deserves study.*

Patients with inactive disease require no special management upon admission to the obstetrical ward, apart from postpartum chest x-ray and bacteriological examination of the sputum or gastric secretions. Their obstetrical management is similarly uncomplicated, in contrast to patients with active disease (3).

RESULTS OF ACTIVE MANAGEMENT OF TUBERCULOSIS IN PREGNANCY

One hundred and thirty eight patients with active or inactive tuberculosis complicating pregnancy have now been observed for periods of three to 33 months after the institution of chemotherapy (Table V). Tentative conclusions from such observation may be warranted. Although such conclusions must be guarded with relevance to the ultimate prognosis of tuberculosis in these patients, they may be more valid with regard to the influence of pregnancy on the disease. Although no definitive data are available that would delimit the effect of pregnancy on tuberculosis, it seems reasonable to assume that such influence as is exerted would be observed during the pregnancy and in the first year postpartum.

Of the 38 patients found to have active disease, four did not have chemotherapy for various reasons, and 34 were treated with chemotherapy. The result of management in these patients is outlined in Tables VI and VII.

TABLE V

Follow-up observation of 138 patients with active and inactive tuberculosis in pregnancy

	Active	Inactive
A. Post Onset of Chemotherapy		
Less than 3 months	—	—
3–5 "	3	20
6–11 "	9	40
12–23 "	14	28
24–33 "	8	10
Average months	15.6	11.4
B. Post Partum		
Less than 3 months	2	6
3–5 "	7	28
6–11 "	7	33
12–23 "	11	24
24–33 "	7	7
Average months	13.5	9.6

TABLE VI

Results of management of 33 patients with tuberculosis in pregnancy, evaluated as active

	Course under observation			
	No.	Stable	Regression	Progression
Chemotherapy	30	4	25	1*
No treatment	3	0	0	3

* Inadequate duration of therapy.

TABLE VII

Results of management of 105 patients with tuberculosis in pregnancy, evaluated as inactive

	Course under observation			
	No.	Stable	Regression	Progression
Prophylactic chemotherapy	102	94	7	1
No treatment	3	2	0	1

A number of observations seem warranted. Firstly, it would appear that inactive disease can mimic active disease roentgenologically, and clear distinction between them may be difficult. This has been commented upon above. However, the overtreatment in the four cases of presumably active disease which remained stable under therapy is far less undesirable than withholding therapy would have been in four similar cases of active disease. Secondly, active tuberculosis in the presence of pregnancy, responds to adequate chemotherapy in a satisfactory manner, similar to equivalent disease uncomplicated by pregnancy. This is

illustrated by regression of disease in 32 of 34 treated cases. Thirdly, just as in tuberculosis uncomplicated by pregnancy, therapy must be prolonged. In one case in which this was not done, relapse of disease occurred. Therapy has since been resumed in this patient and it is hoped that control of the disease will be reestablished. Fourthly, active disease often progresses during pregnancy as without it, if untreated.

It is very difficult to be certain of the potential course of those patients with active disease had they not been treated. Although reported experiences with active tuberculosis in pregnancy are replete with observations of the unhappy outcome of such disease, these data must be evaluated with caution, being derived from experiences in previous decades when the outlook generally for tuberculosis was much poorer (13). Moreover, most of the reported data are collected from retrospective studies, based upon select material often from sanatoria and hardly bear the scrutiny of present-day investigational requirements. Thus, the extent to which pregnancy exerts a deleterious effect on the tuberculosis is difficult to ascertain statistically. It would seem fair to assume, however, that patients with active tuberculosis in pregnancy would bear at least the same risk of extension and progression of their disease as those who are not pregnant. Many experienced clinicians would add "and perhaps a little more."

There are no considerable data recently of pregnant patients with active tuberculosis who have not been treated. In Freeth's small series of consecutive cases, all patients who had active disease, continued to show such activity after pregnancy (1). Cromie reported similar experiences from the Northern Ireland Tuberculosis Authority, although these patients, albeit unselected, were not the result of case finding in a routine survey (14). Of 45 patients with active disease, only 23 remained unchanged or improved, while 22 became worse or died.

Larger data are available from observations of non-pregnant patients. Ames and Schuck (15) studied the subsequent course of people with survey-diagnosed tuberculosis, not previously known. There were 531 persons who, on routine survey x-ray, were found to have minimal tuberculous lesions. Of these, 166 were judged to have active lesions, on the basis of x-ray, clinical and laboratory studies. When observed for over two years, 51 showed progression of their disease. And if all stages of tuberculosis found in this general population roentgenographic survey are considered, 82 of 258 patients with active disease showed progression in an average of 2.6 years of observation, and 18 died. To relate these data more closely to our own problem, it should be noted that of 94 women with active disease found in this routine survey and observed for an average of 2.5 years, 22 showed progression of their disease.

Therefore, both clinical observation and statistical survey analysis agree that active disease even of limited extent carries a significant risk of progression without treatment. This risk is, of course, increased when the extent of the disease is greater. This knowledge makes all the more impressive the results of treatment of active disease in our series. It would appear that in disease of suitable nature (8), chemotherapy of tuberculosis is just as effective in the presence of pregnancy as without it. These experiences indicate that all patients with active tuberculosis in pregnancy should receive chemotherapy.

Of at least equal interest have been our experiences with the prophylactic treatment of 105 patients who were evaluated as having inactive disease, and who have now been observed in the obstetrical chest clinic for a sufficient time to warrant analysis (Table VII).

The course of pregnancy complicated by inactive tuberculosis is also inadequately documented. In Freeth's series, there were eight patients with disease judged inactive. As a result of pregnancy, two became active, two had doubtful reactivation, two remained unchanged and two could not be traced. Of Cromie's 56 inactive cases, 42 remained unchanged as a result of pregnancy while 14 became worse. Again, experiences with non-pregnant persons throws valuable light on the probable prognosis of such inactive lesions. In the general population roentgenographic survey reported by Ames and Schuck (15) there were 398 persons found to have infiltration evaluated as inactive. When these people were observed for an average of 2.7 years, it was found that 32 had progression of their disease and 5 had died of tuberculosis. When their data are evaluated further, it is noted that 365 cases of the total had inactive disease of minimal extent. Yet 27 showed progression of the disease, and females were no less likely to show progression: 13 of 161 cases judged to have inactive tuberculosis had progression of the disease within 2.4 years of average observation. That this has been the general experience, is evidenced by the observation of Bernard and his colleagues (16). In this study in France, 1,503 instances of minimal tuberculosis discovered on routine roentgenograms were followed for three years. These lesions were smaller than 2 cms. in extent. 17.6% showed progression.

Our own experience indicates that, at least under the conditions of this study, patients with disease judged to be inactive will be protected against progression of their disease by prophylactic chemotherapy during pregnancy. Thus, of 102 patients treated with a relatively short course of prophylactic isoniazid, 94 have shown stability of their disease; perhaps of even greater importance was the fact that seven patients showed roentgenographic evidence of regression of their disease under what was planned to be prophylactic isoniazid therapy. Had this therapy not been utilized, at least these patients would have remained unprotected during pregnancy. One patient showed progression of her disease after the discontinuance of prophylactic therapy: this problem has been discussed above.

Our experiences would indicate that all patients with pulmonary tuberculosis evaluated as inactive should have the benefit of prophylactic isoniazid therapy, although the exact conditions of such therapy warrants further study. Reactivation of the inactive lesion is thereby made much less likely and the dangers of inaccurate evaluation of the activity of the lesion, sometimes unavoidable, are minimized.

NEO-NATAL MANAGEMENT IN RELATION TO PULMONARY TUBERCULOSIS IN PREGNANCY

Separation of the infant from mothers with active or potentially active tuberculosis, even with non-infectious sputum, as practiced by us, has been commented upon above. This separation very often entails a good deal of administrative effort, but it appears essential. In our clinic, the social service department

has been of the greatest assistance and should be part of the working of any obstetrical chest service.

The use of BCG vaccination for infants born of mothers with pulmonary tuberculosis must be strongly considered, even in the absence of sputum infectivity. The data noted above indicate that there is no guarantee against activation of a possibly inactive lesion: should this occur, a highly susceptible infant would be exposed to tuberculosis at a particularly dangerous period of its life. We already have evidence that short-term prophylactic isoniazid therapy does not invariably prevent subsequent reactivation of an apparently inactive lesion. Certainly, patients with active disease, even when this is apparently responding well to chemotherapy, carry a risk of chemotherapeutic failure and possible return to an infectious state.

In view of recently reported observations from Great Britain, it is our considered opinion that all infants of mothers with evidence of pulmonary tuberculosis should receive BCG vaccination. Although we have no such program in our own clinic, mothers are informed of the desirability of such vaccination and access to the BCG vaccination program of the Department of Health of the City of N. Y. is arranged if desired. Gaisford reports that from 1949 to 1954, there were 50 tuberculosis deaths in Manchester in children under five, including 12 deaths in children under the age of one (17). No such deaths occurred in 5,125 vaccinated new-born infants under his observation, although 537 of these were known contact cases. Moreover, there were 28 mothers whose tuberculosis first became clinically evident "... after their infants had been vaccinated, yet, despite their not having been segregated, none of these infants developed tuberculosis. Furthermore, no radiological lesions of tuberculosis have been seen in any vaccinated children from tuberculous homes during the four year follow-up ..." although 13 other non-vaccinated infants in the same area and hospital at this time did so develop lesions. "In our contact families almost exactly one half of the patients were suffering from active tuberculosis and in half the disease was quiescent. The percentage of parents accepting vaccination for their new-born infants has been approximately 40%; the remainder serve as unwitting controls, and it was from among these that the 13 tuberculous cases came."

In view of these data, as well as that in the carefully controlled clinical trials among adolescents in Great Britain, recently reported by the Tuberculosis Vaccines Clinical Trials Committee of the British Medical Research Council (18), there seems now little doubt of the clinical effectiveness of BCG vaccination. Such vaccination would appear to be particularly valuable in the select group of infants born to tuberculous mothers.

SUMMARY AND CONCLUSIONS

1. Of 4,740 patients admitted to the Ante-natal Clinic of The Mount Sinai Hospital from April 1, 1953 to January 31, 1956, 162 (3.4%) were found to have radiological evidence of pulmonary tuberculosis. Routine prenatal survey films were responsible for the discovery of the disease in almost all of these patients. Routine chest x-ray survey should be an essential part of an obstetrical program.

2. There were 41 patients with active tuberculosis and 121 with inactive disease. However, the evaluation of the activity of the disease is often difficult. X-ray interpretation is the most reliable method but is inaccurate in almost 10% of cases. Difficulty in evaluation is increased in disease of limited extent and in the presence of fibrocaseous nodular infiltration.

3. Cognizant of the inherent difficulties of evaluation of the activity of a tuberculous pulmonary infiltration, it would seem prudent to regard most patients with tuberculosis in pregnancy as potentially active. This is emphasized by the experiences in our study. Of 105 patients considered to have inactive disease, adequate observation demonstrated that in nine of these cases the disease was active. Of the 105 cases evaluated as having inactive disease, 102 were given isoniazid as a planned prophylactic therapy. Ninety-four remained stable through pregnancy, 7 showed regression of the presumed inactive lesion. One, with treatment of short duration, progressed.

4. Prophylactic therapy for lesions regarded as inactive during pregnancy is thus a logical and desirable regimen. It also serves as a "therapeutic test" for the stability of the lesion.

5. Of 33 patients with disease evaluated as active, 30 had chemotherapy. In 4, the infiltration showed no change: evaluation had been presumably incorrect and these patients had had inactive disease. Twenty-five patients showed regression and control of their disease. One failed to adequately respond. Three patients with active disease had no chemotherapy. All showed progression of their disease.

6. All patients with tuberculosis in pregnancy should be actively treated. Chemotherapy is the mainstay of such treatment: accessory measures should be utilized when necessary. With such a regimen, active tuberculosis responds well. If untreated, progression of the disease is likely to occur. Inactive tuberculosis, actively managed with prophylactic isoniazid, will remain quiescent in almost all cases. Omission of prophylactic therapy carries the risk to both mother and child of reactivation of the disease.

7. Prophylactic measures for the protection of infants against tuberculosis include separation of new born infants from mothers with unstable disease, and BCG vaccination of infants born to tuberculous mothers.

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GENITAL TUBERCULOSIS IN FEMALES

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The incidence of genital tuberculosis varies greatly throughout the world. Involvement of the female genitalia is almost always secondary to primary lesions in the lungs, gastrointestinal tract or other organs. It therefore follows that early detection and adequate treatment of the primary infection will greatly reduce the frequency of secondary involvement of other organs. This has proven to be the case in the United States in recent years. On most gynecological wards there has been a sharp decline in the number of patients seen with advanced pelvic tuberculosis. Such cases also are being less frequently observed in our clinic population.

Sterility is probably the most frequent symptom of this disease which prompts the female to seek medical aid. Most of the statistics on genital tuberculosis today emanate from sterility clinics throughout the world. A review of these reports reveals some startling facts. The incidence of genital tuberculosis in sterility clinic patients in reports from the following places was: New Delhi, 7.5 per cent (1); Israel, 5 per cent (2); Madrid, 14.8 per cent (3); Sweden, 5 per cent (as high as 19 per cent in some clinics) (4); England, 5 to 6 per cent (5); and Australia, less than 0.05 per cent (6). The extremely high incidence of genital tuberculosis in some areas of the world emphasizes the need for widespread public health measures, the dissemination of information and the need for adequate, modern therapeutic measures.

PATHOGENESIS AND PATHOLOGY

Genital tuberculosis is only one manifestation of a general systemic disease. The pelvic infection can occur during the activity of a primary pulmonary lesion or secondary to primary or chronic lesions in other organs of the body. Genital involvement in childhood is infrequent. There is a marked increase in genital tuberculosis during adolescence and early maturity. Almost 90 per cent of the cases occur during the period of active ovarian function from puberty to menopause.

In a recent investigation by Barns (7) the mode of invasion of the genital tract was studied in 107 women with pelvic tuberculosis. Other forms of tuberculosis were found in 78 women. In only eight patients were the co-existing lesions still in an active state. Of 57 patients, the primary site of tuberculous infection was in the lung in 46, in the glands of the neck in five, on the skin in one, and in the abdomen in five. This suggests that the invasion of the pelvis had occurred by the hematogenous route in at least 52 of the 57 patients.

Infection by continuity may occur from the peritoneum, the intestines, mesenteric glands or genito-urinary tract. Ascending infection from the lower genital tract is indeed rare.

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The fallopian tubes are the organs most frequently affected in genital tuberculosis. They are involved in approximately 85 per cent or more of the cases of pelvic tuberculosis.

In many instances tuberculous infection of the adnexa cannot be grossly distinguished from inflammation due to other organisms. The distinguishing factor is the presence of yellowish grey sago-like tubercles on the peritoneal surface of the tubes and the mesosalpinx and the fact that in 50 per cent of the cases the fimbriated abdominal ostium of the tube remains open. In early cases the tube may appear slightly thickened and the tubercles seen grossly on the mucosal surface of the opened tube. With more advanced disease the tubes become markedly thickened and retort shaped or appear distended and loculated. Peritubal abscesses occur because of spill of infected material from the open abdominal ostium of the tube. Interstitial masses of caseated material may accumulate in the thickened muscularis producing hernia-like protrusions toward the serosal surface. Such involvement of the tubal wall may lead to perforation directly into the peritoneal cavity or into the broad ligament. The spill of the caseated material into the peritoneal cavity can result in diffuse tuberculous peritonitis and ascites. A chronic fibrotic stage occurs with healing. The tubes are thickened, hard, bead-like and may contain calcified bodies. The isthmic portion of the tube can be unaffected or may show the so-called salpingitis isthmia nodosa. At this stage of the disease the tubes are usually occluded at some point due to the fibrosis which occurred in the healing of ulcerated areas of the endosalpinx.

The endometrium of the uterus when carefully studied is found to be involved in 70 to 75 per cent of the cases of genital tuberculosis. In the early stages no macroscopic evidence of endometrial infection may appear. As the process advances confluence of the affected areas with caseation and ulceration develops. In more advanced cases there is distortion of the endometrial cavity. This may vary from slight narrowing to almost entire obliteration of the uterine cavity. The process extends into the cervix in 20 to 40 per cent of the uteri involved. If the cervical canal becomes obliterated accumulation of caseous material and pus may end in the development of a pyometria. The myometrium can become involved with areas of caseation and the uterus thin walled to the point where perforation may occur spontaneously. Healing can occur at any stage of the disease and the final anatomic result depends upon the degree of tissue damage present at the height of the local involvement.

Tuberculosis of the ovaries occurs in at least 30 to 35 per cent of the cases of genital tuberculosis. The ovary is rarely involved alone. In practically all instances it is associated with tuberculosis of the peritoneum or other genital organs. The ovary may appear grossly normal in the early phase of the disease or appear studded with tubercles and surrounded by dense adhesions. Caseation can occur with formation of tuberculous ovarian abscesses. The tuberculous process in some instances is limited to small areas of the ovary such as follicle cysts, a corpus luteum cyst or ovarian cysts of another type. On the other hand the entire ovary can be almost completely destroyed by the tuberculous process.

Tuberculosis of the vagina and vulva are rare and are practically always secondary to tuberculosis of the uterus and tubes, the bladder, rectum or some distant organ. The commonest form is the tuberculous ulcer which is serpiginous in type with tubercles at its edges. There are occasional papillary granulomatous lesions or diffuse non-ulcerating tubercles.

The symptomatology of genital tuberculosis depends on the stage of infection and the degree of anatomical disturbance in the genital tract. The patient may be completely symptom free and both patient and physician unaware of any pathological process in the pelvis. From this state of early minimal involvement either active or quiescent the symptoms and physical findings run the gamut of those seen in all stages of pelvic inflammatory disease. All cases of acute and chronic pelvic inflammatory disease which do not respond to the ordinary regimen of care and adequate antibiotic therapy other than streptomycin should be carefully studied for the presence of tuberculous infection. A careful history of previous illness may reveal a known tuberculous illness in the past or a symptom complex which may be suspicious of a previous primary infection in some other organ. Primary sterility is a common complaint but one must not be misled when a history of past gravidity is obtained. In 158 cases of genital tuberculosis studied by Brown et al. (8), 44.3 per cent had been pregnant previously, but only three patients within a year of the diagnosis. The menstrual history may present aberrations of all types. Malkani (1) reported amenorrhea in 43.4 per cent of his 106 cases while Sutherland (9) reported profuse and sometimes irregular menses in 50 per cent of his 109 cases. A history of chronic fatigue and low grade fever associated with a low white blood count is also a frequent finding in these patients. The presence of palpable findings of pelvic inflammatory disease without a history of genital infection should make one suspicious of a possible tuberculous infection.

The following procedures are useful in establishing the diagnosis of tuberculosis: (a) endometrial biopsies, (b) cervical biopsy, (c) smears and cultures of uterine and cervical discharge, (d) cultures of menstrual blood, (e) guinea pig inoculations with endometrial tissue and (f) hysterosalpingography.

Endometrial biopsy is an important diagnostic procedure. The microscopic demonstration of caseation and tubercles is pathognomonic. There are some investigators however who insist on bacteriologieal proof by culture or guinea pig inoculation to definitely establish the diagnosis. It may be necessary to have repeated endometrial biopsies in suspicious cases before positive microscopic findings are seen. The biopsies should be performed pre-menstrually if possible. Tubercle formations are much more frequent and evident just before menstrual desquamation of the endometrium.

Cervical biopsy although not as commonly performed as endometrial biopsy in cases of suspected tuberculosis may establish the diagnosis. Nogales (10) found the cervix affected in 46 of 244 cases of uterine tuberculosis. The vaginal portion and endocervical canal were each involved in 24 instances. In some cases the uterus may be hypoplastic or the uterine cavity obliterated because of infection in early childhood or before puberty. In such instances endometrial

biopsies may be difficult or impossible to obtain. In all such cases microscopic study of the cervical tissue is important. Cervical biopsies should be performed on any areas of cervical erosion and tissue should be obtained from the endocervical canal with a small curet. Tubercle formation seen in the microscopic sections of the cervical tissue removed can establish the diagnosis.

Uterine and cervical discharge may be a prominent symptom in some cases. Stained smears of the discharge may reveal the tubercle bacillus but cultures and guinea pig inoculation are necessary for the identification of the organism.

Cultures of menstrual blood on the first and second day of flow have been performed by Halbrecht (11) who reported positive cultures in about ten per cent of his cases.

Guinea pig inoculation with cervical and uterine discharge or with tissue obtained from the endometrium or cervix is a popular procedure but this may give negative results in many cases of genital tuberculosis.

Hysterosalpingography has become increasingly useful in the study of sterility and menstrual abnormalities. With its increased use the findings in cases of genital tuberculosis are becoming more widely recognized.

The character of the x-ray shadow on hysterography will depend on the degree of endometrial involvement. In the early stages no evidence of endometrial infection may appear. In such cases the hysterogram will show no deviation from normal. As the process advances confluence of the affected areas with caseation and ulceration develops. Hysterograms will then show variations from the normal. In some instances the cavity is slightly enlarged with a hazy cobble stone appearance due to irregularities produced by caseous nodules and small ulcerations. In more advanced cases the x-ray shadow will reveal distortion of the endometrial cavity. This may vary from a slight narrowing to an almost entire obliteration of the cavity. Frequently the cavity appears to be pencil shaped with no visualization of the cornual angles. The process may extend into the cervical canal producing narrowing and irregularity of the outline of the x-ray shadow in this area. In rare instances the uterine cavity will be entirely obliterated so that no dye will enter it and the hysterogram may show a portion of the cervical canal.

The fallopian tubes in very early cases of tuberculous salpingitis show no abnormal pictures on hysterosalpingogram. In more advanced cases the tubal shadows may resemble those seen in some cases of non-tuberculous chronic hydrosalpinx or pyosalpinx. There may be filling defects in the shadow of the tubal lumen due to accumulation of caseated material. When tubal fistulae occur these are seen as branching radiopaque shadows extending at various angles from the tubal lumen. If the fistula perforates into the peritoneal cavity the radiopaque media may be seen to spread freely into the pelvis. When the fistulae perforate into the broad ligament the radiopaque media will remain loculated between the layers of the mesosalpinx. During the chronic fibrotic stage the tubes are thickened and bead-like and may contain calcified bodies which show up on x-ray of the pelvis. At this stage the tubes are usually occluded at some point. Hysterosalpingography may show non-patency at the utero-

tubal junction or at a distal point in the tubes. The tubal lumen is narrow and fistulous branches may still be present. The fibrosis which occurs with the healing process produces small irregular dilatations and strictured areas in the tubal lumen. It is due to this irregularity of the tubal lumen that salpingography is said to reveal a characteristic beading effect in chronic tuberculous tubes. At the point of tubal closure the tubal lumen frequently terminates in a small beadlike dilatation.

TREATMENT

The treatment of genital tuberculosis has changed greatly now that effective anti-tuberculosis drugs are available. The therapy in each case must be individualized since problems of conservation of the internal genitalia will vary with the age of the patient, gravidity, the extent of the pelvic involvement and the patient's response to medication.

In the adolescent patient or the young woman desiring children our therapy should be conservative unless the disease is so advanced that surgical extirpation is imperative. Reports of full term pregnancies following medical treatment of genital tuberculosis are appearing in the literature today (12). When such results are possible the prognosis in patients with minimal involvement is not necessarily poor. The drugs most effectively employed today are streptomycin or dihydrostreptomycin, isonicotinyl-hydrazine (isoniazide) and para-aminosalicylic acid (PAS).

The drug regimen in the individual case may vary depending on the tolerance of the patient to the particular drugs and to the length of the drug therapy planned. Sutherland (9) reported a group of 57 cases treated with one gram of streptomycin daily for 84 days and three grams of P.A.S. four times daily for 84 days. Twenty-four of the 27 cases with adequate follow-up were free of genital tuberculosis at the end of one year. Malkani (1) treated 30 patients with daily oral doses of 150 milligrams of isoniazide for eight to twelve weeks. Follow up in 21 of these cases at the end of five to ten months showed recurrence in two patients. Treatment over a long period of time will probably produce the best results when conservative therapy is planned with the hope of conservation of the genitalia. The regimen suggested by Schaeffer (13) is as follows: One gram of streptomycin twice weekly intramuscularly for a period of three months; isoniazide, 5 milligrams per kilogram of body weight daily, orally (usually 300 milligrams per day), to be started with the streptomycin and continued for one year. Patients must be followed closely after drug therapy since recurrences may occur early or long after therapy is completed. The endometrial curettings should be examined microscopically and bacteriologically at intervals of four to six months. When recurrences are encountered the patient should be given a three month course of streptomycin and isoniozide and prepared for surgery.

In patients suffering from advanced pelvic tuberculosis with tubo-ovarian masses and proven tuberculosis of the endometrium or cervix the prognosis for future child bearing is practically nil. Therapy in such instances must be radical

at all ages if a cure is to be obtained. The patient is prepared for surgery by preliminary administration of anti-tuberculosis drugs for three to four months. Under such therapy the pelvic masses reduce in size and the surrounding exudates and peritubal abscesses are resolved. Operation under these circumstances is performed with much greater ease and with far less danger of intestinal and bladder injuries. The frequency of combined ovarian, tubal and uterine involvement in advanced genital tuberculosis makes it advisable that a total hysterectomy and bilateral salpingo-oophorectomy be performed. Conservatism under such circumstances may court disaster for the patient at a future date. Oral replacement hormone therapy today makes oophorectomy, even in the younger patient, the procedure of choice in advanced pelvic tuberculosis. During the immediate post-operative period, infection with secondary organisms is controlled by prophylactic administration of penicillin, terramycin or aureomycin. Following the operation the anti-tuberculosis drugs are continued for a period of at least one year. Streptomycin with P.A.S. or isoniazid are utilized according to the patient's tolerance.

There are occasions when the diagnosis of pelvic tuberculosis is made only in the pathological laboratory when microscopic study of the extirpated specimen is performed. In such instances if a complete operation has been performed post-operative anti-tuberculosis drug therapy is carried out as described above. If the operation has not been complete the drug therapy is continued for three to four months and then a decision should be made as to the necessity for future surgery. If surgery is performed the anti-tuberculous therapy should be continued post-operatively for twelve months following the second operation.

SUMMARY

1. The evidence of genital tuberculosis varies greatly throughout the world. The incidence in sterility clinics ranges from a low of 0.05 per cent in Australia to 14.8 per cent in Madrid.

2. Genital tuberculosis is a manifestation of a general systemic disease. Its prevention or early treatment is brought about by early diagnosis of the primary lesion and prompt administration of effective anti-tuberculosis drugs.

3. The sites of genital involvement in order of frequency are the fallopian tubes, the endometrium of the uterus, the ovaries, the cervix and rarely the vagina or vulva.

4. The symptoms of genital tuberculosis depend on the stage of infection and the degree of anatomical involvement. The patient may be symptom free or exhibit the signs and symptoms of acute or chronic pelvic inflammatory disease.

5. The following procedures are useful in establishing the diagnosis of genital tuberculosis: (a) endometrial biopsies (b) cervical biopsy (c) smears and cultures of uterine and cervical discharge (d) cultures of menstrual blood (e) guinea pig inoculations with endometrial tissue or menstrual blood and (f) hysterosalpingography.

6. The treatment of genital tuberculosis has changed greatly now that effective anti-tuberculosis drugs are available. In early cases in the child bearing age an

attempt at prolonged conservative therapy is made. Pregnancies have been reported following such treatment.

7. In patients with advanced genital tuberculosis the treatment must be more radical. Pre-operative and post-operative administration of anti-tuberculosis drugs are combined with the total extirpation of the ovaries, tubes and uterus.

8. When unsuspected pelvic tuberculosis is diagnosed post-operatively in the pathological laboratory anti-tuberculosis drug therapy should be administered for twelve months.

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SKELETAL TUBERCULOSIS

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Considerable progress has been made in the control and eradication of tuberculosis. The therapy of skeletal tuberculosis comes within the province of orthopedic surgery. However it is proper to recall that tuberculosis is a disseminated disease. In recent years there has been a striking decrease in the numbers of patients with skeletal localizations who are on orthopedic services of hospitals or in orthopedic convalescent institutions. This diminution has been related to improved public health measures, chiefly the elimination of the bovine vector of tuberculous infection, as well as control of the human variety by the mass case-finding technique of pre-clinical chest fluoro-radiography. A generation ago, it was considered normal for 60 to 80 per cent of the adolescent population to react positively to the tuberculin test, whereas it is now the experience that only 10 to 15 per cent present such a positive reaction (1). To make this situation more hopeful and optimistic, there has become available chemotherapeutic and antibiotic medications in the form of streptomycin, para-amino-salicylic acid and the hydrazine derivatives of isonicotinic acid, isoniazid and iproniazid.

Skeletal tuberculosis is a metastatic seeding from some pre-existing focus. Prior to the development of the specific medications, the threat as well as the fact, of disease dissemination were common experience. Cave (2), in reviewing the cases of 122 children with vertebral tuberculosis, noted an incidence of 60 per cent with pulmonary lesions at some time in the course of their treatment. Reichle and Work (3) demonstrated hematogenous spread of tuberculosis in 20 per cent of routine autopsy material in which healed miliary tubercles were found in the liver, spleen and kidneys in patients never diagnosed as having had clinical tuberculosis. Harris and Coulthard (4) presented a study of 80 cases of Pott's disease treated prior to 1935 and followed for five or more years. They noted a 30 per cent incidence of associated pulmonary tuberculosis and 26 per cent renal or genital tuberculosis. The general mortality in their group was 28 per cent. The chief cause of death was some form of tuberculosis and the majority occurred two or more years after termination of the orthopedic therapy. Swift (5) in a similar analysis of cases which were treated between the years 1911 and 1930, recorded a 15 per cent fatality from tuberculosis involving central nervous system, pulmonary and other distant localizations. One third of this group died within one year of fusion and the others several years after termination of treatment. The foregoing data indicated that tuberculosis had either multiple active foci or a single clinically active phase with many latent lesions any of which could flare unsuspectingly. This attribute of tuberculosis has always contributed uneasiness in concluding that successful arrest or cure had occurred despite adequate local therapy.

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Skeletal tuberculosis mimics pyogenic osteomyelitis in favoring the involvement of the juxta-epiphyseal and metaphyseal ends of the long bones, particularly hips and knees. It departs from further similarity by exhibiting a marked predilection for the vertebral column which accounts for over 50 per cent of all skeletal tuberculosis (6) whereas pyogenic bacteria rarely cause disease of the spine. Tuberculosis of the vertebrae is often classified as central, epiphyseal or anterior depending on the region of the body initially infected. It is the epiphyseal variety that is accompanied with prompt involvement and narrowing of the intervertebral disc sometimes considered so typical of tuberculosis. This is not an invariable finding. In the central form, collapse of the involved body is more apt to occur early. In the anterior or superficial type of spinal tuberculosis, the disease may spread under the anterior longitudinal ligament to invade and erode the anterior portions of adjacent bodies without causing much damage to the intervertebral disc or collapse of any vertebral body until late in the disease. Infrequently, the disease begins in the posterior arch, spinous process or transverse process of the vertebrae. In addition to the regions named above, tuberculosis can occur in any bone, including the mandible (7) and skull (8). With the infection so often located near the articular ends of long bones, tuberculous arthritis is a common sequela. It is known that primary joint infection can occur as a purely synovial disease without demonstrable bone focus. Early diagnosis and treatment of this type of lesion, under favorable circumstances, has resulted in restoration of a freely movable functional joint.

The pathology of tuberculosis presents singular features (9). Once the tubercle bacilli reach their destination and increase in number, a specific histo-pathological train of events follows. The initial transitory acute inflammatory reaction is replaced by an accumulation of monocytes, epithelioid cells and giant cells which tend to form minute, roughly spherical tubercles. A degenerating, caseous central portion develops with proliferation on the periphery of a zone of small round cells and fixed connective tissue cells. As healing occurs, the lesion is sealed and limited with the production of mature, collagenic fibrous tissue by the peripheral fibroblasts. Under unfavorable conditions, there is no attempt at capsular formation but rather a progressive invasion by the epithelioid cells and the tubercle bacilli to form additional tubercles and specific granulation tissue. As cellularity increases, the small blood vessels in the central zone become obliterated and degeneration and abscess formation result. The abscess cavity contains cell debris and purulent liquefied caseous material which spread along lines of least resistance varying with the anatomic site. In cancellous bone, there is easy extension and enlargment of the tuberculous area. The living bone trabeculae become atrophic in the hyperemic zone of reaction and are more or less completely absorbed when they become engulfed by the advancing spread of specific granulation tissue. Not only are the delicate cancellous trabeculae destroyed but there is penetration of the relatively dense cortical bone with stripping of the periosteum and ligaments as the advance proceeds. There is virtually no osteogenic stimulus such as occurs in pyogenic osteomyelitis so that little or no new bone is formed as destruction takes place. Consequently, secondary collapse, crushing

and angulation develop in the involved bones as weight no longer can be supported. An awareness of the pathological changes contributes towards a better understanding of the disease and adds meaning to the x-ray findings. The x-ray evidences of striking bone atrophy and osteolysis are reflections of the pathological processes described. The globular soft tissue enlargements and psoas muscle distortions in vertebral disease indicate abscess formations resulting from active specific granulation tissue destruction and liquefaction. Cleveland (10) made the interesting observation that though bone tuberculosis is essentially a lytic lesion, sclerosis of the vertebral body in spinal tuberculosis does occur. He explained this discrepant density on the basis of interference with blood supply to the massively involved bone. This could occur either via the mechanism of stripping of soft tissues by large dissecting cold abscesses or by a vascular obliterative process such as thrombosis or endarteritis.

In the treatment of tuberculosis, the pathological features of caseation, fibrosis, abscess formation and relative avascularity plus the bacteriological characteristics of the tenacity and invulnerability of the tubercle bacilli to hitherto available medications have been the challenges. The first practical inroad for direct attack on the tubercle bacillus came with the discovery of streptomycin. Girdlestone's statement that "streptomycin seems likely to prove of immense value in the treatment of skeletal tuberculosis" (11) seemed gross understatement in 1951 when it was made. Considerably more had been hoped for and the early reports substantiated the favorable influence of this drug on the disease. Patients receiving streptomycin had a diminution in toxicity with an improved sense of general well-being, cessation of sinus drainage, reduction in sedimentation rate and a return toward normal of the hemoglobin value (12). Cautious reports (13, 14) of complete arrest of synovial infections appeared. Surgical procedures in skeletal tuberculosis assumed less risk under streptomycin cover than had been previously the experience. Johnson, Hillman and Southwick (15) reviewed 149 spine operations for tuberculosis performed in the years 1926 to 1947 and found nine deaths which included miliary and meningeal spread, eight disseminations of tuberculosis to other sites and one pulmonary reactivation. This was contrasted to the results following 78 operations performed in the years 1948 to 1951 under streptomycin control in which there were no deaths, no distant disseminations or pulmonary reactivation. Despite the early enthusiasm for and favorable experiences with streptomycin, the drug proved less than a panacea. Frequent development of bacterial resistance came to be recognized. Long term administration of streptomycin in sensitive individuals produced eighth cranial nerve changes leading to degrees of deafness often permanent and irreversible. The striking initial clinical effects often proved to be temporary and though under streptomycin cover early complications appeared reduced, a larger experience forced the conclusion by Amberson (16) that "Streptomycin alone is not very effective in preventing the development of complications." This was corroborated by Monroe (17) who studied 64 patients with pulmonary tuberculosis treated with streptomycin and after a five year

follow-up noted five orthopedic active lesions not present at the start of therapy.

The first change in drug regimen followed the availability of para-amino-salicylic acid and the discovery that its simultaneous administration with streptomycin had beneficial effects. It reportedly diminished the trend towards bacterial resistance and enhanced the streptomycin effect. Harris (18) found that resistant forms of bacilli did not emerge in any patient treated concurrently and consistently with 1 gram of streptomycin daily and PASA on the average of 10 grams daily. This combination of drugs came to be accepted fairly uniformly.

Another milestone in therapy appeared with the discovery of the anti-tuberculous effect of isonicotinic acid derivatives by workers in the Roche Laboratories. Exhaustive laboratory and clinical investigations of isonicotinic acid hydrazide (isoniazid) and its isopropyl derivative, iproniazid (1-isonicotinyl- 2-isopropyl hydrazine) were carried out at Sea View Hospital by Selikoff, Robitzek and Ornstein (19, 20) with confirmation of "profound and important therapeutic effect . . . beyond anything . . . ever seen with any of the chemotherapeutic or antibiotic agents previously utilized." Isoniazid (Rimifon) was released commercially first, so that experience with it in skeletal tuberculosis came from a multiplicity of sources. As with streptomycin previously, evidence accumulated of the manifestation of drug resistance (15) to isoniazid used alone despite the many initial salutory effects of weight gain, lessening of toxicity and febrile reactions and diminution and closure of abscesses and sinuses. Again empirical drug combinations were tried and found to possess advantages in combating the emergence of drug resistance. Stevenson (21) arrived at these general conclusions for the chemotherapy of orthopedic tuberculosis: (a) No antibiotic for tuberculosis should ever be given alone; (b) Streptomycin, 1 gram daily and isoniazid, 4 milligrams per kilogram of body weight daily, form the best chemotherapeutic combination; (c) It is better to use para-amino-salicylic acid, 15 grams daily with the other two drugs. Wilkinson (22) agreed that streptomycin and isonicotinic acid hydrazide formed a powerful combination lethal to the tubercle bacilli. Iproniazid has remained an experimental drug until the present. Experience with it has been contributed largely by Bosworth. In his preliminary report (23) in 1952 when the material was made available to him by Robitzek and Selikoff, he reported favorable effects in lowering temperature, diminishing pain, improving nutritional status and either closing sinuses or lessening drainage and rendering sinus washings negative in a limited number of severely ill patients. In his subsequent reports (24, 25) he continued his optimism and satisfaction and he regarded iproniazid as the drug of choice in the treatment of tuberculous bone and joint lesions. He suggested accurate dosage of 4 milligrams per kilogram of body weight daily. It should be stated that at the therapeutic level of drug dosage, certain toxic symptoms related to the sympathetic nervous system i.e. dryness of mouth, constipation, urinary difficulties and to the central nervous system, i.e. hyperreflexia, clonus, vertigo, hyperirritability may occur. These usually can be controlled by adjusting the dosage. Bosworth prefers to use

iproniazid as the sole anti-tuberculous medication and believes it to be superior to isoniazid (26). In our limited experience with this new preparation at The Mount Sinai Hospital, it has been used in combination with streptomycin and para-amino-salicylic acid and we find it to be satisfactory. The explanation for this preference may be related to experimental work by Selikoff (27) who found drug resistance delayed by the combination of iproniazid and dihydrostreptomycin.

Throughout the recent studies on the therapy of skeletal tuberculosis, there is an obvious concern about the proper role of surgery. Prior to the chemotherapeutic era, there was no question of the desirability of evacuating abscess cavities or arthrodesing and stabilizing involved articular surfaces. The problem revolved about the risk to the patient of possible disease dissemination or sinus formation with septic complications in case of poor wound healing. Extra-articular foci of disease, except perhaps for involvement of the greater trochanter of the femur, had to be avoided for fear of joint contamination incident to the surgical attack. The recorded experiences with streptomycin emphasized the relative safety with which the required surgery could be performed rather than decried the need of it. Bosworth (29) summarized this attitude well when he concluded that despite streptomycin, most patients with bone and joint tuberculosis came to surgery eventually because of continued local activity or because of already present bone or joint destruction but such surgery proved safer and more efficient. A host of others (29–31) confirmed the importance of the streptomycin cover and the greater aggressiveness the surgical attack could assume. It seemed generally agreed that only synovial tuberculosis or minimally involved bone could be salvaged with chemotherapy alone. Areas of caseous necrosis and abscess with their ischemia were not suitable for drug penetration andits anti-tuberculous effect.

The early investigative work with the hydrazine derivatives of isonicotinic acid held new promise. It had been recorded that capillary dilatation and proliferation followed the use of iproniazid (24). Since the molecules of these newer drugs are smaller than that of streptomycin, the possibility of their passage across semi-permeable membranes and diffusion through tissue spaces to reach avascular areas seemed attainable. Selikoff (32) believes that such is the actual fact. Wilkinson (22), Smith (14) and Stevenson (21) who have used both streptomycin and isoniazid agree, that except for certain specific lesions in the knee and hip and in some cases with draining sinuses where quiescence and arrest may be attained with chemotherapy alone, the broad general principle of using surgery augmented and enhanced by chemotherapy appears to represent the consensus. Bosworth (33) who thus far has the widest experience with iproniazid has similar convictions about the desirability of combining surgery with that drug as well, when joint surfaces are compromised or sequestra exist in bone lesions.

In the preceding discussion, dosage of the several drugs used in tuberculosis therapy was mentioned. The duration of therapy, however, was not emphasized. A certain empiricism prevailed in arriving at dosage schedules as far as all of the medications were concerned. Streptomycin, especially, ran the gamut of 60 day treatments which was then extended to a more popular 90 day course and

later to 180 days and so on. The crystallization of all of these probing approaches has been the realization that prolonged therapy is the keystone to successful attack of the tuberculous infection. Amberson (16) by combining information derived from study of resected lung specimens and from the clinical behavior of patients with pulmonary disease found that consistent continuation of chemotherapy was desirable in most cases for a year or more. Lattimer (34) reported that in genito-urinary tuberculosis, one year of triple drug therapy was mandatory, with the possibility of getting better results from 18 to 24 months. In handling patients with skeletal tuberculosis on The Mount Sinai Hospital Orthopedic Service, we subscribe to the principle of extended chemotherapy with the use of several drugs in combination and most recently have increased our treatment period to at least one year.

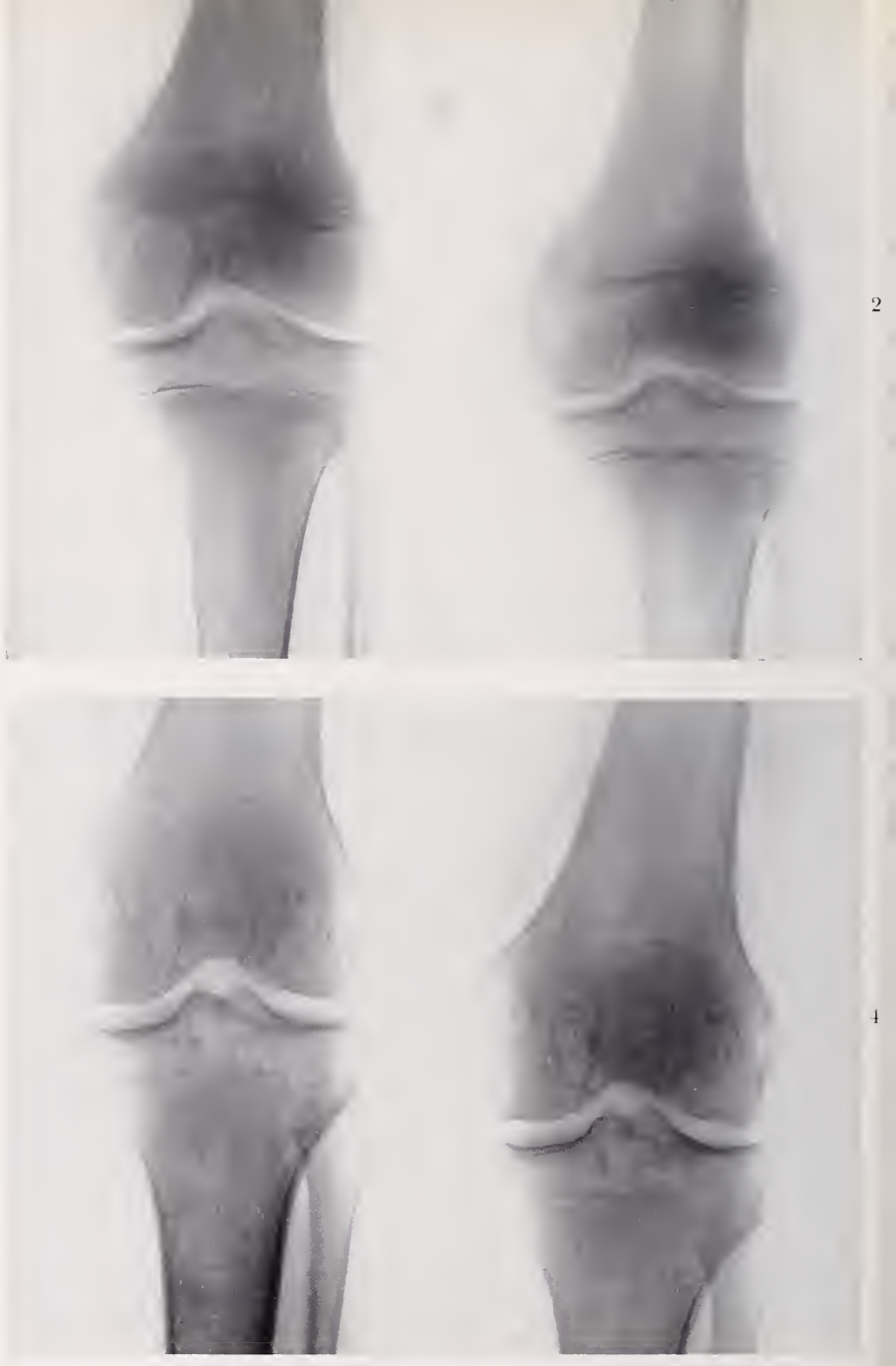
CASE REPORTS

The following case reports will serve to illustrate some of the problems of skeletal tuberculosis:

Case #1. S. C., a 12 year old, white male adolescent, was admitted to The Mount Sinai Hospital on January 30, 1950 with complaints of intermittent pain, swelling and limp referable to the left knee following an automobile accident in October 1948. X-rays of the left knee were reported to be negative initially but about a year following the injury x-rays showed an oval, translucent, well-demarcated zone of rarefaction in the medial condyle of the distal end of the femur (Fig. 1). On examination, moderate swelling and increased local skin temperature of the left knee were found. Motions of the knee were preserved but accompanied with pain on extreme flexion. Aspiration of the left knee recovered thick, yellowish, purulent fluid which showed acid-fast bacilli on direct smear and subsequently was confirmed to be tuberculosis by guinea pig inoculation.

He was given streptomycin, 1 gram daily and para-amino-salicylic acid 6 grams daily and this schedule was continued for 90 days at the Blythedale Convalescent Hospital where he was later transferred. Immobilization of the left lower extremity was effected at first with Buck's traction and later with a long leg plaster cast. Upon completion of the 90 day course of chemotherapy, he was observed for several months with continued partial immobilization of the knee in a plaster cylinder with limited weight bearing on crutches. Evidence of residual inflammatory activity was found in the form of moderate synovial thickening and slight warmth of the joint. X-ray at this time showed no change in the character or size of the oval lesion in the femoral condyle (Fig. 2). There was increased general osteoporosis but the joint surfaces remained intact. Medication was resumed, this time for a six month period, with the dose of streptomycin increased to 2 grams daily and the para-amino-salicylic acid maintained at 6 grams daily. Multiple audiometric determinations were made throughout this treatment period and it was only in the last month of therapy that mild hearing loss developed at high frequency out of the range of ordinary voice reception.

Subsequent to completion of the chemotherapy, he was fitted with an ischial-caliper weight bearing brace, which he wore for a year and a half. Thereafter, he walked about without any external support. Follow-up x-rays in 1954 (Fig. 3) and 1955 (Fig. 4) showed normal epiphyseal closure, persisting osteoporosis, slight squaring of the femoral condylar surfaces but preserved joint space interval. The previous well-delineated oval zone in the medial femoral condyle could still be faintly seen, though trabecular markings in its substance blended better with the adjacent bone. On the last examination in June 1955, the limb was found to be functioning adequately with a painless range of knee motion from 180° extension to 60° flexion.



Case 1

Fig. 1. Roentgenogram of the left knee taken on 1/30/50 showing an oval, well-delineated zone of rarefraction in the medial femoral condyle. The articular surfaces are well preserved.

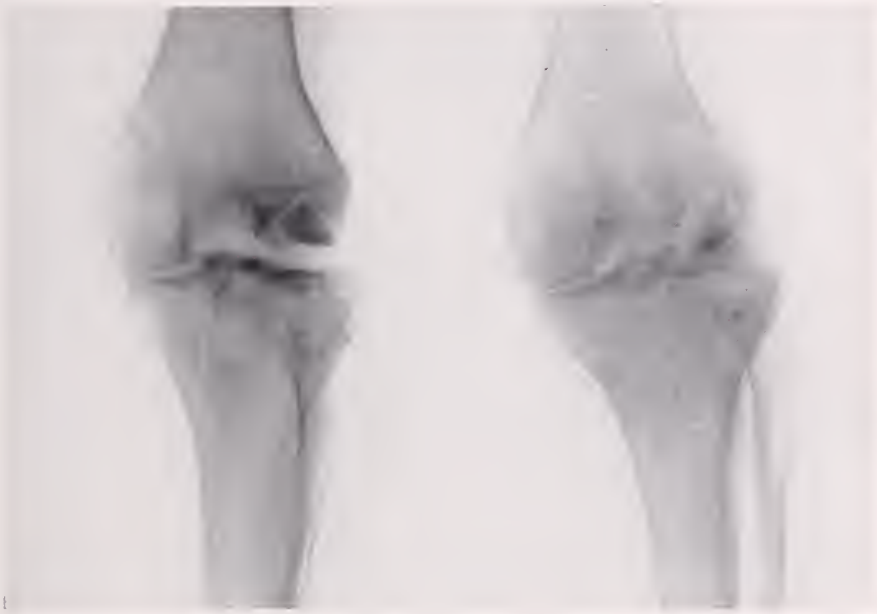
Fig. 2. This film was taken on 8/31/50 when the patient had completed a 90 day course of streptomycin and para-amino-salicylic acid therapy. The oval area of rarefaction in the medial femoral condyle is still visible. There is now moderate generalized osteoporosis.

Fig. 3. Follow-up film taken on 6/21/54 presents noteworthy persistent osteoporosis of the left knee. The oval lesion previously sharply outlined in the medial femoral condyle now blends with the adjacent porotic cancellous markings. There is slight flattening of the femoral condylar surfaces but the joint space is maintained.

Fig. 4. Film taken on 6/28/55 shows little change except for better calcification of the articular ends of the femur and tibia.

Comment: This case illustrates salvage of a tuberculous joint with combined streptomycin, para-amino-salicylic acid and immobilization. The limit of wholly synovial involvement was exceeded by the demonstration of a discrete bone focus which must have communicated with the joint since the tubercle bacilli were readily recovered from the effusion within the joint. Six years have passed since definitive diagnosis and almost five years since completion of chemotherapy. We feel secure in having obtained an arrest of the tuberculous infection in the knee but only additional time will determine whether a permanent cure has been produced.

Case #2. D. T. This 27 year old, white female was admitted to The Mount Sinai Hospital Orthopedic Service on March 15, 1953 for the 6th hospital admission for acute symptoms referable to the left knee. Her history revealed that at age 13 years, several months after an acute pleurisy, she developed pain and swelling of the left knee. The symptoms subsided and she remained asymptomatic until she was 17 years at which point pain and swelling recurred. She was immobilized in a long leg cast at that time and the symptoms again subsided. When she was 20 years old, symptoms of pain and swelling recurred and an arthrotomy and meniscectomy were performed. When she was 24 years in 1949, because of recurrence of her symptoms, her knee was again explored and a patellectomy was done. It was noted that the synovia was markedly hypertrophied and that destructive changes were present about the medial femoral condyle and the patella. Biopsy of the synovia was



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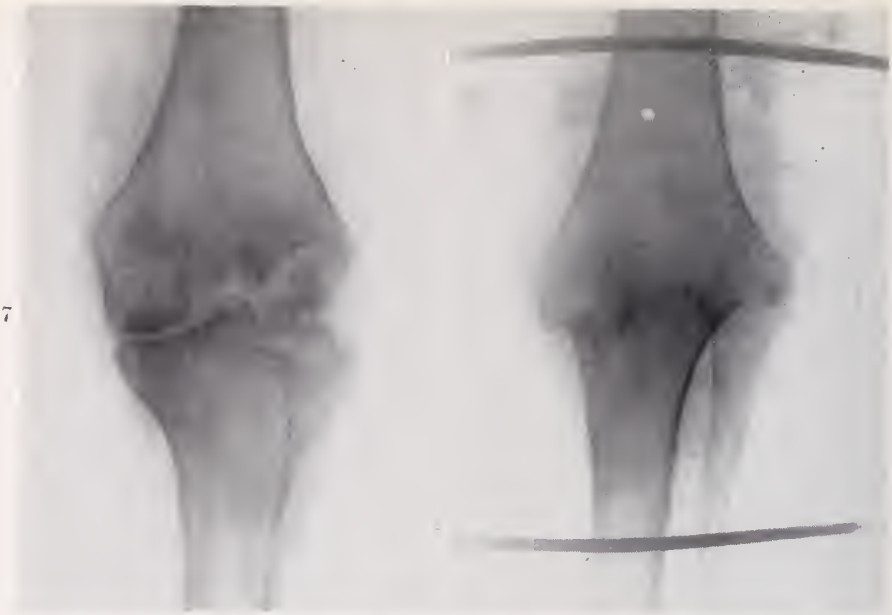
Case 2

Fig. 5. X-ray of the left knee on 10/16/50, when patient had sustained fracture of the lower tibia (not shown on this film), reveals destructive process in the lateral femoral condyle containing a dense sequestrum. Marked narrowing of the joint space is seen on the medial side.

Fig. 6. Film of the left knee on 4/24/51, taken while bone grafting procedure was performed for fracture of the lower tibia, indicates extension of the destruction in the lateral femoral condyle and appearance of an area of osteolysis in the lateral tibial plateau.



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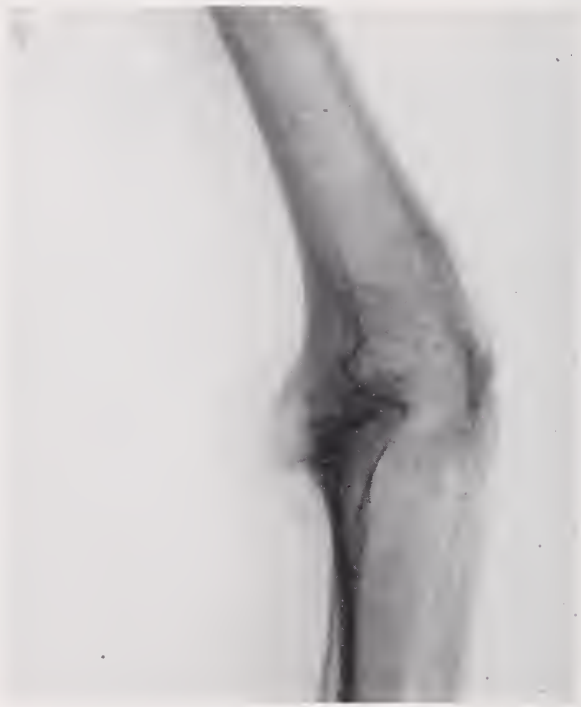

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CASE 2—*Continued*

FIG. 7. X-ray taken on 11/8/51 reflects the aggravation of the destructive processes in both the lateral femoral condyle as well as the lateral tibial condyle. At this time the patient presented signs of an acute suppurative arthritis.

FIG. 8. X-ray taken on 8/1/52 when patient was convalescent following joint excision and arthrodesis, using the Charnley technique for compression of the bone ends by means of appositional Steinman pins.

FIG. 9. X-ray on 7/30/53 shows sound ankylosis of the left knee with osseous bridging.

made but no specific diagnosis resulted. In the same year, she fell fracturing both bones of the leg (Fig. 5) requiring open reduction and plate fixation. In the final stages of convalescence from this procedure, she refractured her tibia (Fig. 6) requiring bone grafting. She developed symptoms again in the left knee in November, 1951 (Fig. 7) which continued unabated for several weeks prior to admission. She was given instillations of hydro-cortone into the knee, one of which improved her symptoms and another caused an acute flare-up for which she was hospitalized. On admission, because of the marked acute reaction throughout the left knee, associated with a very prominent, febrile reaction, she was considered to have a pyrogenic arthritis of the knee and incision and drainage was done with recovery of cheesy, yellowish pus. She was immobilized in a plaster hip Spica for two months, during which she ran a low grade temperature and continued to drain small amounts of material. On May 7, 1952, a second exploration of the knee was performed and following this, tissue which had been removed, returned for the first time showing tubercle bacilli and tuberculous granulation tissue. Streptomycin, 1 gram daily and PASA, 12 grams daily were started. The wounds about the knee healed well. On July 18, 1952, fusion of the knee was performed using Charnley compression (Fig. 8). A plaster cast fixation was maintained for three months following which she wore braces for a short period. The streptomycin and PASA were maintained for three months. Her subsequent history is entirely uneventful; the fusion occurred solidly and has remained solid. She is asymptomatic and walks unlimitedly and comfortably.

Comment: This case demonstrates well those features of tuberculosis which are concerned with its chronicity and periodicity with intervening apparent quiescence. The knee joint showed gradual, slow deterioration with symptoms starting at age 13 years and recurring at infrequent intervals for the next 14 years, during which time there was no spread to any other area. In this period the diagnosis resisted detection because of the inability to find the tubercle bacilli or identify tuberculous granulation tissue. This patient presented a closed lesion throughout, up until the incision and drainage after her last admission. As the x-ray illustrates (Fig. 9) there is now solid trabecular continuity across the previous area of disease so that the knee can truly be said to be healed. Whether the hydro-cortisone which was injected into the knee just prior to the last admission was instrumental in bringing the disease to its clinical recognition, remains an interesting possibility.

Case #3. J. R. This 9 year old, Puerto-Rican youngster was admitted to The Mount Sinai Hospital on December 9, 1954, for treatment of a painful, left knee which started following a fall down stairs, some six months before. On examination, slight swelling of the knee with mild, local tenderness over the medial femoral condyle were noted. He had knee movement from 175° extension to 80° flexion. There was ¼ inch atrophy of the thigh and a few small inguinal lymph nodes. The tuberculin test was positive. Culture of the fluid aspirated from his knee was negative. An open biopsy was performed on December 22, 1954 and the report returned positive for tuberculous granulation tissue containing epithelioid and Langhans giant cells but bacilli were not identifiable. The knee was immobilized in a plaster cast and he was placed on streptomycin 0.5 gram twice weekly, PASA 4 grams a day, and iproniazid, 125 milligrams a day. He received seven months of streptomycin and PASA and ten months of iproniazid. His knee was immobilized intermittently from the time of his admission until his final discharge on November 25, 1955. Though he was kept off weight-bearing throughout the entire period, his knee was entirely free from July until November of 1955, during which period he was kept in bed in mild leg traction which did

permit knee movement. Since his ambulation, he has had increasing knee movement to the point where there remained only 5° difference in range of movement between the involved and uninvolved knees. Clinically, the knee shows no evidence of any residual inflammation and his x-rays (Figs. 10, 11) have remained essentially negative throughout.

Comment: We have considered this case to be one of early synovial tuberculosis. Though the proof lay in the recovery of tissue which showed a histo-pathological reaction consistent with tuberculosis, the acid-fast bacillus was never recovered or identified. To question the diagnosis of tuberculosis under these circumstances would have meant to deny this patient treatment at the most optimal time. This youngster's illness was recent enough to make available to him the benefit of combined medication including iproniazid. He had exhibited minor toxicity from the streptomycin with minimal impairment of hearing in one ear which recovered when streptomycin was discontinued. The iproniazid dosage had been reduced because of the possible relationship to behavior problems which developed, but this was never wholly clarified. The follow-up which has been possible here is so short that final evaluation for end-result assay will have to await the passing of more time.

In summarizing the three previous cases of skeletal tuberculosis involving the knee joint, we have obtained a cure by operative fusion in one and arrest with chemotherapy in the other two. One of the latter presented a definite bone focus and the other apparently only synovial disease.

Case #4. A. A.: This patient was a 22 year old, white female admitted to The Mount Sinai Hospital in June, 1951 with a history of low back pain dating back one year prior to admission. X-rays taken at that time revealed destructive lesions involving L-3 and L-4 vertebrae with some narrowing of the interspace and evidence of a psoas abscess (Fig. 12). The abscess was aspirated and on culture, tubercle bacilli were recovered. A spine fusion was done promptly extending from L-2 to S-1 under streptomycin, and PASA coverage. She was immobilized in a body plaster cast after which she was transferred to another hospital for additional convalescence. The streptomycin at 1 gram daily and PASA at 12 grams daily were continued for approximately one year. She was immobilized, however, for only three months being permitted ambulation in her body jacket. Her subsequent course was essentially satisfactory and later films revealed gradual reduction in the size of the psoas abscess shadow and gradual fusion at the involved areas. On a two year follow-up, the patient was found to be afebrile, gaining in weight, and presenting no evidence of clinical activity of her tuberculous lesion. Though x-rays demonstrated adequate bridging by fusion of the involved vertebrae, the periphery of the fusion failed to limit motion above and below the involved site. Though this patient did not appear for subsequent follow-up examination, we have been informed that her status to date is essentially unchanged. The x-ray taken in 1953, two years post surgery, reveal a persistent defect at the antero-inferior margin of L-3 which has become stabilized with clear cut margins (Fig. 13). There is no osseous bridging across the bodies of the involved vertebrae, L-3 and L-4, though the interspace has narrowed considerably.

Comment: The interesting features of this patient are that the streptomycin, PASA combination permitted rather prompt surgical intervention at a time when the disease presented considerable activity as demonstrated by a prominent psoas abscess and destructive changes in the vertebrae. In the pre-antibiotic

era, this patient undoubtedly would have required more extensive preparation of a supportive variety with prolonged recumbence and additional emphasis on disease stability before surgery would have been considered. In addition, with the streptomycin-PASA medication which was continued for approximately a year, the disease has remained arrested with no evidence of local activity or of clinical dissemination. In view of the limited fusion which occurred following surgical arthrodesis, and failure of the involved vertebrae to heal by intervertebral bridging (Fig. 14) further observation over an additional interval seems warranted.

Case #5. C. R., a 26 year old Puerto Rican female was admitted to The Mount Sinai Hospital on May 6, 1952, because of low back pain, which on x-ray examination revealed destructive changes involving L-5 and S-1 vertebrae, as well as an associated psoas abscess (Fig. 15). The abscess was aspirated and a moderately large amount of caseous purulent material was recovered which showed no acid fast organisms on smear or culture. Though the diagnosis of tuberculosis was made clinically, no confirmatory evidence was possible at this time. Nevertheless, on June 18, 1952, spine fusion was performed bridging L-4, L-5 and S-1. She was placed in a body jacket, kept on bed rest, and given streptomycin, 1 gram daily and PASA 12 grams daily. The immobilization and chemotherapy were continued for six months. In this period, two other surgical procedures were done, a left nephrectomy for a non-functioning kidney in which tuberculosis could not be found and a bilateral, tubal ligation. Both of these operations were tolerated without incident and with excellent wound healing and convalescence. At the termination of this six month period, x-rays revealed satisfactory fusion of the involved segments and a satisfactory and a clinical status so that the patient was permitted increased freedom while wearing a Knight spinal brace. She was readmitted to the orthopedic service on June 20, 1953 approximately one year post-spine fusion, because of palpable lower abdominal masses. At this time, the laboratory work-up was essentially negative including a normal sedimentation rate. A needle biopsy was performed on June 26, 1953 with recovery of about 20 cubic centimeters of purulent material which was aspirated from a left psoas abscess. On July 10, 1953 a more formal approach was made for the evacuation of the psoas abscess. Subsequent culture for the first time returned positive for acid-fast bacilli. Streptomycin, 1 gram daily, and PASA 12 grams daily, were resumed on June 28, 1953. The dose of streptomycin was changed to 1 gram every other day one month later, at which time isoniazid, 200 milligrams daily, was added. This scheme of medication of the three drugs was continued until April, 1954 at which point the streptomycin was stopped but the other two medications continued until June, 1954 when all medication was discontinued. This represented approximately one additional year of combined medication in addition to the six months she had received earlier. On her most recent follow-up in September of 1955, x-rays of her spine showed solid fusion (Fig. 16), abdominal masses were no longer palpable or identifiable and clinically she was in excellent condition.

Comment: The course this patient followed illustrated several interesting aspects. Under streptomycin coverage, spine fusion was possible and successful but psoas abscesses which were present did not abate. She required surgical evacuation of abscess as well as an additional extended period of chemotherapy. Since the tubercle bacillus was not recovered until very late in her disease, no comment can be made of bacterial resistance to streptomycin. The addition of isoniazid to her therapeutic program contributed considerably to arrest of the disease. Draining sinuses were never a problem in this patient and each of her

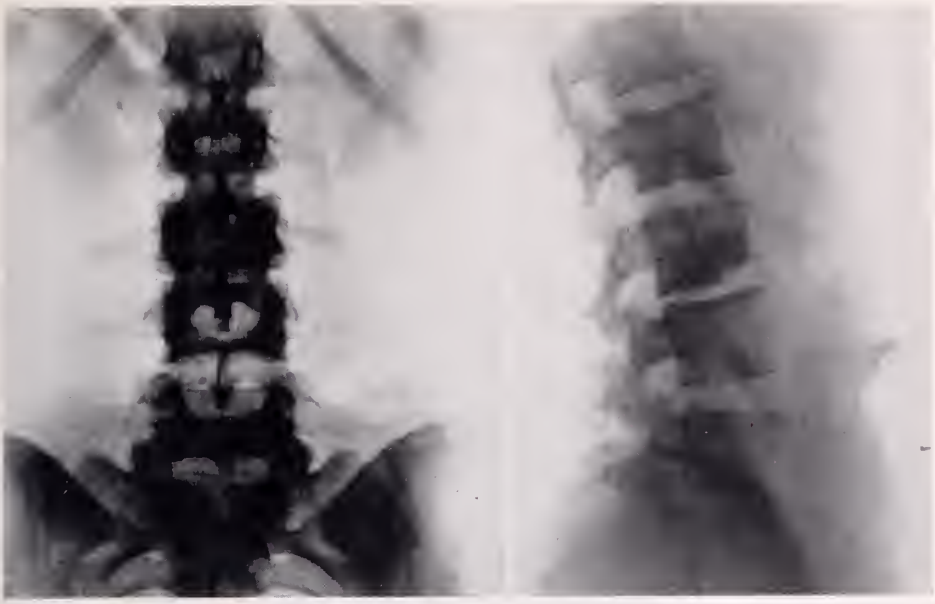
10a

10b

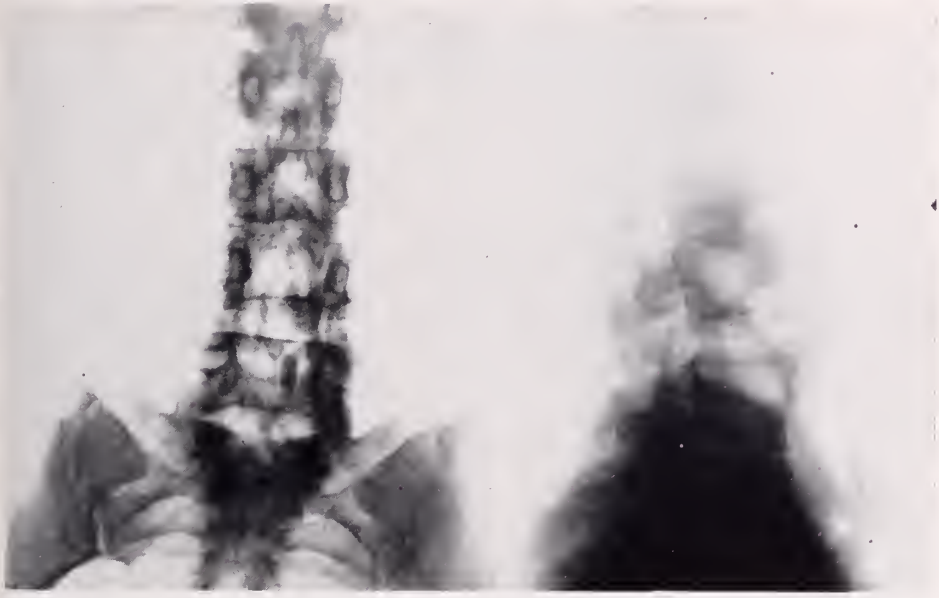
Case 3

Fig. 10a, 10b. X-ray of the left knee four months after diagnosis of synovial tuberculosis and chemotherapy. There is evident osteoporosis without bone lesions.

Fig. 11. Antero-posterior views of both knees after seven months of specific therapy indicates persisting osteoporosis of the left knee. The joint surfaces are intact.



12a 12b



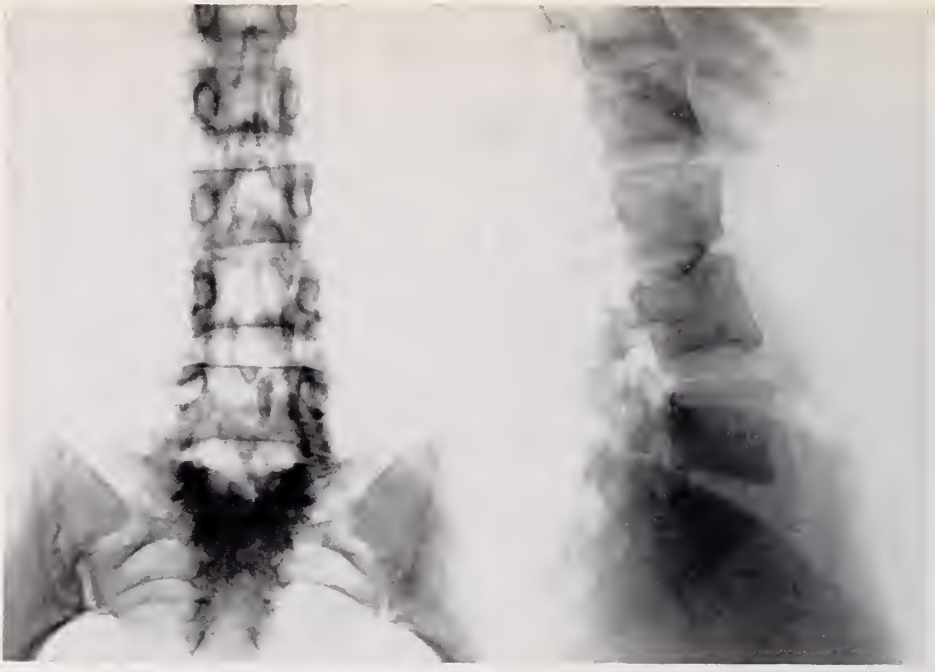
3a 13b

CASE 4

FIG. 12a, 12b. Antero-posterior and lateral views of the lumbo-sacral spine taken on admission show narrowing of the interspace between L-3- L-4 as well as destructive lesions at the antero-inferior margin of L-3 and along the anterior margin of the body of L-4. The illustration does not show the psoas shadow distortion which was present on the right side. There is sclerosis of the lower half of the body of L-3 suggesting ischemic necrosis.

FIG. 13a, 13b. Two years later, after spine fusion and chemotherapy, the margins of the lesions at L-3 and L-4 show sharper outlines.

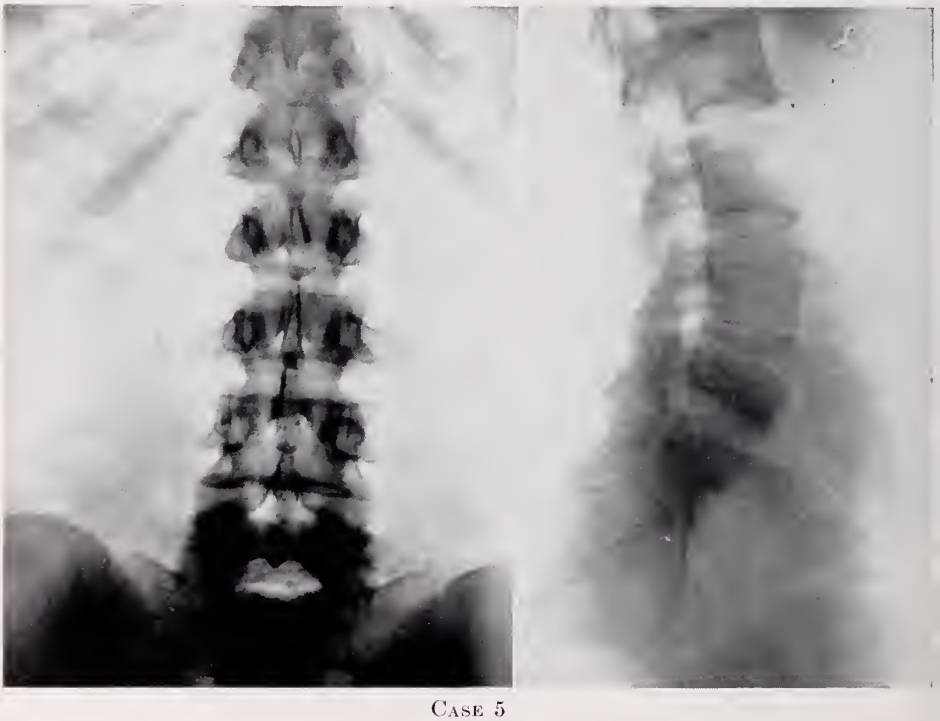
14a



CASE 4—*Continued*

FIG. 14a, 14b. Four years later, the interspace between L-3, L-4 is still narrowed but not bridged by inter-body fusion. The anterior surface of L-4 has largely been reconstituted.

15a



CASE 5

FIGS. 15a and 15b. X-ray of the lumbo-sacral spine on admission. The antero-posterior view shows a large right psoas abscess. The lateral view indicates an osteolytic process involving destruction of the lower half of the fifth lumbar vertebra. There is not the collapse and angulation here which would have taken place with a similar lesion higher in the spinal column.

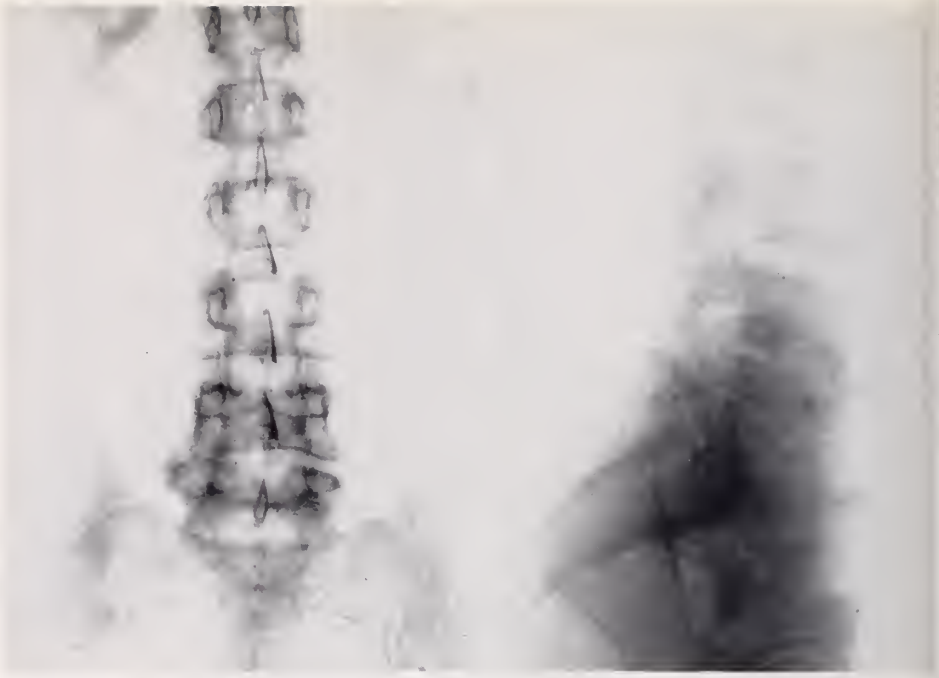
CASE 5—*Continued*

FIG. 16. X-ray almost three and a half years later shows evidence of posterior element fusion mass. The margins of the inferior surface of the fifth lumbar vertebra are sharp and the interspace at the lumbo-sacral level is maintained.

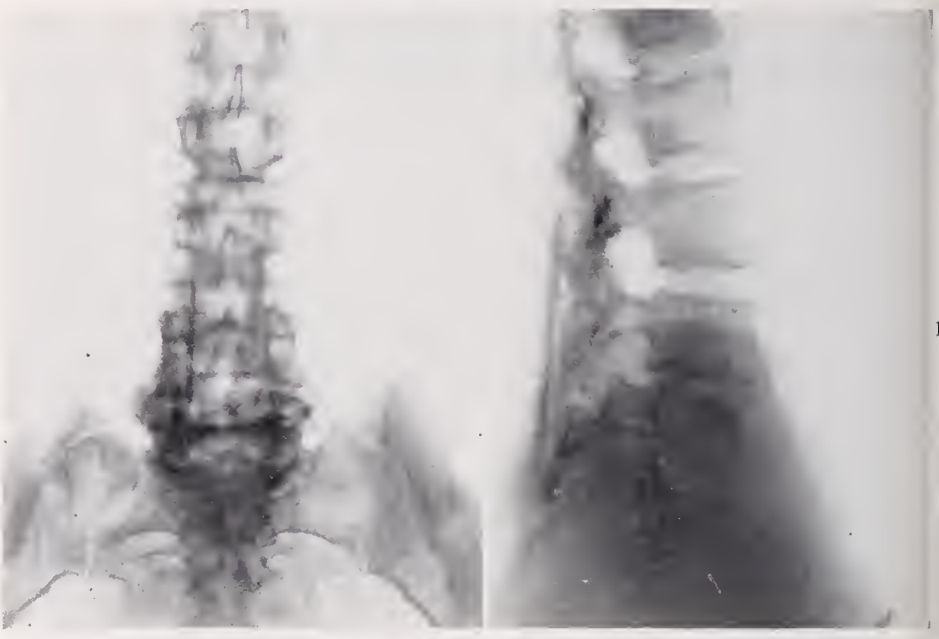
operations was followed by prompt wound healing under antibiotic coverage. This patient as the one preceding, failed to show solid block formation of the involved vertebral segments, and osseous bridging across the interspace between the involved vertebrae did not occur. Though the patient is now clinically silent, with apparent arrest of her disease, follow-up of approximately three years can not be reasonably judged to be sufficient for assessment of final and definitive subsidence.

Case #6. M. M., a 34 year old Puerto-Rican female, was admitted to the Gynecological Service of The Mount Sinai Hospital on March 25, 1953 with a history of low back pain of two years duration with recent association of a lower abdominal mass. Work-up disclosed destructive lesions involving the L-4 and L-5 vertebrae and a retro-peritoneal mass which was believed not related to any gynecological condition. She was transferred to the Orthopedic Service on April 2, 1953 where a tentative diagnosis of tuberculosis of the vertebrae with psoas abscesses was made and streptomycin and PASA were started. On April 21, 1953 an incision and drainage of the psoas abscess was done and on May 6, 1953 spine fusion of the segment L-2 to S-1 was performed (Fig. 17). In obtaining autogenous bone from the adjacent iliac crest, the psoas abscess, though previously drained, was opened into and still contained some purulent material. The patient's post-operative course continued uneventfully and her wounds healed well. Approximately a month after the spine fusion, in the course of investigating apparent intolerance to the chemotherapy, it was discovered that the patient's A-Z test was positive and that she had in fact been pregnant for approxi-

17a



18a



CASE 6

FIGS. 17a and 17b. X-rays indicate narrowing of the interspace between L-4, L-5 with destructive changes in the antero-inferior portion of L-4 and antero-superior part of L-5. There is evidence of marginal osteophytic bridging at the right side of L-4, L-5 on the antero-posterior view.

FIGS. 18a and 18b. One year later there is evidence of posterior spine fusion. The interspace between L-4, L-5 remains narrowed but present. The margins of the opposing surfaces of L-4 and L-5 are slightly irregular but sharper in outline. There is now osteophytic lateral bridging on both sides of L-4, L-5 interspace.

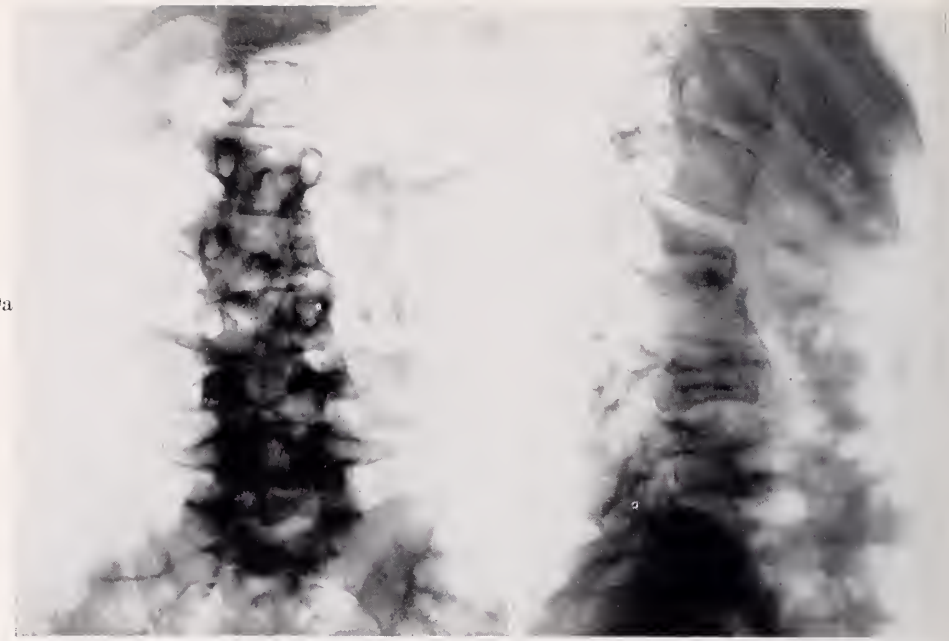
mately ten weeks. Gynecological consultation confirmed pregnancy and though the Orthopedic Service suggested consideration for therapeutic abortion, the obstetrical consultants felt that no obstetrical reason was present for such a course of action. Consequently, the patient's plaster cast was windowed for abdominal expansion and finally removed entirely with spinal support being maintained with a brace and bed rest. The patient was discharged on August 31, 1953 for additional convalescent management at another hospital. Our follow-up information was that she was maintained on specific medication until February 1954, which permitted continuous chemotherapy for a total period of ten months of combined streptomycin and PASA. We also learned that she delivered a still-born fetus in December of 1953. Since no autopsy was performed, information as to whether the fetus had been affected in any way either by the disease or by the medication was not available. On our last follow-up examination, May 26, 1954, the patient appeared clinically quiescent with satisfactory fusion at the involved vertebral site (Fig. 18).

Comment: The combination of problems presented by this patient were significant. She had an active tuberculous lesion in the low lumbar spine with prominent psoas abscesses. The abscesses were drained surgically and the involved vertebrae were fused. It was subsequently determined that the patient had an early pregnancy which did not reach appreciable size until after the surgical procedures of abscess evacuation and spine stabilization had been performed. Interesting arguments developed concerning the advisability of termination or continuing the pregnancy. The contention of the obstetrical service that no real reason for therapeutic abortion existed is borne out by a recent report from the New York Hospital (35) where statistical analysis failed to indicate any advantage of therapeutic abortion in the handling of tuberculosis in pregnancy by present day methods and medication. In this study, the incidence of spontaneous abortions and miscarriages showed no predilection for patients with tuberculosis. The fact that this patient had a still birth need not be a victory or defeat for either point of view.

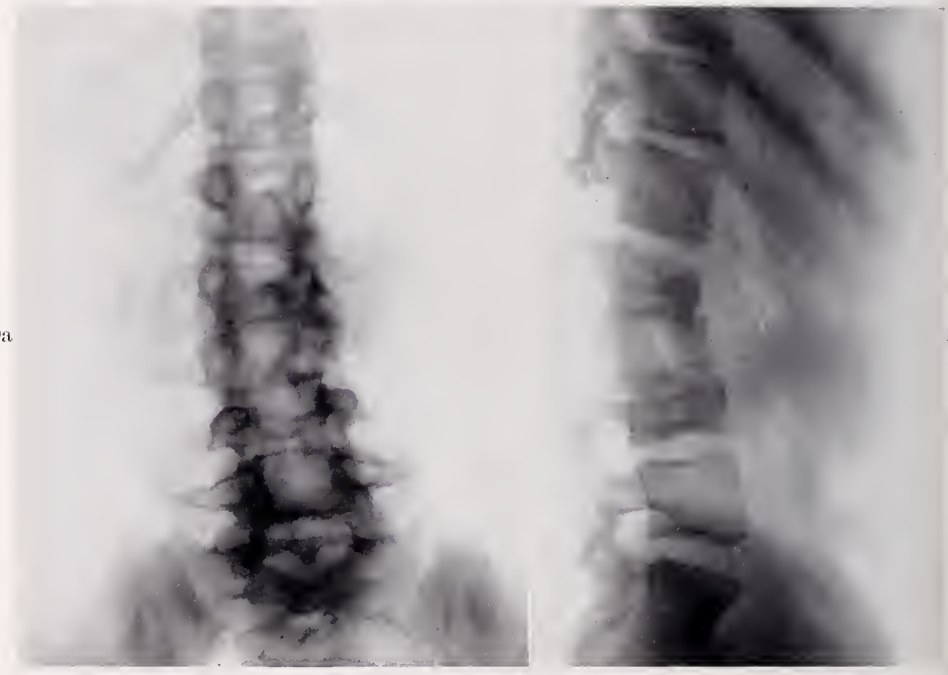
As in the previous cases, too little time has elapsed since the arrest of the disease to arrive at any statement as to ultimate cure.

Case #7. D. W. This patient was an 11 year old, Negro girl who was admitted to The Mount Sinai Hospital on July 23, 1953. Tuberculosis of the lumbar spine had previously been diagnosed in 1952 at another hospital where a spine fusion had been performed on March 10, 1953. Three months post spine fusion, she was transferred to the Blythedale Children's Convalescent Hospital on a proposed routine which included no chemotherapy and ambulation in a body jacket. While at this convalescent institution, she developed low grade temperature, elevated sedimentation rate, and multiple sinuses in the previous operative incision over her back. On August 5, 1953, exploration of the fusion site was done and a secondary debridement, including removal of sequestra, performed. The wound was closed primarily. She was started on streptomycin, 0.5 gram daily, isoniazid, 400 milligrams daily and PASA, 8 grams daily. Acid-fast bacilli were not identified but the pathological report came back showing granulation tissue characteristic of tuberculosis (Fig. 19). She returned to the children's convalescent hospital where her medication was continued until May 20, 1954 (Fig. 20), constituting a total period of approximately ten months. She remained in plaster immobilization for a six month period following the secondary surgery and chemotherapy. The patient's subsequent course remained entirely satisfactory and on repeated follow-up examinations, she was found to be symptom free with normal blood counts, sedimentation rate and adequate function of her back without discomfort. X-rays showed satisfactory fusion of the involved vertebral segment of L-2, 3 and 4.

19a



20a



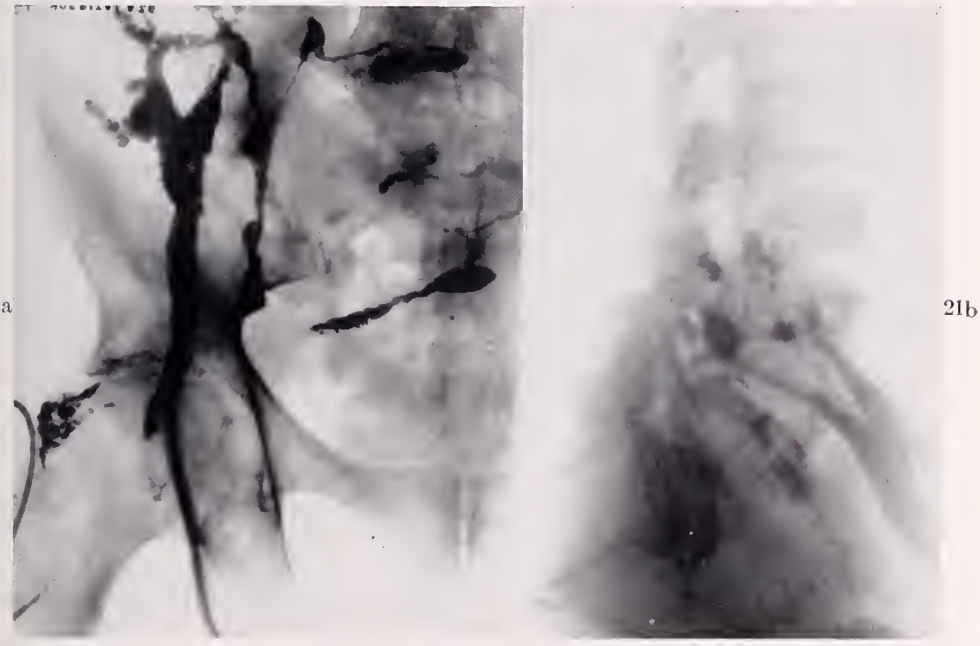
CASE 7

FIGS. 19a and 19b. X-rays of the spine after secondary debridgement show involvement of L-2, 3, and 4 with considerable compression of L-2.

FIGS. 20a and 20b. X-rays seven months later show evidenees of vertebral body growth especially L-2 and L-4 with sharper vertebral outlines and residual though narrowed, intervertebral intervals.

Comment: Though all of the details of this case are not entirely known, information was obtained that some form of drug therapy had been given prior to the original spine fusion. The fact that the wound broke down secondarily and developed draining sinuses when the drug had been stopped, despite a solidifying spine fusion, is indication of the necessity for prolonged chemotherapy and accompanying adequate supportive therapy. Under the second course of drug therapy which included the combination of three medications, and which was continued for ten months, the youngster's course continued in a very excellent manner with normal healing of the operative incision and concomitant evidences of adequate arrest of the disease. We have had the benefit of a two year follow-up now since the wound has healed and all indications of successful arrest remain.

Case #8. F. B. This 49 year old, white male was admitted to the Mount Sinai Hospital Medical Service on January 27, 1954 because of persistent draining sinuses in the left groin over a period of seven years. He had a history of previous admission to a tuberculosis sanitarium in 1948 at which time he was treated with 175 grams of streptomycin which produced a quiescent status of lumbo-sacral Pott's disease and healing of groin sinuses. He was discharged in 1949. However, thereafter, he developed intermittent episodes of drainage which subsided after varying therapies including the usual antibiotics for secondary infection. Work-up at The Mount Sinai Hospital disclosed left groin and thigh sinuses (Fig. 21) which communicated with the lumbo-sacral level, and evidence of renal impairment believed to be due to renal amyloidosis secondary to prolonged suppuration. A needle biopsy of the lumbo-sacral region performed on March 3, 1954 disclosed acid-fast bacilli.



21a 21b

Case 8

Figs. 21a and 21b. There is prominent fistulous tracking from the lumbo-sacral interval to the right groin as outlined by radio-opaque instillation.

The patient was given PASA, streptomycin and isoniazid in adequate doses, but these were continued for only 12 days at which time the patient left the hospital against advice.

Comment: This case, in which we had little stake other than the confirmation of the diagnosis, demonstrates the life cycle of tuberculosis as it existed in the pre-antibiotic era. This patient was known to have had pulmonary as well as osseous tuberculosis and sinus formations with super-imposed pyogenic contamination. He exhibited impairment in renal function which will progress with his uncontrolled disease and may finally lead to an unfortunate end.

Case #9. T. P., an 11 year old, Negro female was admitted to The Mount Sinai Hospital Orthopedic Service on February 19, 1955 with the chief complaint of a bulging mass over the front of the chest, of four days duration. Except for an accompanying history of weight loss and anorexia dating back eight months and the probability of intermittent temperature elevation, no other pertinent information was available. On admission, the child appeared acutely ill. Temperature recordings of a spiking nature to between 102° and 103°F. were noted. X-rays revealed enlarged hilar nodes and atelectasis of the left upper lobe. There was a fusiform soft tissue swelling about the upper dorsal vertebrae as well as narrowing between and involvement of D-9 and D-10. Destructive changes at the margin of the lower end of the manubrium were also present. The consensus was that this youngster had left upper lobe pulmonary tuberculosis with mediastinal adenopathy, upper dorsal Potts disease with para-vertebral abscess and tuberculous osteomyelitis of the lower end of the manubrium with an abscess pointing anteriorly. On the fourth hospital day, one episode of hemoptysis occurred. Streptomycin, 1 gram daily, was started on this day and iproniazid, 150 milligrams daily and PASA 12 grams daily were added five days later. Following these medications, the youngster's temperature dropped very promptly and her entire general condition improved. Aspiration of the anterior chest mass recovered 5 cubic centimeters of purulent material, culture of which was sterile. Gradually the anterior chest swelling disappeared, the lung findings cleared but the destructive changes at the lower end of the manubrium remained prominent as did the destructive change at D-9 and D-10 with narrowed interspace. The youngster's treatment initially remained largely recumbency but on the 56th hospital day, a body cast was applied to enforce immobilization. Gastric washings taken prior to chemotherapy were reported as being positive for tubercle bacilli, however subsequent specimens were negative. After six months in the hospital, she was transferred to the Blythedale Children's Convalescent Hospital where she remained recumbent in a plaster cast. Streptomycin, PASA and iproniazid were continued. She was re-evaluated at the Mount Sinai Hospital on November 21, 1955 and a spine fusion extending from D-9 to D-11 was done. A plaster cast was re-applied and she returned to Blythedale on December 21, 1955 where she remains to date. She is still on triple medication which represents a year of chemotherapy up to this point.

Comment: On admission this child presented a threatening and potentially critical situation as evidenced by disseminated tuberculosis. She had an active chest lesion as well as skeletal localizations in the upper dorsal spine and upper end of the sternum, both with cold abscesses. A most dramatic change occurred in many phases of the youngster's clinical picture, most noteworthy being the drop in temperature, gain in weight, improvement in general well being, clearing of the pulmonary lesion, and of the anterior chest wall and para-vertebral abscesses. However, because of the destructive changes in the upper dorsal vertebrae, surgical fusion of this region of the spine was performed in order to expedite clinical stability of this last remaining demonstrable focus. This child

has been on one full year of continuous chemotherapy and she is still being observed at the children's convalescent hospital.

SUMMARY AND CONCLUSIONS

Skeletal tuberculosis is part of a disseminated disease. Its features of chronicity and latency require prolonged therapy and observation. Public health measures have diminished the incidence of tuberculosis and the presently available chemotherapeutic medications are powerful tools for its control. Drug therapy is best given in combination rather than as single agents. The present goal is for salvage of diseased joints with early diagnosis and aggressive chemotherapy with or without ancillary surgery. We have shown two cases where joint preservation was possible, one with a small localized bone focus and the other with no demonstrable bone focus. Where extensive disease has already become manifest, chemotherapy must be supplemented with surgery. Surgery is now safe. Wound healing can be expected and the threat of dissemination has been virtually eliminated. With chemotherapy, the natural course of the disease has been shortened, and surgery can now be done much more promptly than heretofore.

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INTESTINAL TUBERCULOSIS: DIFFICULTIES IN DIAGNOSIS IN THE ABSENCE OF FLORID PULMONARY INVOLVEMENT

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Tuberculous infection of the gastrointestinal tract is a common disease to those who see and treat large numbers of patients suffering from pulmonary tuberculosis. It is the most frequent complication of untreated pulmonary tuberculosis; the incidence in various autopsy series ranging from 50 to 80 per cent (1). The incidence in sanatoria varies considerably depending upon the percentage of minimal, moderately advanced and far advanced cases admitted to the institution. Blumberg (2) reported roentgen evidence of intestinal tuberculosis in 5 to 8 per cent of minimal, 14 to 18 per cent of moderately advanced, and 70 to 80 per cent of far advanced cases. These statistics correlate well with our clinical knowledge that bowel lesions occur as a result of swallowed infected sputum. This was confirmed experimentally by Medlar and Sasano (3) who fed tubercule bacilli to animals and produced intestinal ulceration.

The problem of recognition of intestinal tuberculosis is simplified at institutions for the tuberculous by the frequent use of small bowel series and the barium enema. Katz (4) reports that at Seaview Hospital, a 2000 bed institution for the treatment of tuberculosis, gastrointestinal x-ray surveys are done routinely as originally advocated by Brown and Sampson (5). Phthisiologists as well as gastroenterologists are aware that the symptoms of intestinal tuberculosis are extremely varied and that no pathognomonic sequence of symptoms and signs can be enumerated. The picture is further complicated by the fact that a large number of patients with pulmonary tuberculosis have gastrointestinal symptoms although no gastrointestinal lesion exists. Anorexia, nausea and vomiting are rather frequent symptoms in uncomplicated pulmonary tuberculosis, and bouts of epidemic diarrhea are common to tuberculosis sanatoria. The onset of diarrhea should arouse the suspicion of tuberculous involvement of the intestine in any patient with active pulmonary tuberculosis.

Radiographic study affords the only means of making a clinical diagnosis of intestinal tuberculosis. The sign described by Stierlin (6) in 1911 in cecal tuberculosis has been noted repeatedly since. Stierlin observed that in ulcerative and infiltrative involvement of the cecum and ascending colon there is a persistent tendency for the affected area to empty itself of barium promptly, implying extreme irritability. As Stierlin originally indicated, the roentgen appearance is not pathognomonic of tuberculosis. In patients with pulmonary tuberculosis and cavitation however, it is much more likely to be due to tuberculous ulceration in the cecum than to functional or other organic conditions.

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Pulmonary tuberculosis and regional ileitis, coexisting in the same individual has been noted recently by Schaffner (7). He reported a series of 109 consecutive cases operated upon with the preoperative diagnosis of acute appendicitis at the Nova Scotia Sanatorium. One hundred and one were either tuberculous or non specific appendicitis. Eight presented evidence of more extensive and obstructing intestinal tuberculosis, and were treated by radical bowel resection. All eight were diagnosed grossly as tuberculosis, but only five proved to be so. The pathologic report in two cases was regional ileitis and in the third, carcinoma. The problem of diagnosis of an intestinal lesion in a general hospital or clinic is not as simple as in a tuberculous institution. Since the report of Crohn, Ginsberg, and Oppenheimer in 1932 (8), the incidence of intestinal tuberculosis seen in general hospital practice has been on the decline. This decreased incidence of primary bowel tuberculosis is due, in large measure, to laws requiring the careful inspection of cattle for evidence of tuberculosis. The impact that the acceptance of regional ileitis as a distinct clinical and pathologic entity had on the reporting of cases of intestinal tuberculosis can best be seen in Great Britain where milk regulation is not enforced. At the London Hospital, England, there were 70 patients treated with a diagnosis of tuberculosis of the ileum or cecum between 1922 and 1937. From 1937 to 1952, only 12 cases of tuberculous enteritis have been proved at operation and during the same time, 40 patients have been operated upon for granulomatous enteritis (9). It is likely that before 1932 a great number of cases of ileocecal tuberculosis were actually non specific enteritis and enterocolitis.

Crohn and Yarnis (10) reviewed all the surgical specimens and the autopsy material at The Mount Sinai Hospital for the years 1926 through 1938 and were able to find only eight cases of primary ileocecal tuberculosis. At The Mount Sinai Hospital, in the six year period following the report of Crohn, Ginsberg, and Oppenheimer (8), 130 cases of regional ileitis were diagnosed, and the incidence of the non-specific granulomatous diseases has been on the increase yearly. Concurrently, there has been an increasing tendency to view with suspicion any diagnosis of primary ileocecal tuberculosis.

The diagnosis of primary intestinal tuberculosis cannot be made with assurance ante mortem. Some reports have considered a roentgenogram of the thorax which did not show evidence of pathology in the presence of tuberculosis of the bowel as sufficient evidence for concluding that the primary lesion was in the intestinal tract. However, as was stressed by Goldfarb and Sussman, minute remnants of the primary pulmonary tuberculous lesion may be missed on clinical and roentgenologic examination (11). Hoon (12) studied 58 cases of intestinal tuberculosis at the Mayo Clinic, nine of whom had no evidence of extra-enteric tuberculosis. These he termed "presumptive" primary intestinal tuberculosis. One of the nine came to post mortem study prior to publication of his report and was found to have pulmonary tuberculosis despite the lack of radiological evidence of thoracic disease.

Although primary intestinal tuberculosis is a rarity, it is the task of the clinician to maintain a high index of suspicion whenever confronted with obscure gastrointestinal symptoms or roentgen signs that defy ready diagnosis. The pos-

sibility of tuberculous involvement of the intestinal tract, even in the apparent absence of an extra-intestinal focus, should be borne in mind.

We recently had the opportunity to observe a most unusual case of abdominal tuberculous lymphodenopathy causing roentgen deformity of the third portion of the duodenum. The correct diagnosis was made at exploratory laparotomy. Pre-operatively this defect was considered to be metastatic implants in the peritoneum from a proven carcinoma of the middle third of the esophagus. Because of a negative chest film and lack of a suggestive history, the possibility that tuberculous nodes were responsible for the extrinsic pressure deformity on the duodenum was not entertained.

With this as a stimulus, we reviewed the surgical material at the hospital in the last two decades and found five additional instances where operation was performed for various intra-abdominal conditions only to have tuberculosis discovered in the intestinal tract or the peritoneal cavity. In a seventh case, tuberculosis was known to involve the right side of the colon, since, three years before, surgery at a neighboring institution for supposed acute appendicitis revealed tuberculosis. The symptoms and roentgen findings on admission were interpreted correctly in the light of the past history, and the patient was spared an operation.

These seven cases illustrate some of the difficulties encountered in the diagnosis of intestinal tuberculosis in the absence of florid pulmonary involvement. An eighth case is detailed which illustrates the reversibility of colonic tuberculosis by the newer drugs.

Case # 1

A 33 year old postal clerk (B. R.) was admitted to The Mount Sinai Hospital on November 25, 1947 because of lower abdominal cramps. He had been well until October, 1944 when he was found to have a "shadow" in the left upper lobe on a routine chest x-ray taken in the course of an army induction examination. Prior to that time, he had noted night sweats but no weight loss, cough, or chest pain. He was sent to a tuberculosis sanatorium in Bedford Hills, N. Y., but never had a positive sputum. Three months after arriving at the sanatorium, he had an attack of severe cramping lower abdominal pain, occurring in paroxysms, lasting about a minute and associated with nausea, vomiting, and retching. The entire episode lasted about ten hours. There was no radiation of pain, and bowel movements were normal. A gastrointestinal series and barium enema done the following week were negative. In the following seven months, he had three similar episodes lasting from six to eight hours, not associated with dietary indiscretions, and subsiding spontaneously.

He remained at Bedford Hills for two years and was discharged as an arrested case. After discharge, he had further episodes of abdominal distress at decreasing intervals. In 1946, he was placed on an ulcer regimen for eight months with only partial relief of symptoms. In the three months prior to admission, he had frequent attacks of pain with nausea but no vomiting, and for the three days prior to admission, he had lower abdominal pain coming in spasms and associated with borborygmi. There was no nausea, vomiting, or diarrhea. In the previous year, he had lost fifteen pounds of weight and noted increasing fatigue and complete loss of libido. His past history included appendectomy in 1930 for ruptured appendix, and in 1939 he was treated for mid-epigastric pain with a bland diet.

The physical examination revealed a well developed, emaciated white male, who was chronically ill. Positive findings were limited to the lungs and abdomen. The lungs revealed

unimpaired resonance, breath sounds were unaltered, and fremitus was normal. Whispered sounds were exaggerated in both apical regions posteriorly and a few fine rales were present in the left mid lung field. In the abdomen was a well healed right lower quadrant McBurney scar. The liver and spleen were not felt. There was tenderness to deep and superficial palpation in the lower mid-abdomen and right lower quadrant with increased resistance in the right lower quadrant.

Laboratory Findings revealed a normal hemogram. The sedimentation rate was 34 millimeters in one hour. The urinalysis was normal, stool guaiac was two plus, tuberculin (1–1000) was negative. X-ray examination of the chest was reported "tuberculous process in the left upper lobe extending from the apex to the third rib anteriorly. These lesions appeared mainly calcified and fibrotic, but the possibility of recent small infiltrations cannot be excluded." Barium meal examination of the gastrointestinal tract showed the esophagus, stomach, and duodenal bulb to be normal. Small bowel study (Fig. 1) revealed the distal foot of ileum involved in an inflammatory process characterized by a moth-eaten appearance of the outer border of the bowel, complete absence of any mucosal markings, and several filling defects. The impression was non-specific granulomatous ileitis involving the distal foot of ileum. Barium enema examination revealed no organic intrinsic lesion in any portion of the large bowel except for the caput coli where there was some irregularity of the contour and irritability. The terminal ileum was distensible, but irregular in contour, and there was disturbance of the musocal pattern. The changes were interpreted as being due to non-specific granulomatous ileitis.

The patient continued to complain of right lower quadrant pain. He had daily temperature elevations to 102°F. These attacks occurred about two and one half hours after meals despite therapy with belladonna, folic acid, and liver extract.

FIG. 1. Case 1. Film taken 4½ hours after barium meal showing the distal foot of ileum involved in an inflammatory process subsequently proven to be tuberculosis. Note the absence of mucosal markings and the moth-eaten appearance of outer border of bowel.

In view of the absence of active pulmonary symptoms, a quiescent lesion on chest x ray and small bowel findings localized to the terminal portion of the ileum, it seemed quite clear that we were dealing with a non-specific granulomatous ileitis. The failure to respond to medical therapy appeared to be an indication for surgical intervention. An exploratory laparotomy was performed January 6, 1948 with the preoperative diagnosis of non-specific granulomatous ileitis. At operation, the terminal seven feet of ileum, the cecum, and ascending colon were grossly involved in a tuberculous process completely encircling the bowel, which was thickened, hypertrophic, reddened, and studded with small and large tubercles. Tubercules were present on the peritoneum of the mesentery. An ileal lymph node was biopsied and on frozen section, was reported as tuberculous granulation tissue. Acid fast bacilli were found on fixed section. As the amount of involved bowel was too great to allow resection, the abdomen was closed and streptomycin therapy initiated post operatively. His post operative recovery was uneventful and he was discharged after a two week period.

After discharge, he was followed in the out-patient department until 1951. He had received six months of streptomycin therapy and in November 1949, when seen in clinic was doing remarkably well. He had no diarrhea and no abdominal pain. Physical examination was negative. Barium enema and small bowel series showed no progression of the disease. When last seen November 1950, he reported feeling well except for occasional episodes of abdominal colicky pain and diarrhea approximately ten to twelve times in the preceding year.

Comment. This case emphasizes that criteria for an unequivocal roentgenologic distinction between regional and tuberculous enteritis are lacking. General contraction of the disease segment which implies diminution in caliber and length, mucosal changes, and loss of pliability are features which both forms of enteritis have in common.

Knowing the findings at operation, one might say that antituberculosis therapy should have been instituted as soon as the workup was completed and that an exploratory operation was not indicated. This observation is purely in retrospect, however. Chemotherapy is dramatic in tuberculosis, but it should not be administered unless a definitive diagnosis has been established. The symptoms and roentgenologic signs suggestive of tuberculosis of the intestine in association with tuberculosis elsewhere in the body may constitute acceptable criteria for the diagnosis of tuberculous enteritis. In this patient, the absence of pulmonary symptoms, the apparently healed lesion on chest roentgenogram, and most important, the apparent localization of the lesion to the ileum, together with poor results on conservative medical therapy, were factors which led to the decision to explore.

Case # 2

A 54 year old Russian born male (N. W.) was admitted August 25, 1938 because of abdominal pain of three months duration. His illness was ushered in by vomiting followed by a sharp pain in the abdomen about two fingers below the umbilicus. This subsided spontaneously after a short while, but recurred intermittently over the three month period. The pain would travel at times to the epigastrium, but never radiated to the back. The symptoms followed meals, but had no relation to any specific type of food, and would last from several minutes to hours. No relief was obtained from alkalis. Three days after the onset of the illness, he visited a neighboring hospital out-patient department where he was given medication which controlled his vomiting, but no therapy was capable of controlling his pain. He had a weight loss of twelve pounds in three months and noted progressive weakness. One week prior to admission, he went on a milk and cream diet on the advice of a physician. He subsequently noted that his bowel movements became loose, and for three days prior to admission, his stools were yellow.

Past illnesses included diabetes for nineteen years but currently controlled by diet, jaundice, due to cholelithiasis 25 years prior to admission, was treated medically with no recurrence, and right lower quadrant pain ten years prior to admission was diagnosed as chronic appendicitis. There had been no recurrence of this pain.

Physical examination revealed a chronically ill, emaciated male. The temperature was 98°F; pulse, 88 per minute. Lungs and heart were normal. In the abdomen there was

moderate tenderness in the lower abdomen in the mid-line. No masses were palpable, but the liver was percussed two fingers below the costal margin.

Laboratory findings included a hemoglobin of 61 per cent, and a white blood count of 10,400 with 78 per cent polymorphonuclear leukocytes. The urine was normal. The Wassermann was negative. The blood urea nitrogen was 21 milligrams per cent. Fasting blood sugar was 140 milligrams per cent. Examination of gastric contents revealed 32 units of free HCl.

X-ray examination included a small bowel series and a barium enema which demonstrated an organic lesion about the caput coli and terminal two inches of the ileum characterized by a constant irregularity in outline and narrowing of the lumen suggestive of an appendiceal abscess. However, carcinoma of the cecum could not be ruled out. Sigmoidoscopic examination was negative. Stool guaiac examinations ranged from one to three plus.

The clinical course in the hospital was uneventful. The exact nature of the organic lesion about the caput coli could not be determined. It was felt that an exploratory operation was indicated with the possibility that the lesion might be neoplastic. During his stay at the hospital, the patient had no further pain of the nature described on admission. Although there was no appreciable improvement of this condition while on the ward, he decided not to submit to an operation, and return home to await further developments.

Readmission to The Mount Sinai Hospital occurred three weeks later with the same complaints that led to the first admission. On the third hospital day, an exploratory laparotomy was performed for a supposed carcinoma of the cecum. At operation the ileocecal region was firmly bound down to the anterior abdominal wall by rather dense adhesions involving omentum and bowel in one mass. Practically the entire small intestine, cecum and ascending colon were diffusely studded by small grayish white lesions which coalesced in areas to constrict the bowel wall. The mesentery of the small intestine was similarly involved. This was grossly interpreted as a diffuse intestinal tuberculous process. A biopsy of the mesentery was reported as tuberculosis. Since the disease was too extensive for any radical operation, the abdomen was closed. The patient made a perfectly smooth recovery and was transferred to another institution for convalescent care.

One week after transfer, he began to cough, expectorating blood tinged sputum which was positive for acid fast bacilli. He was then transferred to Seaview Hospital, Staten Island, N. Y. where a chest x-ray on admission showed increased infiltrations bilaterally with cavitation in the right upper lobe. He was treated, but a progressive downhill course ensued and he expired December 29, 1938. Permission for post mortem examination was not obtained.

Comment. The presumptive diagnosis at the time of first admission was peptic ulcer. After barium enema and barium meal showed the pathology to be localized to the ileocecal region, the impression was carcinoma of the cecum. The importance of the chest roentgenogram in the differential diagnosis of obscure lesions in the ileocecal region is well demonstrated here. With the routine use of the chest plate in all hospital admissions, the diagnosis probably would have been established without operation, and presumably antituberculous medication would have been promptly administered. A primary pulmonary focus undoubtedly existed which flared up after the operation. It is unlikely that such extensive pulmonary involvement could develop in such a short period of time unless active disease were present at the time of operation.

Case #3

M. B., a 19 year old white male student was perfectly well until three months prior to admission when he began to complain of intermittent pain in the right side of the abdomen. The pain did not radiate and was unrelated to meals. Three weeks after the onset of symptoms, he developed fever of 101°F. and the pain localized to the right lower quadrant. He was admitted to a neighboring hospital with the diagnosis of perforated appendix. At operation, the appendix was found to be normal but was resected. A mass was felt retroperitoneally, but was left in situ. A biopsy taken of a mesenteric lymph node was reported as mesenteric lymphadenitis (non specific inflammation).

A stormy post-operative course ensued, the patient had high fever and required several transfusions. He developed a pleural effusion on the left side which was thought to be on the basis of a post-operative infarct. A chest tap revealed blood tinged fluid which was studied for tuberculosis, but the results were negative. Chest film repeated after the tap showed a small amount of fluid still present, and the underlying lung parenchyma could not be commented on. The rest of the left lung field was clear. The right lung showed evidence of pleural thickening. Sputa and gastric washings were negative for tubercle bacilli. The barium enema was normal. The impression on discharge was retroperitoneal sarcoma.

After discharge from the hospital, he began to lose weight, developed diarrhea and vomiting, and was admitted to The Mount Sinai Hospital July 27, 1942. The wound from the appendectomy had opened and was discharging pus. There was a large swelling on the right side of the abdomen. His temperature was 100°F. on admission and rose to 104°F. two days later. It was felt that an exploratory laparotomy was indicated and he was operated on for the excision of the fistulous tract presumably resulting from a retroperitoneal sarcoma.

At operation the small intestinal loops were found to be adherent to one another, the adhesions were very extensive and there was a diffuse tuberculous lesion involving the intestines, mesentery and lymph nodes. An ulcerated loop of the small intestine had to be removed because of obstruction and perforation with numerous abscesses around it.

The surgical specimen consisted of 75 centimeters of resected ileum. The loops were matted together by firm fibrous adhesions. Mesenteric lymph nodes were matted together and showed necrotic areas. Mucosa showed small areas of superficial ulceration at irregular intervals. This was reported as tuberculosis of the ileum and mesenteric lymph nodes.

Comment. Pseudo-appendicitis is one of the common syndromes associated with ileocecal tuberculosis. Davis (13), studying the symptom complexes of intestinal tuberculosis found chronic intestinal obstruction to be the most common syndrome and the picture of acute or recurring appendicitis next most common. This in no way differs from the syndrome of pseudo-appendicitis found in regional ileitis, as stressed by Snapper and Poppen (14). Indeed a history of a previous appendectomy without relief of right lower quadrant pain followed by a fecal fistula is characteristic of regional ileitis.

The chest film following appendectomy showed a pleural effusion which was consistent with the clinical diagnosis of pulmonary infarct. The underlying lung parenchyma could not be studied however. This fact coupled with the presence of old pleuritic reaction in the opposite lung suggests that in all probability a tuberculous process in the lungs and pleura had existed prior to the abdominal episode, despite the negative report.

Case # 4

A thirty-six year old colored housewife (E. H.) was admitted to The Mount Sinai Hospital, September 5, 1940 because of epigastric fullness during and immediately after meals. This "knot-like" sensation as she described it, was relieved only by induced vomiting. A barium meal examination four months before admission was said to have revealed a duodenal ulcer and she was placed on a Sippy regimen without relief. Three months prior to admission she began to have diarrhea, passing five or six watery stools daily without blood or pus. There was a progressive weight loss of twenty-six pounds in this three month period. Occasional episodes of fever occurred during this interval. She denied cough, chest pain or night sweats. Her only previous illness was a bout of pleurisy thirteen years before with uneventful recovery.

Physical examination revealed a well developed, poorly nourished, thin colored female, complaining of abdominal pain. There was some pallor of the conjunctivae. Shotty nodes were present in the epitrochlear, axillary, and inguinal regions. The heart and lungs were normal. The abdomen was protuberant and dough-like. The epigastric region was slightly tender, and there was a palpable, right upper quadrant mass, which was ballotable and tender. Pelvic examination revealed a tender uterus which was fixed. There was a slight fullness in the right adnexal region. The diagnoses considered included gastric neoplasm, and penetrating gastric ulcer with local abscess formation.

The hemoglobin was 67 per cent; the red and white blood counts were normal. The

Mantoux test, 1:100,000 was markedly positive. Stool specimens were repeatedly negative for occult blood. The fasting blood sugar and blood urea nitrogen were within normal limits. Erythrocyte sedimentation rate by the Westergren method was 23 millimeters in one hour. Serology and blood cultures were negative. Gastric analysis showed up to 40 units of free hydrochloric acid.

Roentgen studies of the chest showed no abnormality in the lung fields. Barium administered by mouth demonstrated irregularity and narrowing of the prepyloric region of the stomach, and marked deformity of the first and second portions of the duodenum suggesting neoplastic involvement of the pancreas. No abnormality was demonstrable in the small bowel. Thirty per cent of the barium was retained in the stomach after six hours.

The patient ran a persistently febrile course, her temperature ranging up to 103° to 104°F. Gynecologic consultation ruled out a pelvic lesion as a cause for the fever.

Exploratory laparotomy was performed two weeks after admission, with the pre-operative diagnosis of carcinoma of the pancreas. At operation a large number of glands were found matted together throughout the retroperitoneal space, varying in size from an olive to a pigeon's egg. The glands occupied the peripancreatic, pre-aortic regions and mesentery of the small and large intestine. One of the glands removed on section revealed its entire interior to be replaced by thick greenish pus. The report of the excised node was caseating tuberculous lymphadenitis. Acid-fast bacilli were found. There was no intrinsic lesion of either stomach or duodenum.

Following operation the patient continued to run daily temperature elevations and had recurrent bouts of diarrhea. She was transferred to Seaview Hospital for chronic care on October 16, 1940. Chest films, sputum studies, and gastric washings were persistently negative there. Barium meal examination on January, 1941 at the sanatorium revealed deformities in contour of the pyloric end of the stomach and the duodenum, as were seen at The Mount Sinai Hospital preoperatively. In addition, some loops of small bowel were narrowed while others were dilated. These findings were consistent with tuberculous peritonitis and probably did not represent intrinsic pathology in the small intestine.

On March 10, 1941 the patient developed fever of 106°F., associated with nuchal rigidity and positive Kernig and Brudzinski signs. Acid-fast bacilli were found on smears of the spinal fluid. The meningeal involvement proved to be an acute fulminating terminal episode and she expired March 11, 1941.

Comment. Chronic tuberculous peritonitis is considered by pathologists to be a secondary infection in all cases. It may develop by any one of three routes: (a) generalized hematogenous miliary spread; (b) perforation of a tuberculous intestinal ulcer; (c) along lymphatic channels to mesenteric lymph nodes, with subsequent generalized peritonitis. The pathogenesis of the case described above falls into the third category. Most workers agree that if the mesenteric nodes show evidence of tuberculosis, the initial infection was in the intestinal tract although ulceration may not have ensued.

When tuberculous peritonitis is seen in a general hospital, the disease is usually localized. In the six cases from the Massachusetts General Hospital reported by McCort (15), no active tuberculosis was found outside of the peritoneal cavity.

The roentgen findings are interesting in that retro-peritoneal nodes, regardless of etiology, characteristically give pressure defects but constricting lesions with mucosal distortion of the prepyloric region and proximal duodenum simulating carcinoma of the pancreas are rarely seen.

Case # 5

R. Y., a white male 30 years of age entered the hospital on October 18, 1933 with the chief complaint of abdominal pain. His illess began six years prior to admission with mild lower abdominal cramps not associated with the intake of food. Three months later, diarrhea developed with from four to seven daily loose water, non-bloody stools. Simultaneously his temperature became elevated and rose often as high as 104°F. He lost thirty pounds in weight. A gastrointestinal x-ray series taken at that time showed increased intestinal

peristalsis. The diagnosis of enteritis was made and the patient was sent to a sanatorium. There roentgenological examination of the chest, repeated sputum examinations, animal inoculation of the sputum, feces, and pus from an ischiorectal abscess revealed no evidence of tuberculosis. Under symptomatic treatment the diarrhea and fever gradually subsided and the lost weight was regained. This period of diarrhea lasted seven months. Shortly after cessation of intestinal symptoms, the patient began to have almost daily brief sharp attacks of lower abdominal cramps, and at longer intervals, severer attacks of pain and abdominal tenderness. The latter were accompanied by fever and nausea and an occasional episode of mild diarrhea consisting of three to four stools lasting only a few days. During one of the severer attacks of abdominal pain there was tenderness and rigidity in the right lower quadrant. The picture was not unlike that of acute appendicitis. After four years of illness the patient was referred to the consultation clinic of The Mount Sinai Hospital. There, an examination of the gastrointestinal tract by means of a barium meal revealed a stenotic segment of bowel of either the lower jejunum or upper ileum about two feet in length. The nature of the lesion, however, could not be established. Chest x-ray was negative. He was given symptomatic treatment for approximately one year without significant effect. He was then admitted to The Mount Sinai Hospital for further study with the view of determining whether the lesion was sufficiently discrete to permit operative intervention. Physical examination upon admission was negative except for some slight tenderness in the right lower quadrant.

The stools showed a positive guaiac test but no other significant findings. Roentgenologic survey of the small intestine with the introduction of barium directly into the duodenum by means of a duodenal bucket disclosed a lesion confined solely to a segment of small intestine situated in the distal portion of the jejunum and upper ileum corroborating the previous x-ray findings of a granulomatous jejuno-ileitis. Since the lesion was localized to a discrete segment of small intestine, it was believed that excision of diseased bowel was indicated and a laparotomy was performed with the diagnosis of non-specific granulomatous jejuno-ileitis.

At operation, three feet of terminal jejunum and upper ileum were found to be diseased. The involved intestine was resected and a side to side anastomosis was performed.

Pathologieal examination of the resected specimen showed a chronic cicatricial and polypoid hyperplastic enteritis. The entire wall of the resected portion of the intestinal tract was markedly thickened. The mucosa was hypertrophied, presenting small polypoid masses which in some areas were arranged in longitudinal rows and ridges. The latter, together with intervening scar tissue gave the lumen of the intestine a cobblestone appearance. The mesentery was thickened and fibrotic; it contained numerous hyperplastic lymph nodes. Microscopically, the intestinal wall showed marked hyperplastic and exudative inflammatory changes and contained an occasional giant cell. No definite anatomical tubercles were noted. The enlarged regional lymph nodes, however showed numerous well defined anatomical tubercles. Dr. Paul Klemperer reported the specimens as very suggestive of tuberculosis. No tubercle bacilli were found in the walls of the intestinal tract or in the nodes.

The patient made an uneventful recovery and was discharged on the twenty seventh postoperative day with the diagnosis of granuloma of jejunum and ileum, cause unknown.

The patient was readmitted on June 24, 1935. He had remained perfectly well for a year following the operation and then began to have symptoms which were very much like those which brought him into the hospital on his first admission; diarrhea of five to six stools daily and loss of twenty pounds in eight months. Physical examination was essentially negative. Stools were guaiac negative. The von Pirquet and Mantoux tests were negative. Chest x-ray was negative. Roentgen studies of the gastrointestinal tract showed a few loops of jejunum and ileum to be irregular and fuzzy in appearance. This was not considered a recurrence because on the previous admission resection was made through diseased bowel. During his stay in the hospital, he improved on conservative therapy and he was discharged on July 5, 1935.

The third admission was February 6, 1939. The chief complaint on this admission was related to his peri-anal abscesses. The patient first noted the development of slow, indolent chronic painful peri-anal abscesses November 1936. This subsequently broke down and continued to discharge grayish white pus. Diarrhea began again two weeks prior to admission with seven watery stools per day. There was a twenty pound weight loss in the two months prior to admission.

Positive physical findings were confined to the rectal region. There were several draining sinuses surrounding the rectum. Rectal examination disclosed a stenotic area which barely admitted the tip of the finger. An ulcerated area was present on the anterior aspect of the anus. Smears taken from the draining sinuses were persistently negative. The Frei test was negative. The fistulous tracts were injected with dye and communicated with the sigmoid colon. A barium enema showed irregular and constant spasm of the colon in the descending and transverse portions. The outline of the bowel was irregular (Fig. 2). The chest x-ray was negative. The patient signed out against advice before any definitive studies could be made.

FIG. 2. Case 5. Barium enema showing irregularity of outline of colon. There is marked spasm of the descending and transverse portions of the bowel.

From this time until his fourth admission September 8, 1939, he was virtually bed-ridden because of weakness caused by diarrhea and discharging peri-anal fistulae. He was re-admitted because of chronic weakness, and it was decided that he be placed in an institution to receive appropriate chronic care.

November 1939, five weeks after discharge, marked the first appearance of pulmonary symptoms. The patient developed persistent cough productive of blood tinged purulent sputum. He was admitted to Kings County Hospital, Brooklyn, N. Y., April 1940, where a chest x-ray showed far advanced pulmonary tuberculosis bilaterally and positive sputum was obtained. He was transferred to Seaview Hospital July 12, 1940. Roentgen studies of the chest then showed bilateral cavitation and examination of the sputum revealed acid fast bacilli. The patient's course at Seaview was steadily downhill and he expired August 16, 1940.

Comment. This case demonstrates some of the problems one may encounter in differentiating between tuberculous enteritis and non-specific granulomatous enteritis. The clinical course and findings at operation suggested non-specific disease, but the finding of numerous tubercles in the regional lymph nodes was strongly suggestive of tuberculosis. The histologic findings may be interpreted in one of two ways: either (a) the lesions in both the bowel and the nodes were tuberculosis or (b) the inflammation in the wall of the intestine was non-specific and because of diminished resistance, ulceration and infection, acid fast bacilli were allowed to pass through the wall and thus involve the regional lymph nodes.

Since anatomical tubercles were very abundant in the lymph nodes, it is difficult to ascribe the lesion in the intestinal wall to anything but tuberculosis. It may be objected that since there is no evidence in the intestinal lesion itself for a tuberculous etiology, we cannot call this acid fast disease. However in a considerable portion of cases of ulcero-hyperplastic tuberculosis, tuberculous granulation tissue may be restricted largely to the mesenteric lymphatics and may be very scanty in the lesion. These features may be due, in part, to tissue resistance of the host, and perhaps to an attenuated tubercle bacillus which may not possess normal pathogenicity. We may have reached a stage in this infection when the tuberculous lymphangitis had already burnt itself out leaving a thickened, scarred intestinal wall, obliterated mesenteric lymph vessels and secondarily hypertrophied lymphoid tissue. Secondary infection of the deformed segment of gut is inevitable. Technically, the finding of tubercle bacilli in stained sections of tuberculous lesions is not always easy, and while a positive result is conclusive, a negative one by no means excludes tubercular pathology.

While final proof of the etiology is lacking, since the cause of death was known to be pulmonary tuberculosis, it is logical to conclude that the equivocal intestinal pathology seen at operation was tuberculosis.

Case #6

A twenty-five year old female was admitted to the hospital in February 1934, complaining of crampy intermittent abdominal pain, and vomiting of three months duration. Approximately three years before admission, her physician had treated her for an attack of "grippe". Her illness, which lasted thirty days, was characterized by fever, cough tinged with blood streaked sputum and weight loss of fifteen pounds. Two months after recovery she developed epigastric and right lower quadrant pain, nausea, vomiting and diarrhea. Forty-eight hours after the onset of symptoms, operation was performed at another hospital with the pre-operative diagnosis of acute appendicitis. When the abdomen was opened the appendix appeared normal, but the cecum and ascending colon were studded with miliary tubercules. Several lymph nodes from the mesentery of the cecal area were biopsied, and the abdomen was closed.

The pathologic report was as follows: "Throughout all sections of the mesenteric lymph nodes are found numerous areas of caseation necrosis surrounded by endothelial cells, round cells and giant cells."

A post-operative roentgen study of the thorax showed a left upper lobe infiltration and

FIG. 3. Case 6. Marked irregularity of the cecum and ascending colon is seen in a patient with a history of pulmonary and intestinal tuberculosis.

sputum examination was positive for acid-fast bacilli. The patient was transferred to a tubercular institution where she was treated with pneumothoraces over a period of twenty months. She gained eighteen pounds during this time and was discharged with the diagnosis of arrested pulmonary tuberculosis and tuberculosis of the intestinal tract.

She enjoyed good health for ten months following release from the sanatorium, but then began to suffer occasional episodes of abdominal cramps, nausea and vomiting not related to meals. Relief was obtained by liberal use of tincture of belladonna. Three days prior to admission to The Mount Sinai Hospital, she developed a slight cough productive of flecks of blood and had fever to 102°F. daily. The abdominal cramps and vomiting had become more marked and it was feared that the terminal ileum had become involved in the tuberculous process and intestinal obstruction had resulted from constriction of this segment of the bowel. She was admitted to the hospital with the thought that operative intervention would be necessary because of partial intestinal obstruction.

Physical examination of the abdomen revealed generalized tenderness. There were no palpable masses. Examination of the chest, including roentgen studies showed the right upper lobe involved in an inflammatory process. A partial pneumothorax was present on the left, the previously involved lung being collapsed to two-thirds normal size.

A flat plate of the abdomen showed no evidence of obstruction of either small or large bowel. Examination of the colon by means of a barium enema (Fig. 3) was reported as follows: "A small area of spasticity was seen in the transverse colon, close to its junction with the splenic flexure. Once the barium passed this site, the colon filled readily as far as the ascending colon. There was fairly marked irregularity involving a large part of the cecum and ascending colon with evidence of some spasticity. The deformity of the cecum and ascending colon appeared constant on all the films. If there is a history of pulmonary tuberculosis, the diagnosis is most likely intestinal tuberculosis involving chiefly the cecum and ascending colon."

Clinically, it was felt that active pulmonary tuberculosis was present despite the inability to obtain a positive sputum during the admission. In addition, the rather diffuse character of the intestinal lesion without evidence of obstruction, prompted the decision to withhold surgery at that time. The usual conservative measures for treatment of tuberculosis in vogue at that time were instituted with sufficient success to allow discharge in one month in an improved condition.

Comment. This is another instance where intestinal tuberculosis presented as acute appendicitis. The value of a previous history or chest film indicative of pulmonary tuberculosis in the interpretation of a right sided colonic lesion is well demonstrated by this case. Amebiasis, actinomycosis, and non-specific granulomatous colitis would all qualify as possibilities in interpretation of this non-pathognomonic barium enema. However on the basis of the history of previous infection, there was no doubt as to the diagnosis of tuberculosis.

Case # 7

A fifty-five year old Puerto Rican farmer (D. P.) was admitted to the hospital December 10, 1955 with the chief complaint of dysphagia of three months duration. The patient had

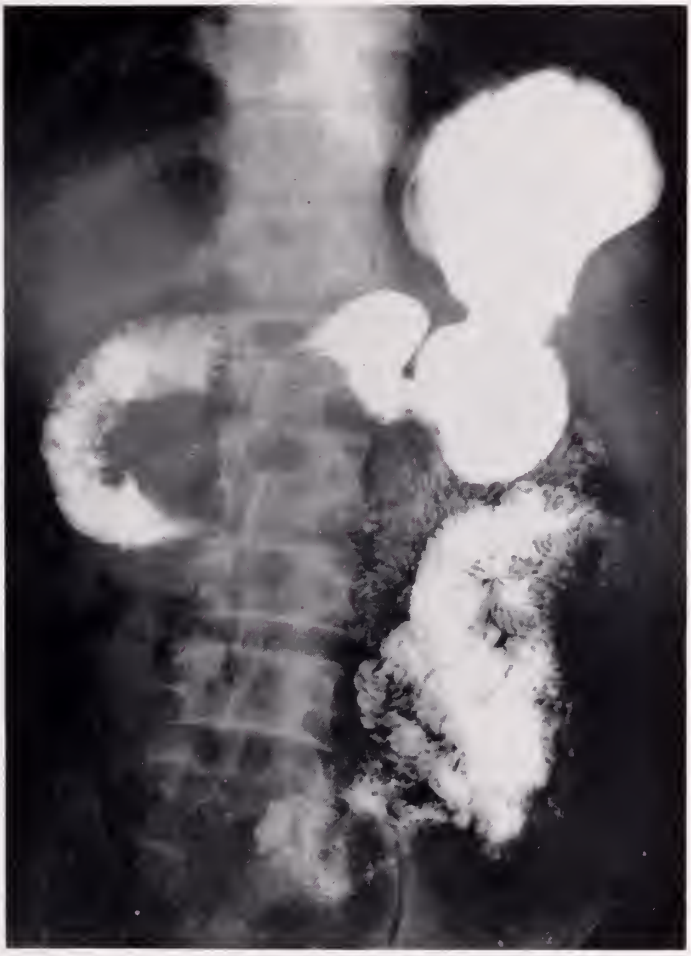

FIG. 4. Case 7. The third portion of the duodenum is narrowed due to extrinsic pressure from tuberculous nodes.

arrived in the United States just fifteen days before entering the hospital, and because of the language barrier, the following history was obtained through an interpreter. Three months before admission, while in Puerto Rico, he noted increasing difficulty in swallowing any solids. He would remain with a choking sensation after attempting to swallow. He sought relief by self induced vomiting. He next tried pureed food which was tolerated for several weeks. Three weeks before admission, he was capable of swallowing only fluids, and even that became increasingly difficult. His appetite had remained good. History was negative for vomiting, diarrhea, chest or abdominal pain. Jaundice, lues and tuberculosis were denied by the patient. There was a weight loss of eighteen pounds in the past year.

The only positive physical findings in this afebrile somewhat emaciated white male was a bilateral, inguinal hernia.

A gastrointestinal series was reported as follows: Just beyond the mid-esophagus, distal to the level of the cricoid there was a constant, irregular filling defect about two inches in length which has the appearance of carcinoma. The esophagus proximal to this is moderately dilated, but some barium does pass through this area with only moderate difficulty. There is no evidence of an intrinsic lesion in the stomach. However, the third portion of the duodenum over a distance of about two inches is constantly narrowed (Fig. 4), and the duodenum proximal to this is somewhat dilated at times. There is evidence of an arcuate impression on the more proximal duodenum at the beginning of the narrowed segment and some irregularity of the mucosal pattern in the same region. Throughout most of this narrowed segment, however, the mucosal pattern appears to be intact. There is no marked obstruction to the flow of barium through the narrowed segment of the duodenum. In addition to the lesion to the esophagus, the changes in the duodenum are most likely the result of extrinsic pressure, presumably due to metastatic nodes. The possibility of an independent, extrinsic process of neoplastic character, however, cannot be excluded.

A chest roentgenogram was negative. An attempt was made to visualize the esophageal lesion endoscopically, and at 27 centimeters an annular mass, friable and granular, beyond which the scope could not be passed, was seen and biopsied. This was reported as squamous cell carcinoma. Bronchoscopy was negative.

Although peritoneal metastases occur infrequently from carcinoma of the esophagus, the roentgen appearance of the third portion of the duodenum suggesting extrinsic pressure presumably from nodes would place the esophageal lesion in the inoperable class. There were many who were opposed to exploration because they believed that peritoneal seeding had undoubtedly taken place. Those who thought that the lesion around the duodenum might be some independent neoplastic process were in the minority, but it was finally decided that the patient should have the benefit of an exploratory laparotomy. An operation was performed with the pre-operative diagnosis of carcinoma of the esophagus with metastases to the peritoneum.

At operation, the entire abdomen was covered with nodes; the retropancreatic and retroduodenal spaces, the gastrocolic ligament and transverse mesocolon were most heavily involved. Several glands were biopsied and on frozen section were reported as tuberculous lymphadenitis, much to our surprise. The esophageal lesion was resected and continuity restored by end to end anastomosis. Careful search failed to reveal regional lymph node involvement. Convalescence, thus far, has been uneventful.

Comment. A serious error would have been committed if the abnormality noted on roentgen study of the duodenum was accepted conclusively as metastatic nodes and palliative measures instituted to treat a supposedly inoperable carcinoma of the esophagus. Although the prognosis for epidermoid carcinoma of the esophagus is poor, some solace may be derived from the report of Garlock and Klein (16) who, in 1954 noted that of 22 patients with resectable squamous cell carcinomas that were operated on five or more years before, six were still alive. On the basis of these figures, our patient has a twenty to twenty-five per cent chance for a five year survival. To have treated him with steroids and roentgen ray therapy for purposes of amelioration as was contemplated, would have deprived this individual of the chance of having his cancer cured.

Case #8

A 46 year old white female (J. M.) was admitted to the hospital March 6, 1952 for treatment of a retro-anal ulceration. Her present illness commenced two months after a cholecysteetomy performed uneventfully September 1949 for cholecystitis and cholelithiasis. At that time she noted a painful swelling in the perirectal region. This ruptured spontaneously and formed a perianal ulcer which discharged moderate amounts of green purulent material. Two years prior to admission she developed right pleuritic pain and a moderate cough productive of clear sputum, fever, weight loss and weakness. These symptoms persisted and in February, 1951 she noted bouts of watery diarrhea and lower abdominal crampy pain. No specific medication or treatment was given. In December, 1951 a biopsy of the anal ulceration was performed at another hospital. The pathologic specimen revealed tuberculosis with acid fast bacilli present. A roentgen study of the chest at that time showed diffuse nodular and streaky infiltration in both lungs and was interpreted as hematogenous tuberculosis. January 6, 1952, she was started on a course of streptomycin

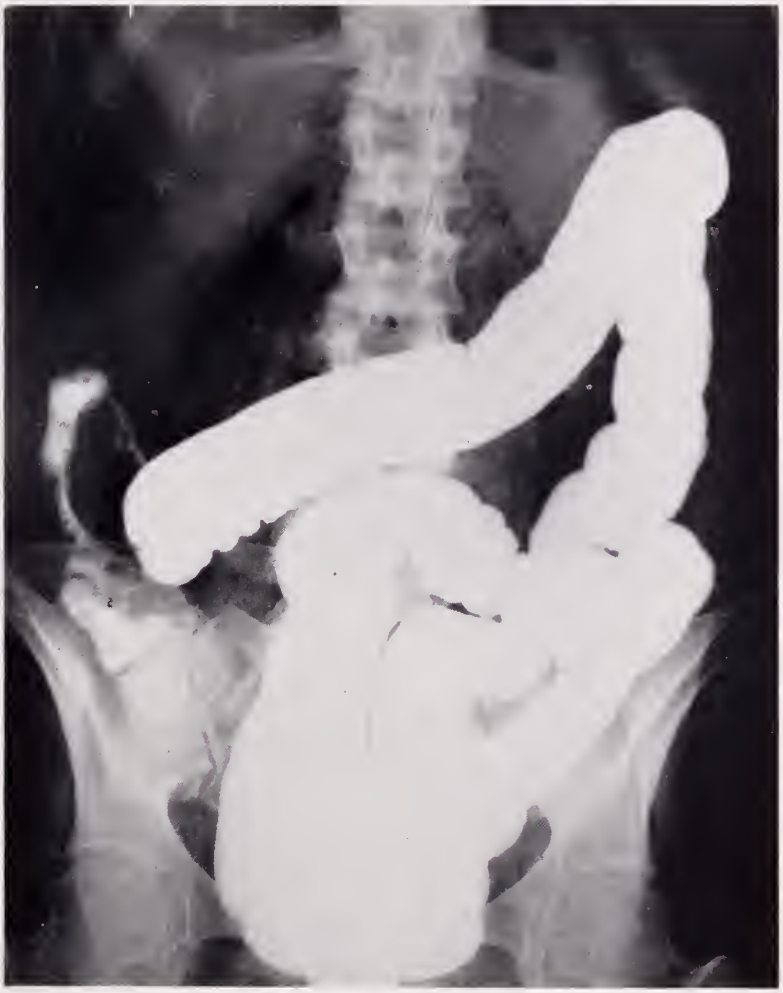

FIG. 5. Case 8. The hepatic flexure and proximal transverse colon are involved in a granulomatous process. Note the areas of narrowing and the thickening of the mucosal folds.

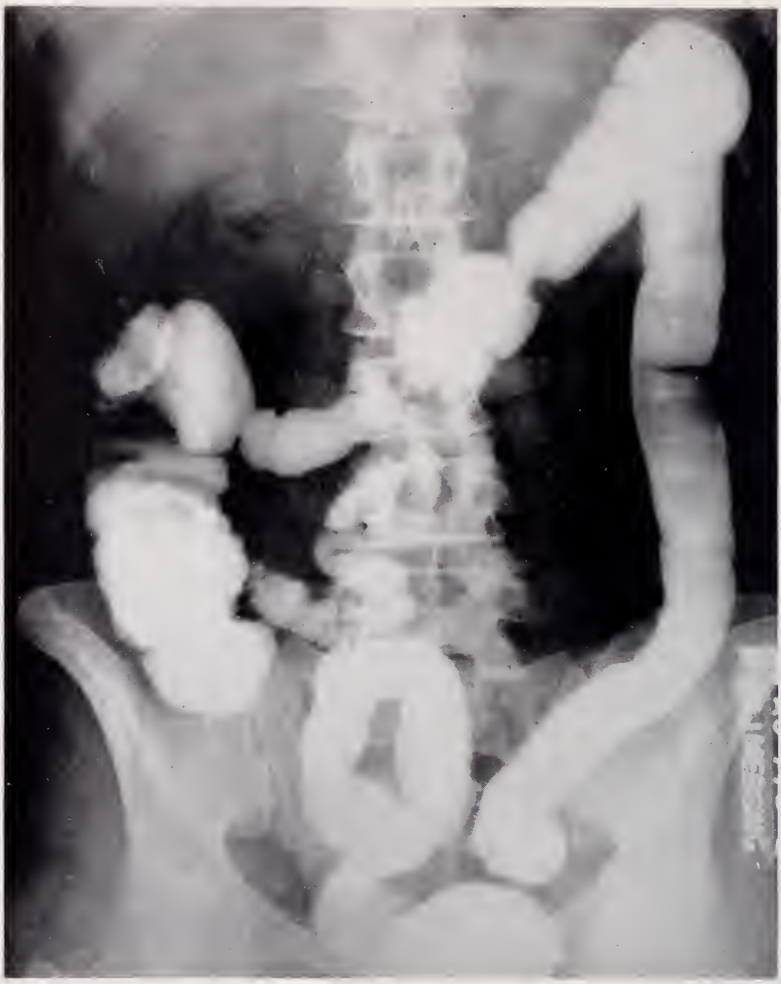

FIG. 6. Case 8. There is almost complete healing of the involved portion of the colon following isoniazid therapy.

therapy receiving one gram per day, five days per week for a total dose of 42 grams. This was administered on an ambulatory basis. The perianal lesion did not heal, however. During the treatment, her weight remained at 112 pounds, her previous normal being 135 pounds.

Physical examination revealed a middle aged white female showing signs of moderate weight loss but in no acute distress. The positive findings were limited to the lungs and rectal region. There were fine moist inspiratory rales throughout the chest. Broncho vesicular breath sounds were heard in the left lower chest posteriorly and there was slight diminution of breath sounds at the right base. Rectal examination revealed two pea sized, dirty ulcerations situated one inch posterior to the anus. The ulcers were raw and granulating, their edges raised and thickened.

A smear from the ulcer showed acid-fast bacilli confirming the diagnosis of active tuberculosis. A roentgen study of the chest on the same day revealed bilateral miliary infiltrations with no apparent cavitation. Barium enema examination (Fig. 5) showed two discrete areas of narrowing in the region of the hepatic flexure and proximal transverse colon. There was

thickening of the mucosal folds but no significant obstruction to the flow of barium existed. The study was interpreted as an inflammatory lesion.

The patient was placed on 300 milligrams of Rimifon® per day. On this treatment she gained five pounds in one month. The anal ulcer over the course of three weeks gradually ceased to discharge, became cleaner and granulated in, leaving only one very small defect immediately retro-anal. While on this course of therapy she remained afebrile and showed no signs of toxicity. Her appetite improved and her cough markedly diminished. During this month of hospitalization one concentrated smear from the urine showed acid fast bacilli, but this finding was not encountered on other examinations. An intravenous pyelogram and cystoscopy were negative. Sputum injected into a guinea pig prior to Rimifon therapy was positive, but successive sputum examinations after beginning therapy were persistently negative. Her hemoglobin was eleven grams; the sedimentation rate 43 millimeters in one hour. These determinations did not vary significantly during treatment. A three plus guaiac reaction was present in the stool on five occasions but tubercle bacilli could not be demonstrated in these specimens. On April 11, 1952 she was transferred to a sanatorium for chronic care, continuing on isoniazid. She left this institution after several weeks for further treatment at home. There was rapid regression of the pulmonary lesions with residual fibrosis, and medication was discontinued October, 1953. A repeat barium enema, September, 1953 showed almost complete healing of the involved area, minimal scarring remaining as a residual (Fig. 6). She has been followed in the chest clinic at varying intervals and when last seen January, 1956 she had no pulmonary symptoms nor was there evidence of reactivation of tuberculosis in any of the organ systems previously involved. She has now been off anti-tuberculous medication two and one half years and is completely asymptomatic.

Comment. This was the first patient to whom Rimifon was administered at The Mount Sinai Hospital. The response of her hematogenous disseminated tuberculosis and perianal ulcer to the drug was dramatic. Although the symptomatic improvement in intestinal tuberculosis obtained with the isonicotinic derivatives is well known, a review of the literature fails to reveal similar documentation of the symptomatic response by serial barium enema studies. This is readily understandable since it is much more feasible to follow the healing process of a disseminated tuberculous lesion by repeated chest roentgen films. The closing of chest cavities as a positive sign of recovery in pulmonary tuberculosis does not have its counterpart in intestinal tuberculosis. On the contrary, the tuberculous bowel, roentgenologically, can appear worse in the healing stage than in the period of acute inflammation, as the bowel often heals by scarring with resultant deformity and adhesions. Bohm (17) discussed three cases of intestinal tuberculosis treated by chemotherapy (Conteben) and showed the transition from the acute to the healed phase by excellent roentgen film reproductions. He stated that the usual roentgen picture of healed intestinal tuberculosis is that of segmental loss of normal mucosal pattern, with coarsening and atypical course of the folds, patches of granular or even polypoid mucosa, localized stiffness and irregularity of the bowel wall. The colon is shortened and normal peristalsis is absent with resultant slow passage of the contrast material. A scarred, contracted pouch-like cecum connected to the rest of the colon by a stiff narrowed tube of bowel is characteristic. The ileocecal valve is usually gaping and scarred.

It is difficult to draw conclusions from one case, but the possibility exists that the isonicotinic acid derivatives restore the bowel to a more normal anatomic form than did their predecessors.

DISCUSSION

Gastrointestinal tuberculosis is protean in its manifestations and can masquerade as any other intra-abdominal condition. A review of some of the preoperative diagnoses in the present series makes this statement apparent. They include (a) non-specific granulomatous ileitis, (b) carcinoma of the cecum, (c)

retroperitoneal sarcoma, (d) carcinoma of the pancreas, (e) non-specific granulomatous jejuno-ileitis, (f) acute appendicitis, and (g) metastatic nodes from a carcinoma of the esophagus.

Because of its propensity for involving the ileo-cecal region primarily, it is only natural that in the random case seen in the general hospital, presenting with intermittent right lower quadrant pain, diarrhea, and weight loss, non-specific ileitis or ileocolitis will be the most likely diagnosis. Investigation for extra-intestinal foci of tuberculosis, especially in the lungs, should always be made when regional enteritis is discovered. If a focus of active pulmonary tuberculosis is found coexisting with a non-neoplastic lesion of the small intestine below the duodenum, it is reasonable to assume that the lesion is also tuberculosis. Conversely, in the absence of such a focus, the intestinal disease is likely to be non-tuberculous. The inability to discover a focus clinically, however, does not rule out its existence. An active focus can occasionally be missed even by the most careful examination so that even this conclusion cannot be stated dogmatically.

With the established efficacy of anti-tuberculous drugs and the rapidity with which intestinal tuberculous patients can become asymptomatic a high index of suspicion must be constantly maintained when considering ileo-cecal disease of obscure etiology.

SUMMARY AND CONCLUSION

1. Six cases of intestinal tuberculosis without florid pulmonary manifestations proven by pathologic study of surgical specimens in whom the pre-operative diagnosis was incorrect are described, and the difficulties encountered in making a diagnosis in a general clinic discussed. A seventh case is presented in which the pulmonary findings resolved the significance of the roentgen findings in the intestine.

2. Since the roentgen feature of granulomatous ileitis and colitis are not always clearly differentiated from tuberculous ileocolitis a careful search for extra-enteric tuberculosis in all cases of ileocolitis should be made.

3. Tuberculosis should be considered whenever gastrointestinal symptoms and especially whenever ileo-cecal findings cannot be explained. An effort should be exerted to establish the diagnosis because cure may be possible if anti-tuberculosis drugs are initiated while the disease is still in a reversible state.

4. A case of disseminated tuberculosis with excellent response to isoniazid is described. The reversibility of the colonic lesion is documented by means of repeated barium enema studies.

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MANAGEMENT OF TUBERCULOSIS OF THE LARYNX

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The treatment of laryngeal tuberculosis has undergone great changes within the last decade, as has the treatment of tuberculosis elsewhere in the body.

These changes have come about solely because of the discovery of the beneficial effects of the great anti-tuberculous drugs—streptomycin, dihydro-streptomycin, isoniazid and para-aminosalicylic acid. Whereas local therapy and general sanatorium care were the mainstays of treatment before the introduction of antimicrobial drugs, these methods are now of lesser importance. Local therapy is now applied infrequently and its use is reserved for those extremely uncommon patients who are allergic to all of these drugs and are unable to tolerate them. Local therapy includes tracheotomy, galvanocautery, anesthetization of the painful tuberculous larynx by injection of the superior laryngeal nerves, and anesthetic sprays. A description of their use is almost academic and may be found in numerous textbooks and manuscripts of the pre-antibiotic era (1, 2).

In 1947, Figi and his co-workers at the Mayo Clinic reported the first case of laryngeal tuberculosis treated with parenteral streptomycin. The result was complete healing in a patient previously deteriorating rapidly and who had not responded to local therapy (3).

The occurrence of laryngeal tuberculosis had been of grave prognostic significance prior to the days of antibiotic therapy. Now, due to the excellent response to antibiotics, laryngeal tuberculosis is merely a complication although it usually indicates a more severe variety of pulmonary tuberculosis, with breakdown of host resistance.

In 1947, Black and Bogen reported 34 cases of laryngeal tuberculosis treated at the Olive View Sanatorium in California. Streptomycin aerosol was used with no beneficial results but parenteral streptomycin was associated with healing in the majority of cases and with improvement in all (4). Withers in 1948 reported similar results in the treatment of 12 cases (5).

In 1951 Wallner, Turner, Lichtenstein, and Sweany reported the results of the treatment of 70 cases of pulmonary tuberculosis complicated by laryngeal tuberculosis (6). They emphasized the poor results of treatment when laryngitis complicated the pulmonary picture prior to antibiotics. Most of these cases had far advanced bilateral tuberculosis of the lungs with cavitation. Pain was completely relieved in all but two of the 39 cases who had had pain. Hoarseness was alleviated in all but six. The most spectacular results were seen in ulcerative and granular lesions and, in general, the more marked the involvement, the more dramatic was the improvement. Of interest is the fact that in some cases there was little correlation between clearing of the larynx and improvement of the pulmonary picture. The larynx was occasionally seen to improve despite deterioration in the patient's pulmonary and general condition.

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Tuberculous infection of the larynx may occur in one of two ways, either hematogenous or implantation via the sputum. These lesions may therefore be termed respectively hematogenous and sputogenous (7).

Hematogenous tuberculous laryngitis is rare. It is an accidental occurrence in which the organisms circulating in the blood stream settle in one of the laryngeal structures. The laryngeal lesion is usually small, raised and granular and when it involves the true vocal cord, it is usually unilateral. In this respect it may resemble carcinoma of the vocal cord. The lesions do not spread widely.

Sputogenous tuberculous laryngitis is much more common. It has been my observation that this form of tuberculous laryngitis is often found in patients who do not have good host resistance. The lesions are usually much more widespread, are bilateral, and may be associated with extensive laryngeal edema, ulceration or both. The lesions begin in the interarytenoid area, first involving the posterior parts of the larynx and then spreading to involve the entire larynx including the epiglottis. That these cases are a result of breakdown in host resistance is indicated by several clinical observations. First, this type of tuberculous laryngitis is frequently seen in cases of pulmonary tuberculosis, known previously to have been relatively stable, with no laryngeal symptoms. When deterioration occurs, it is often heralded by the appearance of fever, constitutional symptoms and laryngeal tuberculosis. Second, this type of laryngitis often spreads to involve the pharynx, base of tongue and oral cavity with extensive destruction of the base of the tongue and epiglottis. This again is manifestly an indication of breakdown of general and local tissue resistance.

The clinical differentiation between the two forms may not be possible. With chemotherapy, it is not essential to do so since both forms respond well.

The histological picture of tuberculous lesions of the larynx is similar to that seen in other organs, but varies with the stage of development, with the part of the larynx involved, and the presence or absence of secondary infection and with the chronicity of the lesions. Grossly, various stages of involvement of the larynx are recognized. These are hyperemia, infiltration, ulceration, edema and fibrosis. Most lesions when seen exhibit more than one or all of these changes. From a practical standpoint again, their differentiation is not important, since the response to anti-tuberculous drugs occurs in all stages.

The principal symptoms of tuberculous laryngitis are impairment of the voice and pain. The hoarseness is due to infiltration of the true vocal cords and may progress to complete loss of the voice or aphonia due to destruction of the cords. Difficulty in speaking may be encountered due to infiltration in the interarytenoid space and consequent inability to approximate the cords.

Pain is the most troublesome symptom of tuberculous laryngitis and may be constant or only present on swallowing. The degree of pain is due more to the location of the lesion than to the extent. Pain on swallowing is severe when the epiglottis is involved or when there is ulceration of the arytenoids or ary-epiglottic folds. When the epiglottis, arytenoids and posterior surface of the larynx are involved, swallowing may be almost impossible due to the pain, which is felt in the diseased area, but is often referred to as a shooting or stabbing pain into the

upper neck, angle of jaw and ears. In the pre-chemotherapy days, this inability to take nourishment was often the cause of death due to malnutrition.

As in bronchial tuberculosis, the response to the anti-tuberculous drugs is rapid and dramatic. Triple drug therapy, utilizing dihydro-streptomycin, isoniazid and PAS may be used. Also effective are streptomycin or isoniazid in conjunction with PAS Nevertheless, since laryngeal tuberculosis usually indicates serious pulmonary disease, use of all three drugs would appear to be desirable (8).

A thorough study of the effects of these drugs was made by Wallner, Thompson, and Lichtenstein at the Municipal Sanatorium in Chicago (9). By means of serial biopsies, they studied the action of dihydro-streptomycin, isoniazid and PAS on tuberculous lesions of the larynx and pharynx. Gross and microscopic changes were correlated with the symptomatic improvement during the course of treatment.

The first change found to occur in patients with tuberculous lesions of the larynx and pharynx under antimicrobial therapy is relief from pain. This subjective improvement is noted even before there is objective diminution of edema, infiltration or ulceration, and occurs rapidly after the onset of treatment, often within several days. Almost all patients show improvement within four days and pain is usually gone entirely in two to three weeks. The diminution of pain is followed by a gradual decrease in edema, infiltration and ulceration. Coincident with these changes, the voice improves.

Epithelialization of ulcerated areas usually takes place within three months of the onset of therapy, but this by no means indicates healing of the lesion. This was shown by Wallner and his associates who found in biopsy specimens taken approximately three months after the onset of therapy that the epithelial layer had regenerated, but that active tubercles were still present in the deeper structures. The lesions appeared grossly healed. In at least one case, tubercle bacilli were found in the subepithelial tissues three months after the beginning of treatment. After about four months, complete absence of tubercles was noted as well as absence of tubercle bacilli. As the duration of therapy increases, there is greater formation of fibrous tissue stroma.

These studies are a laboratory corroboration of the clinical fact that prolonged therapy is essential in the treatment of laryngeal tuberculosis. It is to be remembered that the duration of the therapy is not directly proportional to the extent of the laryngeal or pharyngeal lesion. All lesions require full courses of therapy, regardless of size. Even the small hematogenous laryngeal lesions require prolonged therapy, because they are indicative of more extensive disease elsewhere in the body. This is of course true, as well, in the extensive sputogenic cases.

The duration of treatment is dictated as well by the progress of the pulmonary lesion or lesions which are coexistent in the vast majority of cases. One year is considered to be the absolute minimum time required for therapy, and this only if the pulmonary lesion has reached a state of stability both clinically and radiologically.

A comparative study of the gross and histological effect of the different antituberculous drugs was made by Wallner and his group (9). All of the medications had the same effect. Grossly, there was diminution of edema, infiltration and ulceration with eventual healing. Microscopically, the sequence of events as shown by serial biopsies was disappearance of tubercles and tubercle bacilli and finally replacement of necrotic material by fibrous tissue.

However, the drugs differed in the time required to achieve maximum improvement. Streptomycin and dihydro-streptomycin produced the most rapid improvement, both clinically and microscopically. Isoniazid is also very effective but somewhat slower. PAS is the slowest of the drugs in bringing about healing.

A common observation has been that laryngeal lesions have a tendency to heal under antimicrobial therapy and to remain healed despite progression of the pulmonary lesion, even to a fatal determination. This is so despite the presence of large amounts of sputum containing numerous tubercle bacilli.

Vocal rest is a time-honored means of therapy which is still valuable. In the early weeks of therapy of tuberculous laryngitis, no speaking would be permitted. Whispering is also forbidden, since this is more traumatic to the larynx than actual talking. The patient should be given a pad and pencil to communicate his needs and desires and he should be encouraged to do so. This latter is particularly important, since complete silence is a most odious chore. He may be permitted to speak when healing is progressing toward its termination.

The question of sanatorium or hospital confinement in these cases is decided by the internist after consideration of the home situation. If there are no small children at home and the environment is good, both physically and emotionally, these patients may be treated on an ambulatory basis. A short term of hospitalization may be necessary or advisable when there is severe pain or marked hoarseness due to a tuberculous laryngitis.

The question of the taking of biopsies in tuberculosis of the larynx may well be discussed here. In the pre-antibiotic days, biopsy was considered by many to be a dangerous maneuver and fraught with great risk of spread, increase of necrosis and possibly perichondritis of the larynx. This does not pertain to the present day chemotherapeutic management of tuberculosis of the larynx. Such complications do not occur. Carcinoma may coexist with tuberculosis, and if there is any question of accuracy of diagnosis, biopsy is called for.

SUMMARY AND CONCLUSION

The treatment of laryngeal tuberculosis is essentially that of the parent condition, namely pulmonary tuberculosis. Tuberculosis of the larynx responds very well to antibiotic therapy, using a combination of the known effective antituberculosis drugs. Healing is brought about in a great majority of cases in about four months but treatment is continued for at least one year and is stopped only if the pulmonary status is satisfactory. Effective drugs presently used are streptomycin, dihydro-streptomycin, isoniazid and PAS Apart from voice rest, local therapy is now rarely used.

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SOME REMARKS ON DIABETES AND TUBERCULOSIS

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The particular susceptibility of the diabetic to tuberculosis has been noted by physicians for centuries (1). Before the introduction of insulin, tuberculosis was found in almost 50 per cent of diabetics at post-mortem examination (2). Even after the discovery of insulin, as patients began to survive episodes of diabetic coma, tuberculosis continued to be a most important cause of death among diabetics. The marked increase in life span led indeed to a percentage-wise increase in mortality due to tuberculosis (3).

Statistical reports of the incidence of tuberculosis among diabetics have varied greatly. This has depended upon a number of factors, such as the material used, whether clinical or post-mortem, the population from which the figures were drawn, the year in which the study was concluded and the location of the hospital in which the study was done. Root reports that tuberculosis is two to three times as frequent in diabetics as would be expected. In juvenile diabetics it has been ten times as frequent as in non-diabetic children, and in adolescent diabetics sixteen times as frequent as in non-diabetic high school students (3). Munkner computed the incidence of tuberculosis among diabetics to be three to four times that in the general population (4).

As a cause of death among diabetics the figures for tuberculosis have also varied considerably. Bell reports that between 1910 and 1948 tuberculosis has been a cause of death in between 2.6 per cent and 4 per cent of diabetics (5). Lundbaeck found tuberculosis to be the cause of death in 7 per cent of his long-term diabetics (7). This was most marked in the younger age groups. In children, Joslin and Wilson report tuberculosis to be the cause of death in 11.9 per cent between the years 1944 and 1950 (6). Joslin has reported a sudden drop in the mortality to tuberculosis among diabetics from 2 to 3 per cent before 1950 to 0.9 per cent since 1950 (8).

Probably the most extensive study has been that conducted by the Philadelphia group (9, 10). In surveying about 30 per cent of the cases of diabetes in Philadelphia they found the incidence of tuberculosis to be 8.5 per cent as compared with 4.3 per cent in a group of industrial workers comparable in age, sex and race. Active tuberculosis was also more common in the diabetics, especially in those under 40 years of age where it was three times as prevalent as in those over 40 years of age. In this younger group active tuberculosis was present in greater frequency in those with long duration of diabetes, in those who were underweight, and in those requiring the largest amounts of insulin.

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The reason for the particular susceptibility to tuberculosis of the diabetic remains obscure. Dolger points out that the diabetic under treatment is not more susceptible to infections in general than is the non-diabetic (11). Certain infections, however, especially in the presence of ketosis, appear to find in the diabetic particularly fertile soil. Infections of the urinary tract and staphylococcal infections of the skin are prime examples. Before the introduction of antibiotics a pneumococcal type 3 otitis media or mastoiditis was known as a "diabetic otitis". Sosman believed that primary tuberculosis characterized by hilar and basilar lesions could be nicknamed "diabetic tuberculosis" because of its prevalence in the diabetic population (12). Boucot and her group, however, found this to be a reflection of the increased frequency of activity of the tuberculosis in diabetics and just as prevalent in active tuberculosis in a comparable non-diabetic group (9).

Numerous theories have been advanced to explain the greater prevalence of tuberculosis in diabetics. Root found tuberculosis developing in 8 per cent of diabetics within three years after recovery from coma (3). The influence of a previous history of coma has not been noted by Boucot or Reaud. The importance of the nutritional state is emphasized by all. Undernutrition in the diabetic, as in the non-diabetic, predisposes to tuberculosis. A rapid loss of weight, even of an obese diabetic, as illustrated by Cooper and Marshall, may lead to the development of tuberculosis (15). Long has suggested, as something to be considered, a liberation of glycerol attendant upon fat catabolism in the diabetic and thereby improving the medium of the organism for the tubercle bacillus (16). Getz et al suggest that relative deficiencies of vitamins A and C may play a role in the development of tuberculosis but no studies in diabetics were noted (18).

Steinbach and Duca found in pancreatectomized albino rabbits that the amount of tuberculosis increased with the degree of hyperglycemia (17). Boucot, however, found the prevalence of tuberculosis to be 6 per cent in patients with preponderantly high blood sugar levels and 9 per cent for the remainder of the group (9). This trend held for all groups except those taking no insulin. Indeed, in the more severe diabetics, requiring more than 40 units of insulin daily, more than twice as much tuberculosis was found in those with no blood sugar level above 200 milligrams per cent than in those with consistently marked hyperglycemia.

More recently, hormonal factors have been proposed, namely hyperfunction of the pituitary or adrenal cortex. Roche et al working with cortisone treated and alloxanized rats found considerable similarity in susceptibility to and type of tuberculosis between the two groups (19). It is true that both an excess of adrenal cortical hormone and diabetes have in common a disturbance of carbohydrate metabolism. In addition the stress of coma or of repeated episodes of ketosis or acidosis may produce a relative hyperadrenal state. Gais believes that this may explain the high incidence of true insulin resistant diabetes in tuberculosis (13). It is to be expected that in the present atmosphere of interest in the adrenal cortex this theory should prove especially attractive.

Still other things must be considered; for example, a possible combined genetic trait predisposing both to diabetes and to tuberculosis.

It may well be, as Joslin's most recent figures tempt one to believe, that with the improvement in treatment of tuberculosis attendant upon the development of the various chemotherapeutic agents, the answer to this problem may become merely academic. At any rate, it is doubtful whether a single simple theory will explain everything. As Long wrote almost 30 years ago, "When the truth is finally known, I am sure it will develop that native immunity to tuberculosis is the resultant of the interplay of many factors so intimately connected that distinctions on specific morphologic or chemical bases will be impossible" (16).

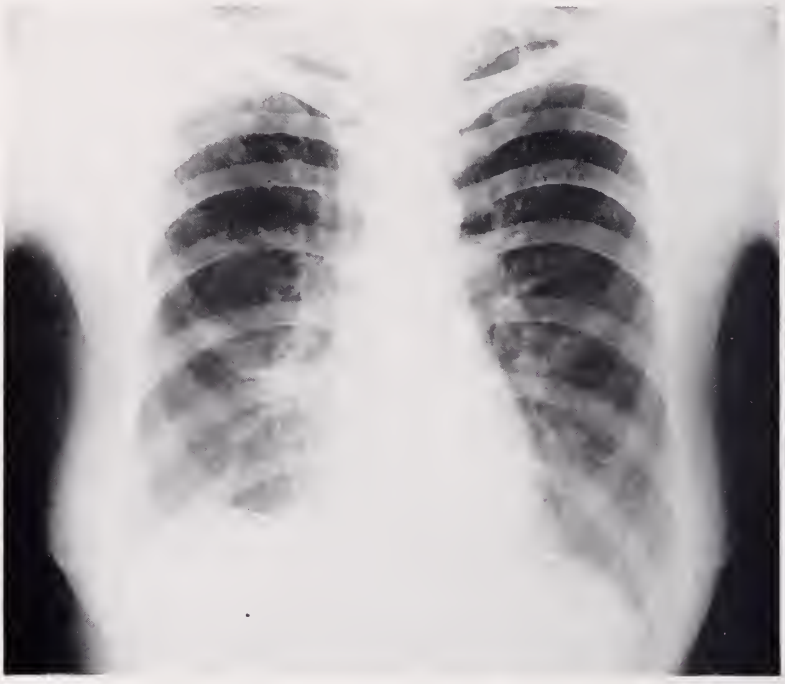
The diagnosis of tuberculosis in the diabetic is probably the most important factor in treatment. Early diagnosis is of utmost importance and yet only too infrequent. The onset of the tuberculous process is insidious, as it is in the non-diabetic. The symptoms are also similar but are often clouded by symptoms of the diabetes which has gotten out of control. Early diagnosis must be radiographic diagnosis. One must be on the alert and subject diabetic patients who show a sudden change in insulin requirements or who lose weight, to prompt x-ray examination of the chest. In addition, routine chest x-rays, at least annually, should be done on all diabetics, more frequently in those who are underweight. All too often, among diabetics, tuberculosis is discovered only after the disease has become moderately or far advanced. Boucot found 63 per cent minimal lesions among the diabetic group as compared to 74 per cent minimal lesions in the control group. In addition, as has been noted, there was a much higher proportion of activity in the diabetics. Regardless of the stage of tuberculosis, the incidence of activity among the diabetics was three times that of the control group. Of the active cases, 32 per cent of the diabetics had cavities, while only 21 per cent of the comparison group had cavities. Among the non-diabetics, none had pleural or pericardial complications, whereas, among the diabetics, there were three pleural effusions and one tuberculous pericarditis.

There is little doubt that the relatively poor prognosis for the tuberculous diabetic is largely attributable to this delay in diagnosis. Whether tuberculosis in the diabetic follows a more fulminating course is disputed. Munkner finds evidence that this is so (4). Reaud feels that the response to therapy in the diabetic is just as good as in the non-diabetic (14). Root feels that with adequate treatment of both diseases, if the diabetic is discovered at the same stage of tuberculosis, the prognosis may be even better than in the non-diabetic (2). It will be interesting to observe the results of Boucot's follow-up of her large group in Philadelphia.

Two clinical features of tuberculosis exist more commonly in the diabetic and are probably also related to the greater severity of the disease. One of these is the increased incidence of pulmonary hemorrhage. The second is the greater likelihood of breakdown of the apparently stable, chronic case. At The Mount Sinai Hospital Pre-natal Diabetes Clinic three patients with radiographically stable pulmonary lesions have been followed through delivery. All three were started on prophylactic isoniazid therapy a few weeks before delivery. Two of these followed for at least a year after delivery, showed no change in the character of their tuberculous lesions. The third was lost to follow-up shortly after delivery and stopped taking her medication. Four months later she was seen again

in clinic with symptomatic tuberculosis and a radiographic increase in pathology from the original minimal lesion to an extensive pneumonic process with cavitation and bronchogenic spread to other lobes.

It is rapidly progressive cases like these which have led to the opinion that diabetes exerts a special effect upon the tuberculous process. Undoubtedly this



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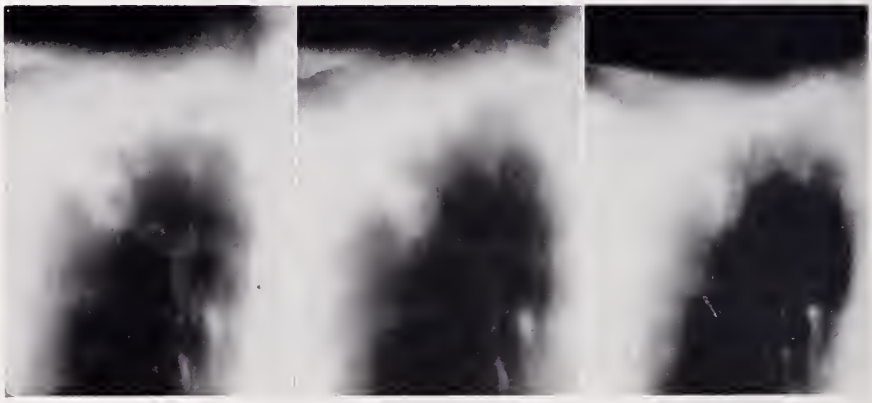

b *c* *d*

FIG. 1. *a*. Roentgenogram Feb. 6, 1956, showing caseous nodule in right infraclavicular area, with spread to right lower lobe. *b*. 8 cm. antero-posterior tomographic section of same date, showing cavity in area of caseous infiltration. *c*. 8 cm. antero-posterior section Feb. 25, 1956, showing closure of cavity after 3 weeks of chemotherapy with isoniazid, dihydrostreptomycin and P.A.S. *d*. Tomogram at same level on April 16, 1956, showing continued reabsorption of lesion under chemotherapy, despite presence of diabetes.

is true in the presence of acidosis or coma or even after repeated episodes of ketosis. That the prognosis should be any poorer in the carefully treated diabetic is hard to believe for any one stage of tuberculosis.

Figure 1 illustrates the rapid response of tuberculosis in a diabetic treated vigorously for both diseases. She is a 47 year old white female who suffered the onset of hemoptysis a few days before examination. Chest x-ray showed an infiltration in the right upper lobe (Fig. 1a), and examination of the sputum repeatedly revealed tubercle bacilli. Incidentally noted during the initial examination was a 4 plus glycosuria. Fasting blood sugar was 325 milligrams per cent. The patient was started immediately on insulin, and within a few days she was aglycosuric on 30 units of NPH insulin daily. After preliminary studies, she was given dihydrostreptomycin, 1.0 gram daily, PAS 10.0 grams daily, and INH 300 milligrams per day. Within three weeks the cavity noted on the first tomographic series (1b) had closed (1c) and sputum became free of tubercle bacilli.

The effect of tuberculosis on the diabetic is more clear-cut. Although there have been reports of amelioration of the diabetic state with the onset or progression of tuberculosis, most cases show an exaggeration of the carbohydrate imbalance and a gradually increasing need for insulin. This frequently reaches such a degree, or develops so rapidly, that the physician becomes engrossed with the treatment of the diabetes, and the underlying tuberculous process is overlooked. The resulting ketosis and weight loss complicate the picture even further and apparently enrich the soil even more for the acid-fast organism.

The best treatment of tuberculosis in the diabetic, of course, is prevention. A program of adequate nutrition, along with insulin therapy, is of greatest importance. Weight loss, when necessary, should be regulated at a reasonably slow rate. Fad diets are to be condemned. In addition, general hygienic measures are of utmost importance to the diabetic. Avoidance of known contacts need only be mentioned.

In the cases where tuberculosis develops, early diagnosis is of paramount importance. All diabetics should have annual chest x-rays. Any sudden increase in insulin requirements or loss of weight, even though it appears voluntary, should be followed by a roentgenographic examination of the chest. By earlier diagnosis, the prognosis of tuberculosis in the diabetic will be immeasureably improved. Treatment of both diseases must be aggressive. The beneficial effect of maintaining optimum nutrition with insulin has been stressed by all writers. It is of interest that the good results observed in the status of the tuberculosis, after the diabetes was treated with insulin, led physicians in the 1920's to use insulin in the treatment of the tuberculous non-diabetic (21–23). On the other hand, hypoglycemic reactions also must be avoided because of the danger of aspiration and spread of the lung disease. The diet should be nutritious and relatively high in calories in order to maintain or increase the weight of the patient. Weight loss, even of obese patients, should be postponed until after the tuberculous process is well under control.

Other aspects of the treatment of the tuberculosis need not be any different from that employed in the non-diabetic with the same extent of pathology (20).

Bed rest is indicated only in far-advanced or toxic cases. Activity, however, should be restricted. Surgical indications are similar to those for the nondiabetic. As far as drug therapy is concerned, in most cases it is wise to use all three drugs available; dihydrostreptomycin, two or three times a week, PAS and isoniazid in the usual doses are employed. These drugs have little, if any, effect on the diabetes. It is true that isoniazid was suspected at first to have some effect on carbohydrate metabolism. It has been reported both to lower and to raise blood sugar levels in the diabetic (24). Undoubtedly, the lowering of the blood sugar in the tuberculous diabetic can be attributed to control of the tuberculosis and relief of toxicity. One report, that isoniazid raises the blood sugar (24), tempted Bookman to use it in a patient with organic hyperinsulinism, who had had a subtotal pancreatectomy but who refused further surgery. This patient showed no discernible clinical or chemical effect after treatment with isoniazid (25).

PAS has not been reported to show any effect upon carbohydrate metabolism. It is of interest to note without comment, a case of fatal PAS toxicity in which the course was climaxed by the acute onset of diabetes (26). At postmortem examination, islets of Langerhans were reportedly absent.

Treatment then, should be early, vigorous and bilateral. Using as much insulin as is necessary to obtain optimum weight and nutrition, plus a broadside attack on the tuberculous process by the various antibiotic and chemotherapeutic agents should produce results which are as good in the diabetic as they are in the nondiabetic.

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RELAPSE AND REHABILITATION IN THE ERA OF ANTI-TUBERCULOSIS DRUGS

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INTRODUCTION

It is becoming evident that the beneficial effects obtained in hospitals and sanatoria with present day methods of medical and surgical treatment endure for at least the first few years after discharge. This is graphically shown in a preliminary survey herein presented of 153 tuberculous patients discharged during the last three years from the Altro Work Shops, an industrial rehabilitation center. Clearly the widespread use of streptomycin, p-aminosalicylic acid and isoniazid, which has resulted in so spectacular a decline in tuberculosis mortality, is exerting a parallel favorable effect in the rehabilitation phase of treatment of this disease.

For these patients from the Altro Work Shops the cumulative three-year relapse rate was six per cent. The relapse rate for an equal period among patients discharged during the era of collapse therapy (1930–1939) was 19 per cent. A larger study of Altro Work Shops patients extending over a period of five years after discharge will determine whether today's improved results hold up in the later years as well.

The more favorable prognosis of the drug-treated patients is leading to the gradual adoption of a somewhat accelerated rehabilitation course. This is in keeping with the recent trend toward reduction of the span of the active treatment phase of tuberculosis. Home-treated and clinic-treated patients can particularly benefit from an orderly regimen of progressively increased physical activity during the recovery phase of the illness. It is felt that the knowledge gained from the new experience at the Altro Work Shops with drug-treated patients may be helpful in the management of patients undergoing other forms of rehabilitation and likewise patients who do not undertake a formal rehabilitation program. Physicians caring for drug-treated patients are facing afresh the problems of when to begin activity, at what pace to increase it and when, finally, to permit the patient a full day's work.

THE ALTRO WORK SHOPS

The Altro Work Shops is the oldest sheltered workshop for the rehabilitation of the tuberculous in the world. It was founded in 1915 when the trustees of the Montefiore County Sanatorium learned from a follow-up survey that half the patients discharged from the Sanatorium with arrested or quiescent disease were either dead or had suffered a relapse within twelve to eighteen months. There were then practically no community facilities for the rehabilitation of the discharged patient.

To help combat this sad record, a sheltered workshop in the form of a garment

From the Altro Health and Rehabilitation Services and the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

factory was set up. Garment work was chosen because many patients had engaged in this or a kindred trade before they became ill. Moreover, a fair amount of skill at the sewing machine could be acquired rapidly by the uninitiated.

The workshop program is aimed at the gradual physical "hardening" of the patient through the allotment of an increasing work dosage on an individual prescription basis by the staff physicians. This regimen at the workshop is combined with close medical and social service supervision of the patient and his family as a unit. The favorable health record of 964 workers who passed through the workshop in the first 25 years of its operation has been published previously (1–3). As will be shown, this record is being considerably improved in the present era.

In 1948 the field of the workshop's operation was widened by the admission of patients with cardiac ailments and in 1953, some patients recovering from mental illness were accepted. A wider choice of occupation at the workshop has been afforded the patients by the recent introduction of a clerical trades training program and a course of instruction in the repair of sewing machines.

WORKSHOP REGIMEN

The manner of the workshop's operation has been detailed elsewhere (4, 5) therefore only some highlights will be given here. The workshop is a modern garment factory which produces washable uniforms sold commercially mainly to hospitals and hotels. The factory is located in Bronx County and has steadily been enlarged so that it now has a capacity of 200 workers. Aside from some key personnel, the factory is manned by patients.

The patient spends the entire working day at the factory. The patient's day is divided into alternating periods of work and rest. Beginning at three or four hour work level, the patient's hours are gradually increased until he can do a full day's work without undue fatigue. He is then *graduated* into outside industry or sent for further vocational training if his old job appears unsuitable. During the early phases at the workshop the earning capacity of the patient is limited, therefore subsidies may be granted to keep the family budget at adequate levels.

WORK DOSAGE

The work dosage and the tempo of increasing it depends to a degree upon the duration and severity of the tuberculosis, the number of previous relapses, and the duration of the stability of lesions and bacterial conversion. None of these historical data, however, are as informative in this area as a carefully supervised work trial. A three month probationary period permits us to observe the patient's clinical and psychological responses to the assigned tasks. If these are satisfactory, the patient goes on to complete the course of the workshop.

MEDICAL CRITERIA FOR ADMISSION TO THE WORKSHOP

At the present time, only patients with lesions stable on serial chest films for six months or longer are admitted. Tubercle bacilli must be absent from cultures of the sputum or gastric contents for a like period. With some drug-treated patients, it may become possible to lower these intervals to three or four months of stability before workshop admission for part-time work.

In the past, the workshop has accepted also a group of tuberculous patients for permanently sheltered employment. The total number of such patients was not permitted to exceed ten per cent of the roster. This group was commonly designated as the "good chronics" and it consisted of patients who either had limited respiratory reserve or who were unable to be rid of tubercle bacilli in their secretions even after all known forms of therapy had been tried. When such patients showed stable serial chest films without gross cavitation and offered a prospect of becoming self-supporting under the sheltered conditions of the workshop, they were accepted for the graduated work program. By means of carefully graded regimens many of these succeeded in achieving the goal of self-sufficiency at the workshop. With the coming of the chemotherapy era, these patients had not been so numerous and often they had been referred back for more definitive therapy since it was felt that for them not all methods of effective treatment had been exhausted.

MATERIAL AND METHODS

This communication presents a preliminary report of all tuberculosis patients employed at the Altro Work Shops beyond a three month probationary period and discharged from the workshop during the years 1953–1955. Forty-nine patients were discharged during 1953, 56 patients in 1954 and 48 patients in 1955. Since the average stay at the workshop was about a year, those discharged in 1953 could be observed for a maximum period of roughly four years from the date of admission to the workshop and for three years from the date of discharge. Those discharged in the years 1954 and 1955 had proportionately shorter periods of observation. Thirty patients did not complete the probationary period because they could not adjust to the workshop regimen or because of undue stress in the home. Half of these patients remained at the workshop for less than one month.

UNTRACED PATIENTS

Five patients were untraced at the time of the closing of the study. (To judge by past experience, some of these will be traced again.) One patient returned to Puerto Rico soon after discharge from the workshop; three other patients were lost during the first year after discharge and another in the third year.

CHARACTERISTICS OF ALTRO PATIENTS

Sex. There were 85 men and 68 women, a division of 55 per cent males and 45 per cent females. This is a more equal division of the sexes than maintained at the workshop previously when males outnumbered females by more than three to one.

Racial Background. Table I shows that the workshop population is divided almost equally among whites, Negroes and Puerto Ricans. The increasing number of Negroes and Puerto-Rico-born patients entering the workshop reflects the special need of these groups in New York City's population for rehabilitation services. The Negro and Puerto Rican group combined contributed a little more

TABLE I

Racial distribution of patients discharged from Altro 1953–1955

Racial Group	Number	Per Cent
All Races	153	100.0
White	47	30.7
Negro	54	35.3
Puerto Rican	51	33.3
Other	1	0.7

TABLE II

Altro patients admitted in two periods by extent of disease upon admission

Stage of Disease upon Admission	1953–1955		1930–1939	
	Number	Per Cent	Number	Per Cent
All Stages	153	100.0	519	100.0
Minimal	38	24.8	66	12.7
Moderately advanced	65	42.5	249	48.0
Far advanced	50	32.7	204	39.3

than 40 per cent of all new cases reported in New York City in 1954 and 30 per cent of all deaths from tuberculosis in the same year. Together, these groups constitute only about 16 per cent of the city's total population.

Age and Marital Status. The median age at admission of the men was 37 years and the women, 29 years. Previously the patients were somewhat younger; males were 30 and females 25. The increase in age at admission can be accounted for partly by the postponement of the primary tuberculosis infection to adolescence or adult life.

Patients who were married or had been married outnumbered the single patients 84 to 69. However, single women slightly outnumbered married women who usually returned to their household activities after hospital discharge.

Stage of Disease. At Altro admission, 25 per cent of patients had disease processes of minimal extent; 42 per cent were moderately advanced and 33 per cent were far advanced. As Table II shows, this represents some improvement in this category when compared with the stage distribution of patients admitted to the workshop during the period 1930–1939. Then, patients with disease of minimal extent comprised only 13 per cent of the total whereas the present-day figure is about double that. Correspondingly, the proportion of moderately advanced and far advanced disease decreased in the present-day group. Despite this improvement, it is somewhat discouraging to note the small proportion of patients with minimal disease in the present-day group. Parallel findings were reported in New York City in 1954 when roughly four out of five newly-discovered cases of pulmonary tuberculosis were already in an advanced stage of the illness when discovered (6).

Bacteriologic Status. The results of the bacteriologic examination for tubercle bacilli before admission to the Altro is classified into three sub-groups (Table

TABLE III

Altro patients admitted in two periods by sputum history before admission

Sputum History before Admission	1953–1955		1930–1939	
	Number	Per Cent	Number	Per Cent
All Sputum Histories	153	100.0	519	100.0
Minus-minus	29	19.0	127	24.5
Plus-minus	122	79.7	353	68.0
Plus-plus	2	1.3	32	6.2
Not reported			7	1.3

Minus-Minus, sputum never positive; Plus-Minus, sputum converted from positive to negative; Plus-Plus, sputum still positive.

III). Patients who had never had tubercle bacilli cultivated from sputum or gastric lavage samples are listed under the minus-minus category. Those patients whose secretions had been successfully rid of tubercle bacilli before admission to the workshop are listed in the plus-minus group. Finally, patients whose sputum or gastric contents still contained tubercle bacilli on culture or guinea pig inoculation at the time of admission to the workshop are listed in the plus-plus group.

This table is noteworthy for several reasons. In the first place, only two patients, or about one per cent in the present-day era had sputum still containing tubercle bacilli on culture at the time of admission to the workshop whereas in the "collapse therapy" era (1930–39), the workshop accepted about six per cent of patients with positive findings. Even at that time, a great improvement had already taken place; for in the period at Altro extending over 1915–1929 positive-sputum patients constituted 24 per cent of the admitted group.

The greater effectiveness of present-day hospital treatment methods is also reflected in the increase of the proportion of successfully "converted" patients; 68 per cent of the total in the "collapse therapy" era and 80 per cent in the recent Altro group. This is in contrast to the 36 per cent of the Altro patients who belonged to the "converted" group in the period of 1915–1929.

Patients leaving the tuberculosis institutions today after chemotherapy and excisional surgery are, as a group, much more successfully managed than was the case in the "collapse therapy" era. The improvement seems even more impressive when comparisons are made with the experience with patients in the 1915–1929 period when a short sanatorium course of haphazard bed rest was the mainstay of therapy.

Previous Sanatorium or Hospital Treatment. All but two patients had had some period of institutional treatment before entering the workshop. The median period between sanatorium discharge and admission to the workshop was 7.6 months. When patients were referred from the Westchester Division of Montefiore Hospital there was considerably less delay since requisite preparations were completed at the sanatorium before the prospective applicant's discharge.

Table IV contrasts the main forms of treatment in the present-day Altro group with the collapse-therapy group. Whereas in the earlier period half the patients

TABLE IV

Altro patients admitted in two periods by type of treatment prior to admission

Type of Treatment	1953–1955		1930–1939	
	Number	Per Cent	Number	Per Cent
All types of treatment*	153	100.0	519	100.0
Bed rest only	74	48.4	256	49.3
All collapse therapy	52	34.0	263	50.7
Pneumothorax	13	8.5	203	39.2
Phrenic crush	0	0	24	4.6
Thoracoplasty	18	11.8	36	6.9
Pneumoperitoneum	21	13.7		
All excisional surgery	25	16.3		
Segmental resection	4	2.6		
Lobectomy	11	7.2		
Pneumonectomy	10	6.5		
Bed rest at home	2	1.3		

* See Table V for drug treatment.

had received some form of collapse therapy before admission to the workshop, in the present-day group only one in three had had such procedures, often years before for a previous relapse. On the other hand, one in six patients admitted in the 1953–55 group has had some form of resectional therapy which was virtually unknown in the period before the coming of the antimicrobial drugs. It is of interest that bed rest without collapse measures or excisional surgery was used for half the patients in both periods. The difference is that in the present day almost all Altro patients also received antimicrobial agents.

Antimicrobial Drug Treatment. There can be little doubt that the anti-tuberculosis drugs which the present-day Altro patients received before admission to the workshop and, in some instances, continued to receive at the workshop, contributed much to the favorable results achieved with these patients.

Table V shows that about seven of every eight patients discharged from the workshop in 1953–55 had had some antimicrobial agent as part of treatment

TABLE V

Altro patients discharged 1953–1955 by anti-tuberculosis drug therapy received

Drug Therapy	Number	Per Cent
Received no drugs	19	12.4
Received drugs	134*	87.6
Discontinued before Altro admission	89	58.2
Received drugs at Altro	45	29.4
Drugs continued at Altro	34	22.2
Drugs begun and cont. at Altro	5	3.3
Drugs discontinued at Altro	6	3.9

* Received streptomycin—115 patients; p-aminosalicylic acid—106 patients; isoniazid—46 patients. All but 15 patients received combined drug therapy.

before admission to the workshop. By 1955, all patients discharged had received drug treatment. The drugs used were streptomycin, p-aminosalicylic acid and isoniazid, variously combined. Most patients had had their drug regimens discontinued before application for admission to the workshop. Some of those patients were treated at a time when six-week or three-month drug regimens were considered adequate.

A little less than one third or 45 patients in the group were still receiving or were begun on anti-tuberculosis drugs while at the workshop, mostly in combined regimens of two drugs. The isoniazid-p-aminosalicylic acid combination was preferred over combinations including streptomycin since the former eliminated the need for injections and therefore interfered less with tasks at the workshop. The six patients whose drug regimens were discontinued at the workshop were under shared medical care.

From the beginning, the policy at the workshop called for the continuation of drug therapy throughout the patients' rehabilitation course. In the group discharged in 1953–54 the proportion of patients on maintenance antimicrobial therapy was 20 per cent. For those discharged in 1955, the figure of maintenance drug therapy rose to 50 per cent. Unless new and more potent anti-tuberculosis agents are introduced, it is probable that almost all patients will present themselves for admission to the workshop while on maintenance antimicrobial drug therapy and these agents will be continued through the rehabilitation course and beyond.

Length of the Work Course. The median length of the rehabilitation course for Altro patients who completed the program and were graduated from the workshop was 13.7 months. In the 1930–39 period, the span required for full rehabilitation was 19.3 months; in the 1915–1929 period the duration was 24.3 months. With increasing confidence in the protective value of the antimicrobial agents, the workshop course is being further shortened for the new rehabilitants.

RESULTS OF REHABILITATION

The results achieved with the present-day Altro patients, most of whom had received antimicrobial agents are extremely favorable when compared with the results obtained in the "collapse therapy" era (1930–39).

Manner of Discharge from the Workshop. One measure of the success of the rehabilitation process is the proportion of patients who successfully complete the course without incident. Table VI shows that roughly seven of ten patients admitted to the workshop completed the course and were graduated into outside industry as *fully rehabilitated.* The percentage was the same for the present-day Altro workers and for those fully rehabilitated during the "collapse therapy" era. This proportion of graduates is considered satisfactory.

Partially rehabilitated patients-workers who were discharged with consent to undertake suitable part-time employment, schooling or vocational retraining—amounted to 16 per cent among the recent patients compared to six per cent in the 1930–39 group. The increase reflects greater availability today of rehabilitation training facilities in the New York City area than was the case in the Thirties.

TABLE VI

Altro patients admitted in two periods by reason for discharge from workshop

Reason for Discharge	1953–1955		1930–1939	
	Number	Per Cent	Number	Per Cent
All reasons for discharge	153	100.0	507*	100.0
Fully rehabilitated and graduated	104	68.0	347	68.4+
Partially rehabilitated	25	16.3	30	5.9+
Not rehabilitated	24	15.7	130	25.6
Tuberculous illness	5	3.3	93	18.3
Psychological, soc. or eco. maladjustment	11	7.2	20	3.9
Non-tuberculous illness	8	5.2	17	3.4

* Excludes twelve workers still at Altro at time of study.

Of greater moment are the data relating to patients who were *not rehabilitated.* The difference between the groups of patients in the two periods is significant. Whereas in the 1930–39 period the failures amounted to one in four, they were reduced to slightly less than one in six in the 1953–55 period.

Moreover, the improvement in the present era is revealed most strikingly by reduced discharges for tuberculous illness. In the earlier period the incidence was 18.3 per cent, a percentage considered quite satisfactory at the time. For the 1953–55 period the incidence was 3.3 per cent. Relapse rates are analyzed below but it may be remarked here that the above percentages are not to be construed as relapse *rates* since they do not take into account the varied lengths of stay of the relapsed patients. Furthermore, Table VI does not show relapses which occurred *after* Altro discharge.

Tuberculosis Relapse Rates at and after Altro. To study the relapse rates of the Altro patients, an adaptation of the modified life-table method as first suggested by Frost (7) and elaborated by Downes (8), Hilleboe (9) and Puffer (10) has been used. In order to include relapses which were experienced at the workshop as well as those which occurred after discharge, the date of *admission* to the workshop was used in these computations.

"Relapse" is defined here as reactivation of tuberculosis as demonstrated by adverse changes in the chest roentgenogram or by the appearance of tubercle bacilli on smear or culture in the sputum or gastric contents of patients whose secretions had been free of bacilli for at least three or more months.

Table VII shows a notable drop in relapse rates among the Altro patients of the antimicrobial era. For the first three years after admission, seven patients suffered a relapse, four while at the workshop and three after discharge. Of the seven, one relapse occurred during the first year; four, the second year; and two, the third year. The cumulative three-year relapse rate, as computed by the modified life-table method was 6.1 per cent. For purposes of comparison, 343 Altro patients with sputum "conversion" in the 1930–39 period were used. For that group the three-year cumulative relapse rate after admission was more than three times as great, i.e. 19.1 per cent.

Some details relating to the seven patients who suffered relapse in the 1953–55 group are of interest. Three of the patients had never had antimicrobial therapy

TABLE VII

Relapse rates of Altro patients in two periods during three years following Altro admission

Number of Years Following Admission to the Workshop	1953–1955 (153 Patients)			1930–1939 (343 Patients*)		
	Cumulative Percentage with Relapse	Cumulative Percentage without Relapse	Number of Relapses in Specified Year	Cumulative Percentage with Relapse	Cumulative Percentage without Relapse	Number of Relapses in Specified Year
1	0.7	99.3	1	5.8	94.2	20
2	4.0	96.0	4	13.7	86.3	27
3	6.1	93.9	2	19.1	80.9	17

* For comparison only Altro patients of the 1930–1939 period with plus-minus sputum history (sputum conversion) were used in this table.

before they relapsed. The remaining four had had streptomycin and p-aminosalicylic acid for periods ranging from two to fifteen months. The relapses among these four occurred three to five years after drugs were discontinued.

None of the seven patients with relapse died. All but one were treated again in a tuberculosis institution with some drug regimen including isoniazid. Four relapsed patients have again attained an arrested status. Three are still ill but are recovering.

Mortality Rates for Altro Workers. Mortality rates among tuberculosis patients are a less useful measure of the effects of therapy in tuberculosis than they formerly were. These rates have dropped sharply, and the deaths that do occur are, more often than not, due to causes other than tuberculosis.

In the 1953–55 group of Altro patients, there were five fatalities. Four occurred at the workshop and one after discharge. Only one of these can truly be ascribed to active tuberculosis. A 52-year-old man with far advanced pulmonary tuberculosis and a persistently positive sputum was accepted as a permanently sheltered case at the workshop. He suddenly had a massive hemoptysis to which he succumbed.

As to the other four fatalities, two patients succumbed to bronchopneumonia; one, to coronary occlusion, and one, to lymphosarcoma. The two patients who died of non-tuberculous lung infections were young women aged 27 and 38 years respectively. Each had successfully undergone pneumonectomy for tuberculosis several years before admission to the workshop and showed mild degrees of dyspnea on exertion. Both succumbed rapidly with signs of severe pulmonary insufficiency and *cor pulmonale* during an episode of atypical pneumonia. Neither patient showed any evidence of reactivation of tuberculosis. These two cases illustrate graphically the dangers of simple lower respiratory infections in patients with one lung. Fortunately, prolongation of pre-operative antimicrobial therapy for nine months or longer, as is now widely practiced, has considerably reduced the need for so extensive an operation as pneumonectomy for most cases of surgically-treated pulmonary tuberculosis.

COMMENT

The foregoing analysis of the experience at the Altro Work Shops with tuberculous patients undergoing a rehabilitation course with close social service and

medical supervision shows the favorable results achieved with a group of 153 patients discharged from the workshop during the years 1953–55. As stated, almost all of these patients had received some form of anti-tuberculosis drug therapy during the phase of active treatment.

When the first group of streptomycin treated patients with arrested pulmonary tuberculosis presented themselves at the workshop for rehabilitation in 1949–1950, there was no experience available to indicate the magnitude of the risk involved in putting such patients to work. The tempo at which the work hours were increased was therefore slowed for them until they showed themselves capable of withstanding the workshop regimen. As shown, they proved to be even more stable than patients admitted in earlier years. When isoniazid was added to the treatment schedules, it was soon apparent that patients who had received this drug or were continuing to receive it, were just as fit for work. Hence, little by little, the period for achieving full work tolerance at the workshop has been shortened.

The present-day Altro three-year relapse rate of six per cent as against the 19 per cent in the 1930–39 era is especially gratifying in view of two factors which, it was feared, might adversely affect both the outcome of the rehabilitation course and the patients' subsequent health records while they were living under normal conditions again.

The first factor related to the type of patient being discharged in recent years from the tuberculosis institutions and being accepted at the workshop for rehabilitation. The precipitous fall of crude hospital mortality rates from 30 per cent in the period preceding the antimicrobial era to about ten per cent or less, has meant that many patients with very extensive pulmonary tuberculosis which previously proved fatal are now surviving with drug therapy and excisional surgery. These salvaged patients are obviously among those most in need of rehabilitation and Altro has been accepting a sizable number of them. The small risk of relapse in this group has proved a pleasant surprise.

A second factor which was expected to raise the relapse rate was the gradual change in racial composition of patients accepted at the workshop in the recent period. The high proportion of Negro and Puerto Rican applicants, both groups showing consistently higher morbidity and mortality rates for tuberculosis than whites, has proved no hindrance to the successful outcome of the rehabilitation course, nor has it led to any undue rise in relapse rates at or post-Altro.

It is to be stressed again that the data herein presented only extend for a three year period beyond the beginning of the rehabilitation phase and do not involve a very large population. Too, it has been pointed out that mere postponement of relapse or death by the available antimicrobial agents which are essentially bacteriostatic is a possibility and it will therefore be necessary to await observations extending over a five- to ten-year period before it can safely be stated that the favorable results recorded in hospitals and in the rehabilitation phase are lasting. Certainly the present trend appears highly encouraging.

Patients undergoing formal rehabilitation programs with medical and family social service supervision are an excellent group to use for assessing the long-term results of therapy applied during the active phase of the disease. By reducing to

a manageable minimum the physical and socio-economic stress which many patients experience after discharge from the hospital, we can more readily differentiate the relative value of the various treatments themselves.

Until recently most data relating to the effects of various regimens of antimicrobial agents and excisional surgery have been based on in-hospital experience. It is necessary to carry these invaluable observations into the post-hospital period; for, in the end, it is what the patient can do under normal living conditions that is the truest test of all preceding therapeutic efforts.

Effects of Antimicrobial Therapy upon the Rehabilitation Phase. There are *four* key points in the course of recovery from pulmonary tuberculosis at which a qualitative change occurs in the patient's regimen. The first of these comes when the patient is allowed up from bed; the second, when he is permitted to begin his exercise and early rehabilitation activities; the third is the day he is discharged from the hospital and is ready to undertake a part-time work-adjustment program outside the home. The fourth and final key point in the patient's recovery is the time when he has completed his rehabilitation activities and is ready to return to a regular job and normal living.

As shown later, antituberculosis drug therapy has speeded the patient's attainment of all four of these important points resulting in a considerable shortening of the overall period of disability for most drug-treated patients.

Drug-treated patients may be allowed out of bed sooner. In a matter of a few weeks, most patients have no fever or other toxic signs. There is a quick return of a sense of well-being. Before the use of these drugs, many months would usually elapse before a patient would be allowed out of bed and could remain out of bed without return of signs of toxicity.

The second point, i.e. the time for beginning some rehabilitation activity in the hospital or at home has also been pushed forward. Formerly, it was the custom to wait three months after the sputum or gastric aspirates were negative on culture, and cavities, if present, had closed before initiating rehabilitation programs. Sometimes it took many months and years for the patient to achieve such a status. With drug therapy, sputum conversion usually comes about more rapidly and more often. For example, in previously untreated patients, one may expect roughly 40 per cent of them to show sputum conversion within four months after the start of the drug therapy; 75 per cent within eight months and 85 per cent within one year.* These are *optimal* figures since they do not include patients previously treated with drug therapy, surgically-treated patients and custodial-type patients where sputum conversion may be long delayed. But the estimates give some indication of how much sooner patients receiving antimicrobial agents can undertake activities than heretofore.

The third crucial point is the day of discharge from the hospital. Shorter hospital stays are the rule for most drug-treated patients. Instead of remaining in the

* These rough estimates are based on the "conversion" rates reported by Tucker and Livings (11) in the latest Veterans Administration studies on chemotherapy of tuberculosis (1955) and were adjusted to the stage distribution of newly discovered patients in New York City in 1954 as reported by Lowell (6).

hospital until they attain a four-hour work tolerance, patients are now being permitted to leave with one- or two-hour work tolerance; some are permitted to leave even sooner. Almost all such patients are being asked to continue their drug therapy after discharge and throughout the rehabilitation period. Rehabilitation centers such as Altro are now experimentally accepting patients on maintenance drug therapy with two-hour work tolerance.

The fourth and final step in recovery is reached when the patient is ready to return to a regular occupation. As was indicated in the recent Altro experience, the antimicrobial agents have helped to expedite the achievement of full rehabilitation and contributed to making the course smoother for the rehabilitants.

The available drugs have certainly given a greater sense of confidence to the physician handling a serious disease. The drugs also have had a beneficent effect upon the psychological attitudes of many patients who now can count their gains in months rather than in years.

In conclusion, the new drugs have affected favorably all phases of the treatment and rehabilitation of patients with pulmonary tuberculosis. They by no means have eliminated the need for hospitalization, especially for the more seriously ill and for those with poor home conditions. There is still need for expert medical and surgical care; for adequate nursing and a nutritious diet, for family casework service, and for a properly supervised post-hospital work-adjustment period before the patient returns to the workaday world.

Whether the available antituberculosis agents will continue to exert their favorable mass effects, or whether a limiting plateau soon will be reached cannot be foretold.

SUMMARY

This communication has presented findings among a group of 153 tuberculous patients with arrested disease, who were discharged during 1953–55 after a rehabilitation course at the Altro Work Shops, an industrial rehabilitation center.

Most patients (88 per cent) received some antituberculosis drug therapy before admission to the workshop or while there.

A comparison of relapse rates among Altro patients of the antimicrobial era (1953–55) was made with those found among patients who attended the workshop in the "collapse therapy" era (1930–39). Patients discharged from the workshop during 1953–55 had a three-year cumulative relapse rate of 6.1 per cent as compared with a relapse rate of 19.1 per cent over the same span among Altro patients during the "collapse" therapy era, 1930–39.

Because of the improved results, it is recommended that tuberculosis patients undergoing rehabilitation continue to receive antimicrobial agents throughout the course and beyond.

The favorable effects of the antituberculosis drugs widely observed in hospitals are being seen now as well as during the rehabilitation phase of treatment and for a short period thereafter. Long term studies will show how enduring these gains prove to be.

Most patients receiving the antimicrobial agents are able to be allowed out of

bed sooner, become "non-infectious" more promptly and are made fit to begin rehabilitation activities earlier. Drug-treated patients appear to require shorter hospital stays as well as shorter periods of work adjustment, "hardening," or vocational rehabilitation.

Tuberculosis remains, in the antimicrobial era, a widespread chronic and relapsing disease, still requiring for its control a complex of medical and socio-economic approaches.

ACKNOWLEDGMENT

Acknowledgment is made to Mrs. Elsie B. Paskus for her invaluable aid in collating the medical and social data used in this study and to Mrs. Florence Bailin, Statistician, Altro Health and Rehabilitation Services for help in coding the data.

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LONG-TERM OBSERVATION FOLLOWING ISONIAZID THERAPY

Two Case Reports

IRVING J. SELIKOFF, M.D.

It is now four years since the first patient was treated with isoniazid at The Mount Sinai Hospital. It was therefore considered of some value to record the experiences with this patient in the following case-report, as well as those with another patient, the first to have ambulatory treatment with isoniazid.

CASE ONE. J. M. (MSH # 638275)

This 46 year old white housewife was admitted to The Mount Sinai Hospital on March 6, 1952. Two and a half years before, two months after a cholecystectomy, she had developed a perianal swelling, which soon burst and had continued as a discharging fistulous tract and ulcer. There was also a history of pleuritic pain at this time, with fever and malaise.

She remained in chronic ill-health until 1951 when there was an exacerbation of fever, weight loss, cough and weakness, now accompanied by diarrhea and abdominal cramps. The anal ulcer persisted. A provisional gross diagnosis of carcinoma was made and a biopsy of this area was done at another institution on Dec. 19, 1952. Tuberculosis was found, with characteristic histological appearance and with acid fast bacteria. Chest x-ray at this time showed disseminated tuberculosis.

She was treated at this time with streptomycin 1.0 gram daily from January 6, 1952. However, because of failure to improve, it was discontinued and she was admitted to the Mount Sinai Hospital for additional therapy on March 6, 1952.

At this hospital, widespread disseminated tuberculosis was found. Chest x-ray (Figure 1) showed bilateral extensive infiltrations characteristic of hematogenous disseminated tuberculosis. A barium enema showed intestinal tuberculosis. (This is separately reported by Drs. Edgar Kogan and Henry D. Janowitz in this symposium). A large perianal ulcer was present (Figure 3), previously found to be tuberculous on biopsy, and at this time showing acid-fast bacilli on smear of the cleansed ulcer crater.

The patient's clinical condition mirrored her widespread disease. Her normal weight was 135 pounds. On admission, as for the previous two months, it was 112 pounds. Her temperature was subfebrile; she was toxic, anorexic. The diarrhea was particularly annoying because of the perianal ulcer. There was a moderate cough, largely unproductive.

Laboratory studies showed, in addition to the acid-fast bacteria in the ulcer, strongly positive guiac tests for fecal blood on five successive occasions, thymol turbidity of 10–11 units on three occasions and acid-fast bacteria in a smear of concentrated urine. Intravenous pyelogram and urine cultures did not, however, confirm suspicion of genito-urinary tuberculosis. Tuberculin test was, of course, positive. Many other roentgenological, biochemical, hematological and bacteriological examinations were not remarkable.

Therapy was begun on the fourth hospital day, March 9, 1952, with isoniazid, 300 milligrams daily in three divided doses. There was rapid clinical and anatomical improvement. By the end of one week, appetite had returned, she was afebrile and the cough had decreased; the margins of the anal ulcer showed evidences of healing and the discharge, previously purulent, had disappeared as had the considerable pain and tenderness. The progress continued, and at the end of the third week of treatment, she appeared grossly clinically well. There was no longer any cough, there had been a five pound weight gain and there was no toxicity nor fever. The ulcer had shown marked healing and gave no symptoms; it was completely healed shortly after she was transferred to a tuberculosis institution on April 9, 1952, after one month of treatment (Figure 4).

From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

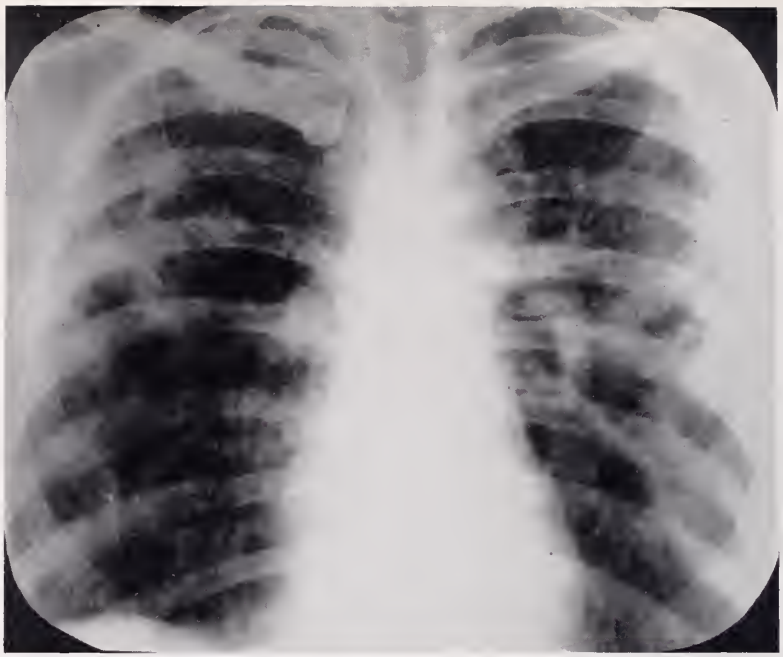

FIG. 1. (X-ray). *J. M March 7, 1952.* Chest x-ray on admission showing bilateral extensive disseminated active tuberculosis.

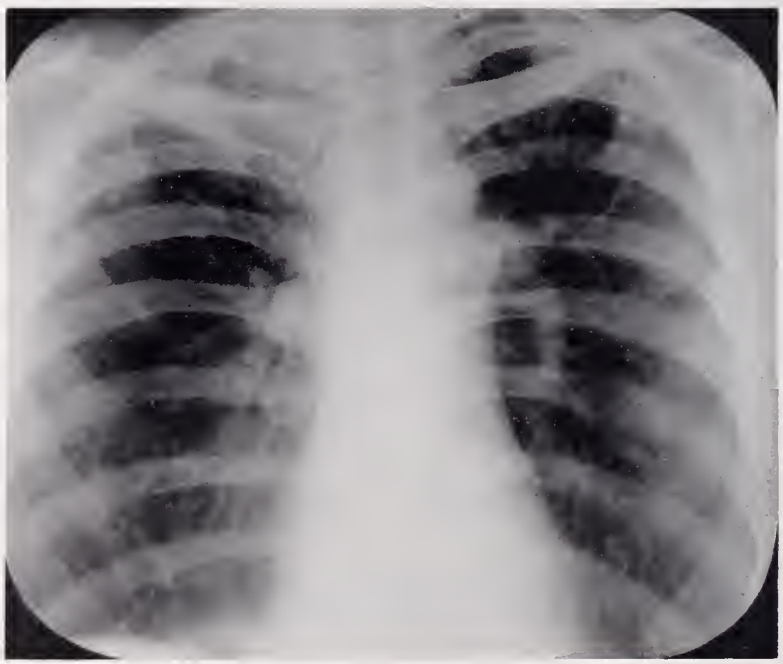

FIG. 2. (X-ray). *J. M. Jan. 6, 1954.* Marked clearing after 20 months of isoniazid therapy.

FIG. 3. (Photo). *J. M. Anal Ulcer, March 8, 1952.* Before therapy.

FIG. 4. (Photo). *J. M. Anal Ulcer, April 14, 1952.* Healed after one month of isoniazid therapy.

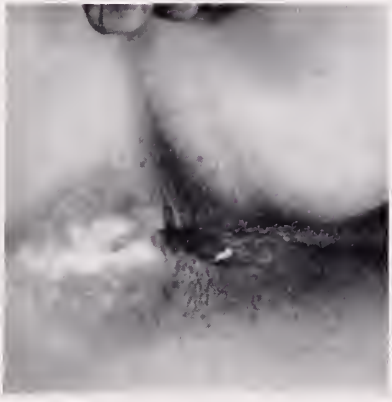

FIG. 5. (Photo). *J. M. Anal Ulcer, Sept. 10, 1955.* Healing persists. Remains healed with post-therapy observation of more than two years.

Isoniazid therapy was continued at the receiving institution and, when she elected to return home after several weeks of further hospitalization, it was continued until October, 1953, a total of almost twenty months of chemotherapy. She tolerated therapy well, and gave no evidence of drug toxicity. Laboratory studies of urine, stool and anal smears showed no tubercle bacilli during this time and bacteriological examinations of the sputum, apart from a positive culture early in the course of therapy, similarly remained negative.

The patient has continued under the observation of the Chest Clinic at the Mount Sinai Hospital. She remains well. Marked reabsorption of the pulmonary infiltrations has left fibrotic residuals on the chest film (Figure 2). The anal ulcer has remained healed (Figure 5). The patient is asymptomatic with no cough, sputum, diarrhea; her weight, which climbed to 150 pounds in six months, has remained at this level. Sputum tests are consistently negative on smear and culture. When seen in the Clinic on January 10, 1956, almost four years since first treated, and more than two years since cessation of isoniazid therapy, examination showed no evidence of any reactivation of the disease. The patient was well, working full-time, and asymptomatic.

CASE TWO. R. De L. (MSH # 599775)

This 37 year old white female was admitted to The Mount Sinai Hospital on August 1, 1949. A thoracoplasty, done in 1936, had failed to control her disease and she continued with infectious sputum. The left lung showed nodular infiltrates but no cavity nor active

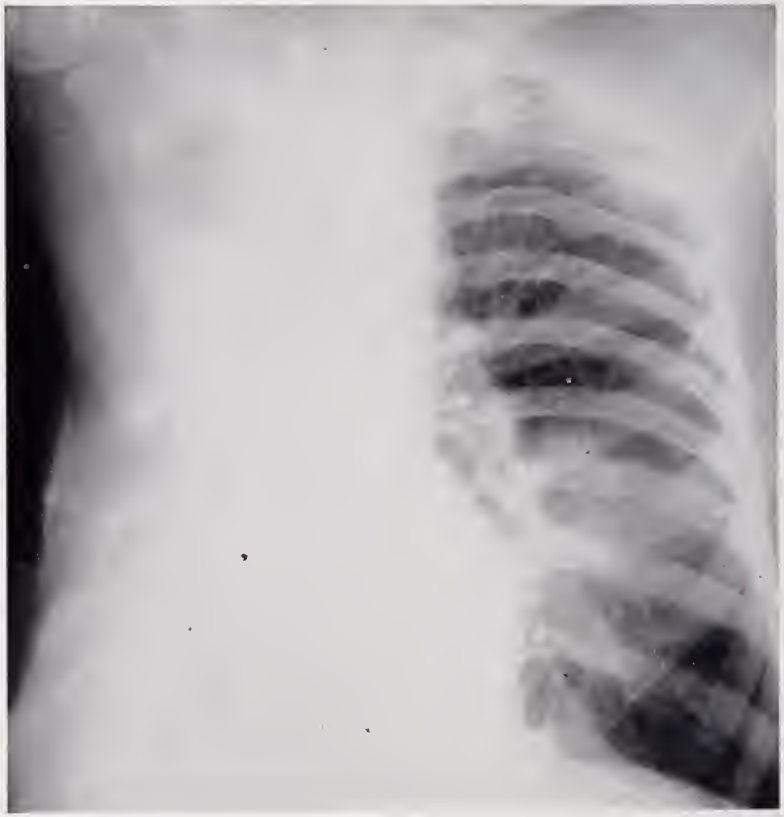

FIG. 6. (X-ray). *R. DeL. Oct. 2, 1951.* Reactivation of tuberculosis in remaining lung after right pneumonectomy.

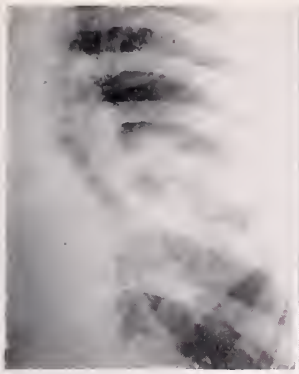

FIG. 7

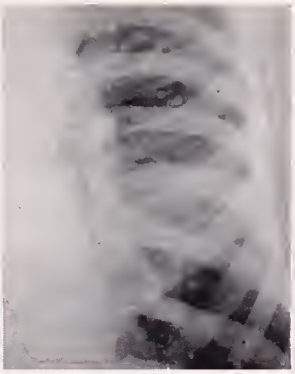

FIG. 8

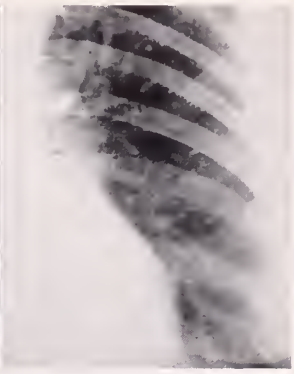

FIG. 9

FIG. 7. (X-ray). *R. DeL. Oct. 2, 1951.* Enlarged view of pre-treatment film showing cavity in area of reactivation.

FIG. 8. (X-ray). *R. DeL. Feb. 24, 1952.* Cavity closure and marked reabsorption of infiltration after twenty-one weeks of therapy.

FIG. 9. (X-ray). *R. DeL. Feb. 6, 1956.* Arrested disease twenty-six months after stopping therapy. Patient is well, active and asymptomatic.

disease. A right pleuro-pneumonectomy was done on August 3, 1949 (Dr. Irving A. Sarot). The removed specimen showed a destroyed lung, fibrotic, with tuberculous bronchiectasis and fibro-caseous tuberculosis.

Sputum was negative after the right pneumonectomy, and the left lung appeared stable. Unfortunately, reactivation of an apparently quiescent area of infiltration occurred early in 1951 and bacteriological studies of the sputum showed tubercle bacilli. Despite streptomycin and PAS therapy, by October, 1951, the area of infiltration had increased in size and a cavity appeared in the remaining lung (Figures 6, 7). With the reactivation of the disease, there was approximately a ten pound loss of weight and a considerable amount of coughing. The patient refused hospitalization. Home environment was exceptionally good, with excellent personal care and sanitation.

Elsewhere, clinical toxicity studies with hydrazide derivatives of isonicotinic acid had just been completed (1) and therapeutic trials had just been begun (October 2, 1951) (2). Because of the serious situation of this patient, hydrazide therapy was begun October 5, 1951, with the patient remaining at home. Iproniazid (the isopropyl derivative of isoniazid) was given, 300 milligrams daily, in three divided doses; this being approximately 4 milligrams per kilogram. Therapy was continued with this derivative for two months, when the parent substance was substituted at the same dosage. Streptomycin 1.0 gram twice weekly and PAS, 10 grams daily were added in the sixth month of therapy. This chemotherapy continued without halt for twenty-seven months.

There was immediate clinical response to hydrazide therapy, with weight gain and cessation of cough. Sputum became negative on smear but a rare culture showed tubercle bacilli until the seventh month of therapy. There was rapid resorption of the exudative infiltration and the cavity could no longer be clearly seen by the third month of therapy and appeared closed after twenty-one weeks (Figure 8).

The patient was on modified bed-rest for the first three months and remained on limited activity for another year. She has been on full activity as a housewife since. All therapy was ambulatory, as an office procedure. Apart from minor but somewhat troublesome side-effects of iproniazid therapy and gastro intestinal difficulties with PAS, there was no drug toxicity.

There has been no reactivation of her disease since therapy was stopped twenty-six months ago. The disease in the remaining lung continues arrested (Figure 9) and the patient is clinically well, fully active and asymptomatic.

SUMMARY

Two case reports are presented: one, of the first isoniazid-treated patient at The Mount Sinai Hospital and the second, of the first patient ever managed with ambulatory isoniazid therapy. Both patients recovered from serious disease and both have remained well. Observation has continued more than four years, and includes more than two years post-therapy follow-up.

The sustained improvement of these patients, among the first to be treated with isoniazid, suggests that long-term observation will confirm the initial good results of such therapy.

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OBSERVATIONS ON THE SEX CHROMATIN IN TESTICULAR DISORDERS

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Observations by Barr and his group (1–5) have indicated a readily recognizable difference between the resting nuclei of males and females. In the majority of nuclei of various tissues and organs of female human subjects and animals, a chromatin body of characteristic size, shape and location is demonstrable. Absent from the normal nuclei of males, this "sex chromatin" is approximately one micron in size and is usually planoconvex in configuration, lying in contact with the nuclear membrane. It is identifiable in embryonal cells (6) as well as in pathological tissues (7, 8). The sex chromatin is not influenced by the hormonal status of the host (9). Fusion of portions of the XX chromosomal complex of females is believed to account for the presence of the structure in the cells of females. Since the Y chromosome is relatively small, the XY combination of males presumably does not produce a body of comparable size. The presence of chromatin-positive nuclei, therefore, signifies that the individual is a genetic female or at least presumably bears two X chromasomes. The sex-chromatin pattern of nuclei is usually examined in skin biopsies (3, 9) or in oral smears (10, 11). Excised tissues or organs are often equally satisfactory for study (7, 8). A different type of sexual dimorphism in accordance with genetic sex has been described in peripheral leucocytes (12).

With expanding application of sex-chromatin studies to patients with abnormal sexual development, it was soon discovered that many women with ovarian agenesis (Turner's syndrome) possess a male type of nuclear morphology in the skin and buccal mucosa (13, 14, 9). Contrariwise, recent communications from Plunkett and Barr (15) and from Bradbury, Bunge and Boccabella (16) indicate that female sex chromatin exists in the epidermal (15) and oral mucosal (15, 16) nuclei of certain men with congenital testicular hypoplasia and Klinefelter's syndrome (17). The present report deals with the results of a study of the sex-chromatin pattern in the testicular tissue of patients with various testicular disorders, including the Klinefelter syndrome. In some instances the chromatin pattern in epidermal nuclei was also examined.

MATERIAL AND METHOD

Testicular biopsy sections were obtained from 14 patients with testicular

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TABLE I

Clinico-pathologic features of patients whose testicular biopsies were examined for sex chromatin

Case No.	Age in Years	Hypogonadism	Gynecomastia	Urinary Gonadotropins*	Testicular Histopathology	Testes	Female Chromatin in Leydig Cells	Comment
1	22	+	+	High	Tubular fibrosis; Sertoli cells only	Scrotal, small	+	Klinefelter's syndrome. Testes undescended in childhood, descended after hormone therapy
2	26	+	+	High	Tubular fibrosis; spermatocytes I present	Scrotal, small	0	Klinefelter's syndrome
3	28	+	0	High	Tubular fibrosis; Sertoli cells only	Scrotal, small	+	Klinefelter's syndrome
4	35	0	+	High	Tubular fibrosis; rare tubule shows spermiogenesis	Scrotal, small	0	Klinefelter's syndrome
5	43	+	+	High	Tubular fibrosis; Sertoli cells only	Scrotal, small	+	Klinefelter's syndrome. Diabetes mellitus
6	36	+	+	High	Tubular fibrosis; germinal aplasia	Scrotal, small	0	Congenital familial testicular deficiency. Male-type nuclei in skin biopsy (19)
7	47	+	+	High	Tubular fibrosis; germinal aplasia	Scrotal, small	0	Congenital familial testicular deficiency. Male-type nuclei in skin biopsy (19)
8	36	+	0	Normal or low	Tubular fibrosis; Sertoli cells only	Scrotal, small	0	Scleroderma for 1^1_2 years. Azoospermia 7 yrs. previously.
9	19	+	0	Low	Tubular fibrosis; spermatocytes I present	Scrotal, small	0	Hypogonadotropic hypogonadism
10	58	+	+	High	Tubular fibrosis; undifferentiated cells, spermatogonia and Sertoli cells	Scrotal, small	0	Congenital testicular deficiency (20)
11	22	0†	+	Normal or low	Hypospermatogenesis	Scrotal, normal	0	Mental retardation

12	28	0	0	High	Hypospermatogenesis	Scrotal, normal	0	Azoöspermia
13	29	0	0	—	Maturation arrest at spermatocyte I	Scrotal, normal	0	Azoöspermia
14	38	0	0	—	Tubular fibrosis; Sertoli cells only	Inguinal (bilateral) small	0	Azoöspermia
15	21	0†	0	—	Normal	Scrotal, small	0	Oligospermia
16	19	0	+	—	Normal	Scrotal, normal	0	Familial gynecomastia. Male-tyep nuclei in skin biopsy.

+ = present; 0 = absent; — = not available.

* Assayed by a slight modification of the method of Klinefelter, Albright and Griswold (18). Normal value 5 to 50 m.u.u./24 hrs.

† Hypogonadism clinically suggestive but unverified.

disorders and from two in whom the clinical manifestations were consistent with testicular dysfunction but whose testes were normal histologically. As indicated in Table I, there were five cases of the Klinefelter syndrome (Cases 1–5). Three other patients exhibited a Klinefelter syndrome-like condition. Two of these (Cases 6 and 7), previously reported (19), were brothers with congenital familial testicular deficiency. The third (Case 8) manifested a testicular disturbance for at least seven years prior to the appearance of scleroderma for which he was currently under observation. Additional cases included instances of hypogonadism due respectively to idiopathic hypogonadotropic hypogonadism (Case 9) and to a previously reported (20) congenital testicular defect (Case 10), two patients with hypospermatogenesis (Cases 11 and 12), one with maturation arrest at the primary spermatocyte stage (Case 13), and one with bilateral cryptorchidism (Case 14). Testicular biopsy was performed in Case 15 because of an eunuchoidal appearance, small penis, small soft testes and oligospermia. Normal testicular histology was encountered in this patient as well as in another with familial gynecomastia (Case 16).

The patients ranged from 19 to 58 years of age. Clinical manifestations of hypogonadism, gynecomastia, elevated urinary gonadotropins and small scrotal testes were frequently present.

Fresh testicular tissue obtained by biopsy, usually bilateral, was fixed in formalin or Bouin's solution. Sections were prepared in routine fashion and stained with hematoxylin and eosin. Skin specimens were treated according to the procedure described by Moore, Graham and Barr (3). The nuclear chromatin was studied under oil immersion. The most suitable cells for this purpose are those with relatively clear vesicular nuclei in which mitotic activity is minimal or absent. Testicular cells which satisfy these requirements are the interstitial cells of Leydig and the Sertoli cells. Excluded from the study were patients whose testicular sections contained cells which could not be read because of technical imperfection.

RESULTS

Typical sex-chromatin bodies, identical with those encountered in the nuclei of females, were demonstrated in the Leydig cells of three of the five patients with classical Klinefelter's syndrome (Cases 1, 3 and 5). Although these individuals manifested clinico-pathologic evidence of hypogonadism, their androgen deficiency was quite consistent with otherwise normal male structures. The histopathologic pattern in the testes of these patients was characterized by varying degrees of fibrosis and atrophy of the seminiferous tubules. Those tubules which still retained a lumen were lined by Sertoli cells exclusively. No cells of the germinal series could be identified in these patients. Conspicuous masses of Leydig cells were present.

Female nuclear morphology could not be demonstrated in two other patients with the Klinefelter syndrome. The clinical and testicular histopathologic features of these individuals closely resembled those with chromatin-positive nuclei except in one respect. Spermatogonia and primary spermatocytes were pres-

ent in Case 2, while a rare tubule in Case 4 revealed all the cells of the germinal series.

Three other patients (Cases 6, 7, and 8) with hypogonadism, advanced defects of the seminiferous tubules and prominent accumulations of Leydig cells also failed to manifest female-type nuclei. It is of interest that the unobliterated tubules in these specimens contained Sertoli cells only. The clinico-pathologic features of these individuals superficially resembled those of the patients with the Klinefelter syndrome.

Female sex chromatin could not be identified in the testes of any of the remaining cases. It should be pointed out, however, that Leydig cells were not present in the sections obtained from the two men whose hypogonadism was due respectively to idiopathic gonadotropic failure of the adenohypophysis (Case 9) and to a congenital testicular defect (Case 10).

Although all of the testicular sections from the 16 patients contained abundant numbers of "readable" Sertoli cells, female sex chromatin could not be recognized in any of their nuclei.

Male-type epidermal nuclei were present in three patients (Cases 6, 7 and 16) who were subjected to skin biopsy. The Leydig cell nuclei of these cases were also chromatin-negative.

SUMMARY AND CONCLUSIONS

1. A characteristic body of sex chromatin is encountered in the cells of normal females but not in those of normal males. The sex chromatin pattern was studied in the testicular biopsy sections of 14 patients with various testicular disorders and in two others with suspected but unverified male hypogonadism.

2. Typical female nuclear morphology was identified in the Leydig cells of three patients with the Klinefelter syndrome. It was not present in two others with classical Klinefelter's syndrome, in three men with Klinefelter syndrome-like disorders, or in the remainder of the group examined.

3. The significance of a female sex-chromatin pattern in the nuclei of testicular Leydig cells is not clear. This finding suggests that genic or chromosomal factors may play a role in the pathogenesis of certain instances of the Klinefelter syndrome.

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DR. GEORGE BAEHR

Dr. George Baehr, physician, scholar, soldier, administrator, social minded civic worker, contributor to medical science from lymphoma to typhus fever, from lupus to transfusions, past president of the New York Academy of Medicine, Commanding Officer, Base Hospital # 3 in World War I, Medical Director of Civil Defense in World War II, leader in a courageous program to extend the boundaries of medical care to the masses, founder of the Consultation Clinic and the Clinico-Pathological Conferences, past president of the Medical Board of our hospital and of this association, to you we award this Jacobi Medallion.

DR. SAMUEL KARELITZ

Dr. Samuel Karelitz, round of face, sparkling-eyed, came to us filled with boundless enthusiasm and insatiable curiosity. A pioneer in the treatment of intestinal intoxications in infants by intravenous infusions, you also contributed to the use of immune globulins in the prophylaxis of measles. A clinician in direct descent from, and in the tradition of, Jacobi, Koplik, Schick and Bass, a fearless fighter for the welfare of your less distinguished brethren, to you we present this Jacobi Medallion.

DR. ELI MOSCHCOWITZ

To Dr. Eli Moschcowitz, who combines the traits of a noble physician and loyal son of Mount Sinai, bibliophile, pathologist, teacher, world traveler, honored brother of a distinguished Mount Sinai surgeon, and prestidigitateur extraordinaire; aptly deserving the appellation conferred upon St. Luke—The Beloved Physician; the award of this Jacobi Medallion has been made.

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GLOMERULOSCLEROSIS

PAUL KIMMELSTIEL, M.D.

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It must be remembered that the original description of a nodular glomerular lesion was based on purely morphologic observations and that a correlation of eight such instances with diabetes, hypertension, and nephrosis could be no more than tentative. We safely qualified the conclusions, therefore, awaiting with much apprehension to have them confirmed from other quarters or to find them to be a stillborn. Reports of similar cases, gradually but slowly, appeared in the literature until it finally became clear that the glomerular lesion was very closely

diabetes, namely, those taking place in the parietal layer of Bowman's capsule and in the tubular basement membrane.

Beginning with the nodular glomerular lesion, much emphasis has lately been put on capillary aneurysms which are believed by some to constitute the initial change. This concept was first presented by a German pathologist (Hückel) and later emphasized by Ashton and by Friedenwald and Becker, who believed that the aneurysms in retinal vessels are fundamentally of the same nature as the lesions in the glomeruli.

I do not believe, however, that the histogenesis of these two processes is identical. In the first place, retinal aneurysms are saccular, glomerular capillary dilatations are fusiform or cylindrical, and it is a matter of choice whether one

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wishes to refer to them as true aneurysms. Secondly, we have no proof that glomerular aneurysms in the human antecede the formation of spherical nodules. The impression gained from a large number of cases seems to point toward the opposite direction. We have therefore no tangible evidence to presume that the nodules originate from deposition of PAS (Periodic Acid-Schiff) positive substance into the dilated capillary lumen. In fact, if that were the case, we would expect them in the periphery and not in the center of lobules, for it is only the peripheral capillary which is occasionally found to be dilated. It also seems to me that the experimental proof quoted by Friedenwald, Becker, and others still requires further confirmation before such far-reaching conclusion can be drawn.

The lesions produced by cortisone in rabbits have a certain resemblance to diabetic glomerulosclerosis but certainly cannot be identified with the human lesions. Most of the photomicrographs are not even suggestive and the aneurysms produced in this manner are not observed in human kidneys. It is possible that the time factor in these experiments may play a role, for Bloodworth has shown that these glomerular lesions are transient, but it is yet too early to accept these glomerular changes, partially resembling certain features of diabetic glomerulosclerosis, as equivalent to the lesions in humans. I would not go as far as Ricketts, who states that "a method of experimentally producing capillary lesions resembling those of human diabetes has finally been discovered."

Then there is the recent wave of lipoid enthusiasts, whose experiments I have watched with great interest. The lipoid deposits are prominent in human diabetic glomerulosclerosis and were observed from the very beginning. The role that they play in the pathogenesis is still to be explored. Certainly there is no consistent parallelism in the blood level of lipoids or even macro-lipoprotein molecules and the occurrence of glomerulosclerosis in diabetes. If hypercholesteremia does occur, we don't know whether it is primary or whether it is secondary to the renal lesion. The only tangible evidence was given by Hirsh (in 1953) who observed a sharp transient rise of fatty acid esters parallel to elevation of blood sugar. Hartrofft with choline deficient rats, produced fat emboli from fat cysts in the liver into glomerular capillaries which finally converted into PAS positive spheroid nodules resembling diabetic glomerulosclerosis. The results of these experiments, however, can hardly be compared to human disease. They could not be produced in mice.

It seems that our attention has been drawn away from the one lesion which is specific and pathognomonic, namely, the central lobular nodule and focused on capillary aneurysms in the periphery which are not consistently present in humans, and, if present, are not specific. Further experimental work may bring us closer to the goal.

The next structure involved is the parietal layer of Bowman's capsule. Here the deposit of a "wax-like" material underneath the epithelium is observed which is entirely homogeneous in the beginning and pathognomonic at this stage, but which later becomes fibrillary and organized by connective tissue at which time its histologic characteristics become less and less specific.

The specificity of the capsular lesion is not fully realized. Robbins, in fact,

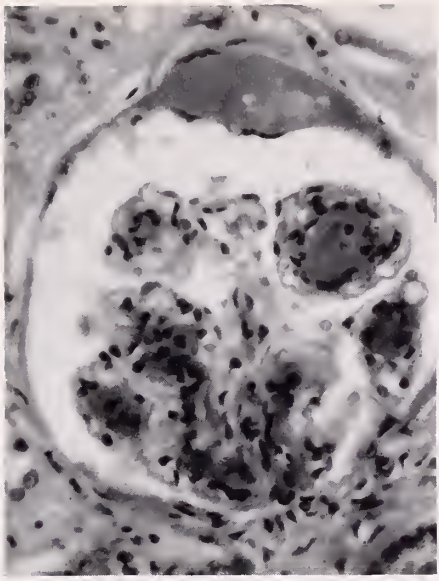

FIG. 1. Deposition of waxy material under epithelium in parietal layer of Bowman's capsule.

believes it is nonspecific. My own observations published in 1952, however, are in full agreement with Koss and Barrie, who stated independently that these capsular deposits are specific for diabetes.

Finally, there is a thickening of tubular basement membrane which is not as well studied as the two other changes. McManus was the first to emphasize this change. It is difficult, however, to establish this lesion as being specific for diabetes, particularly since a thickening of this membrane occurs under numerous conditions, specifically in conjunction with tubular atrophy due to relative ischemia. If one examines these cases, however, one can observe that hyalinization of tubular basement membranes in diabetic glomerulosclerosis differs from other similar processes in that it is often peculiarly patchy in distribution, not referable to a recognizable pathologic process in an arterial branch, that the thickening is irregularly segmental within the involved tubule, and that it precedes epithelial changes, particularly atrophy. In this respect it resembles amyloid deposits. We recently observed a case in which this change was so pronounced that diabetes was correctly suspected from histologic sections, even though no glomerular lesions were found.

The common denominator of these three lesions—I now infer—is that the protein-carbohydrate-lipid mixture is deposited where the epithelial basement membrane or its counterpart in the glomerulus is in immediate juxtaposition to collagenous tissue. The term "collagen" is used here in a broad and rather poorly defined connotation. This juxtaposition is obvious in tubules and in the parietal membrane of Bowman's capsule. In the glomerulus, however, I must postulate—as Fahr has already done—a tubular- and capillary-basement membrane. If you

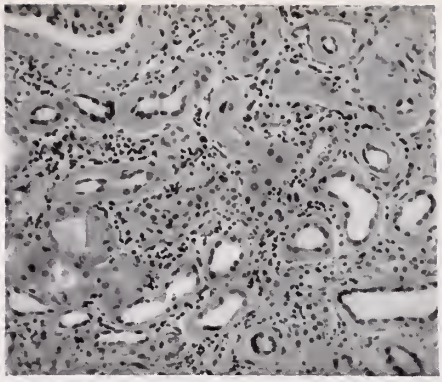

FIG. II. Marked hyalinization of tubular basement membrane

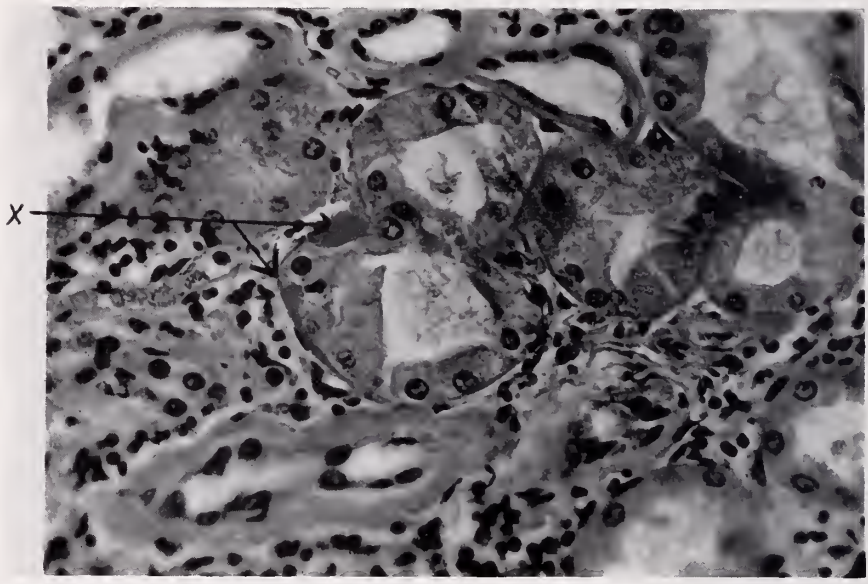

FIG. III. Hyalinization of tubular basement membrane without significant changes of epithelium. (×)

accept this, and we have much indirect reason to do so, it follows that the only area where this can take place in the glomerulus is a point of reflection of the epithelial membrane from one capillary lobule to the next, i.e., in central portions comparable to the mesentery of the intestine.

The idea of a double membrane stems from embryologic considerations, namely, the invagination of capillary loops into the end of the tubule, the basement membrane of which would cover the capillaries like the peritoneum covers the intestines. Histochemistry and differential staining have given added, though perhaps somewhat equivocal, evidence to this concept. Differences between epithelial and endothelial basement membrane can be made out by comparison

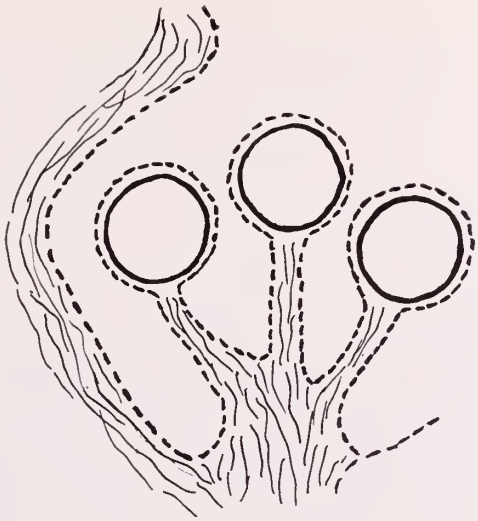

FIG. IV

of PAS, aniline blue, and silver stains, by pectinase treatment prior to PAS stain or counterstains with colloidal iron. The findings with the electron microscope are still somewhat conflicting. Some authors seem to have demonstrated actually two membranes (Dalton), others only one. Even if both membranes seem to have amalgamated into a microscopically indivisible unit it does not follow that the epithelial and endothelial components are biochemically or functionally one and the same.

In fact, it is reasonable to assume that the two cellular layers, differing in their specific functions, intimately attached to the opposite surfaces of the membrane, are likely to be involved in its formation or at least affect its surface function in their respective manner. Rinehard, for instance, reports a mucoid coat originating from epithelial cells on the outer surface of an endothelial basement membrane.

At any rate, it is only at the "hilus" of the capillary loop that the epithelium and its respective portion of the basement membrane comes in contact with a tissue structure different from that in the peripheral portion of the capillary. Whether this tissue structure is true mesangium in this portion of the glomerulus is not relevant to our problem because the fact remains that collagen is frequently

deposited here in increasing amount, parallel to age and arteriosclerosis, a process to which I have descriptively referred as axial thickening. The electron microscopists have interpreted the cells in these areas as accumulations of syncytial endothelial elements rather than fibrocytes or fibroblasts, but it seems that irrespective of its origin, collagen-like material appears at this site, which is the only area in the glomerulus where contact is made with the epithelium and its portion of the basement membrane.

According to this hypothesis, then, the specific changes take place in the epithelial basement membrane at the point of its contact with mesenchymal collagen, or, if you wish, in the epithelial layer of the basement membrane in the glomerulus, thus accounting for its peculiar and pathognomonic position. This is in contrast to the nonspecific lesions which take place in the vascular and mesenchymal apparatus of the kidney and elsewhere manifesting themselves as accelerated vascular sclerosis, as axial thickening and in the glomerulus as the diffuse type of diabetic glomerulosclerosis, related to changes in the basement membrane or that portion of this membrane belonging to endothelial cells. In reality, of course, both types of glomerulosclerosis frequently occur together.

These two types of glomerular involvements seem to reflect our concept of diabetes as a complex metabolic disorder which involves more than just abnormal carbohydrate metabolism resulting from insulin deficiency. It is true that glomerulosclerosis does not develop parallel to age, but specifically depends on the duration of demonstrable disturbances of carbohydrate metabolism. If the lack of insulin, however, were the decisive responsible factor for the development of specific diabetic glomerulosclerosis or the acceleration of arteriosclerotic processes, then vascular-renal changes would be preventable by proper control and there should be a proportionate relation between the severity of diabetes in terms of insulin requirement and severity of vascular-renal disease. We know, however, that the latter is not true. In fact, diabetic glomerulosclerosis cannot be related to the severity of diabetes. Further, Dolger has shown that proper balance of carbohydrate metabolism does not prevent the delay or onset of renal or retinal changes. Others, particularly the Joslin group, have taken the opposite point of view, but the consensus now is that even though the severity of renal lesions may parallel the severity and duration of glycosuria, the many exceptions to this rule prove that unknown factors enter into the complicated metabolic disturbances of diabetes. We should therefore look upon diabetes as a metabolic disease, the earliest clinical manifestations of which are frequently, though not invariably, referable to insulin deficiency.

This concept of diabetes as a metabolic disorder characterized by the combination of a specific disturbance of carbohydrate metabolism, i.e., insulin deficiency, and a nonspecific factor of a rather vague and yet undefined nature is reflected in the glomerular changes which are of a specific and of a nonspecific type. It is the latter, together with accelerated arteriosclerosis, which may take an independent, progressive course, irrespective of the insulin control. It occurred to me that the specific morphologic changes take place in the epithelial layer of the glomerular tufts in contact with mesenchyme in the parietal layer of Bowman's membrane and in the tubular basement membrane.

INTERCAPILLARY GLOMERULOSCLEROSIS

A Clinico-Pathologic Study

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Most of the recent studies of the pathologic lesions of the kidney associated with diabetes mellitus have emerged from institutions for the care of the chronically ill, where older patients in the terminal stages of diabetes and its complications tend to accumulate (1). In an attempt to gain a more dynamic concept of the progression of intercapillary glomerulosclerosis, it was felt that a study of the kidney lesions in all degrees of development, with a correspondingly varied clinical picture might be of value. Our hospital population and postmortem material appeared suitable for such a study, since diabetics of all ages with varying degrees of severity and progression of their diseases are encountered. In the majority of cases, the diabetes is associated with or even incidental to, a different major medical or surgical problem to which the patient ultimately succumbs.

MATERIALS AND METHODS

A consecutive series of 109 postmortem cases where diabetes mellitus had been reported as a clinical diagnosis were surveyed. These were encountered in the last 1,454 postmortems, an incidence of 13.3 per cent of diabetes mellitus among our autopsies in the last two and one-half years.

The kidneys of each of these cases were examined by one of us (H. M.) for all pertinent pathologic changes, and the other (G. B.) gathered the available clinical data on this series and correlated it. Neither was aware of the findings of the other until both studies were completed and compared.

Several newer techniques of investigation were applied to supplement the microscopic study of these kidneys by routine stains. First, the Periodic Acid-Schiff stain was used to outline the basement membranes of the glomerular capillaries and to indicate the presence of mucoproteins or mucopolysaccharides (2). Secondly, a new modification of the Mallory stain, known as the Aniline-blue Chromotrope-2R method of Rocque (3) has been employed to indicate differences in chemical nature or colloidal state or possibly both, in some of the kidney deposits.

The most fruitful method has been that devised by Drs. Churg and Grishman (4) for their studies of glomerular morphology. This consists of the preparation of extremely thin sections, between 0.5 and 1 micron thick, to which phase microscopy can be applied for evaluating finer structural details. The special

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stains mentioned above can also be used with striking results in these thin sections.

RESULTS

A pathologic diagnosis of Intercapillary Glomerulosclerosis (ICG) was made only in the presence of a fully developed hyaline nodule characteristically located

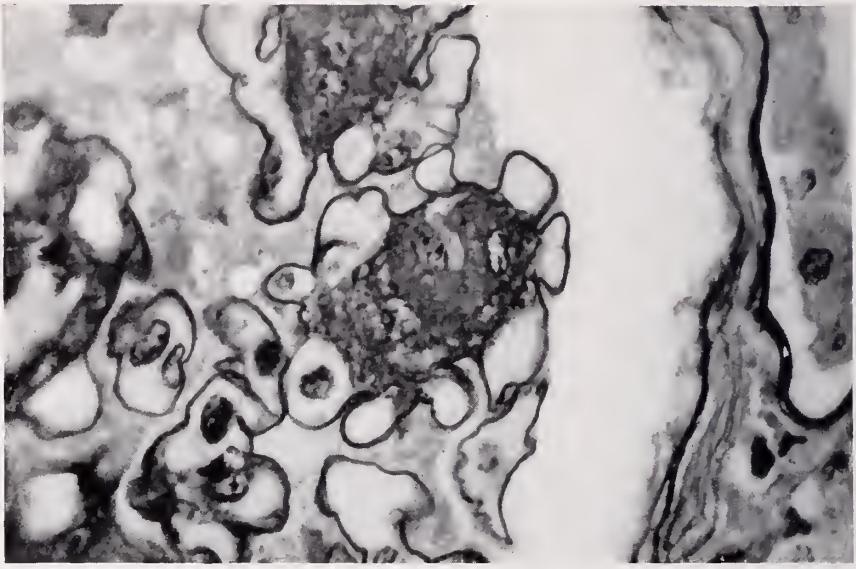

FIG. 1. Nodule of intercapillary glomerulosclerosis surrounded by wreath of patent capillary loops. Thin section, P.A.S. technique, × 870.

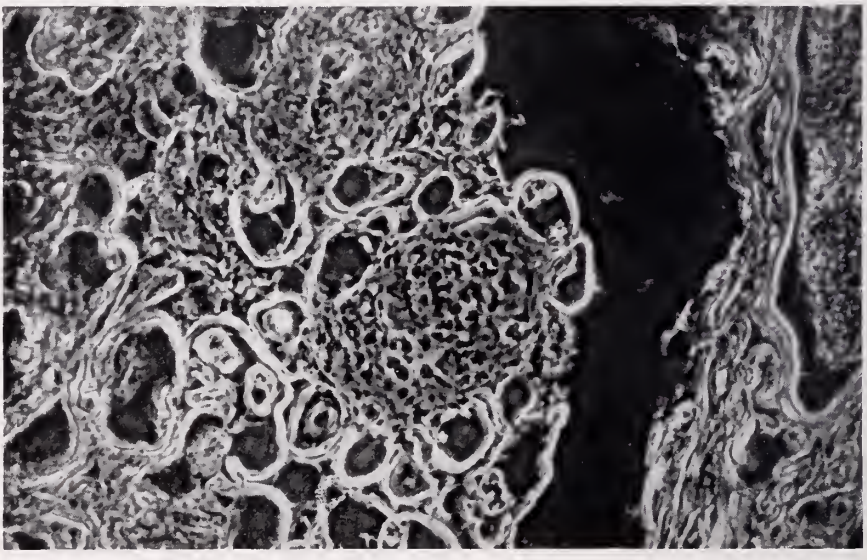

FIG. 2. Same nodule under phase microscopy. Note the increased visibility of the thick outer and the thin inner basement membranes of the capillaries. Thin section, × 870.

in the glomerulus. All other associated pertinent changes were recorded, however. 35 cases of ICG were found in this group of 109 postmortems, an incidence of 32.1 per cent. This figure is similar to the 33 per cent found by Allen (5) in a comparable study performed 15 years ago at this institution. These were further

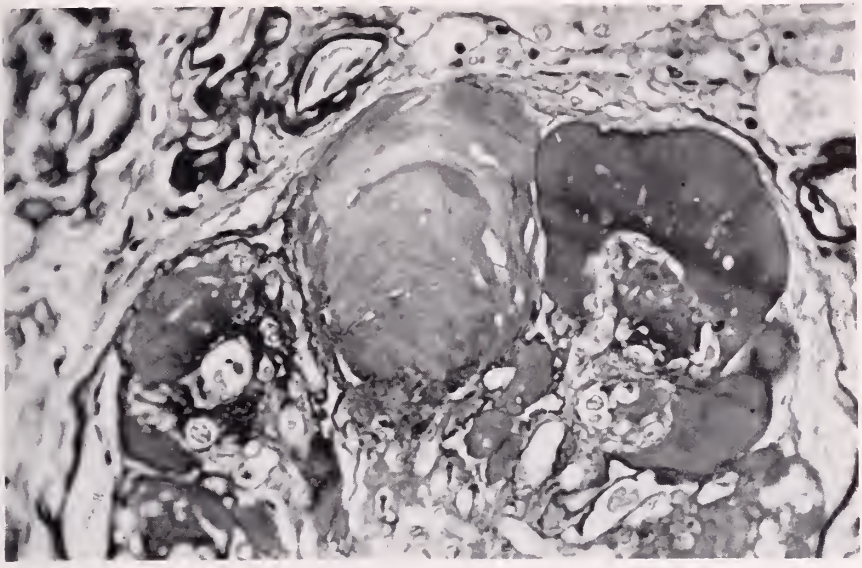

FIG. 3. Advanced intercapillary glomerulosclerosis. Note the large lamellated I.C.G. nodule in the center of the field, and the dilated capillary loops filled with hyaline eosinophilic material to its right. Thin section, P.A.S. technique, × 385.

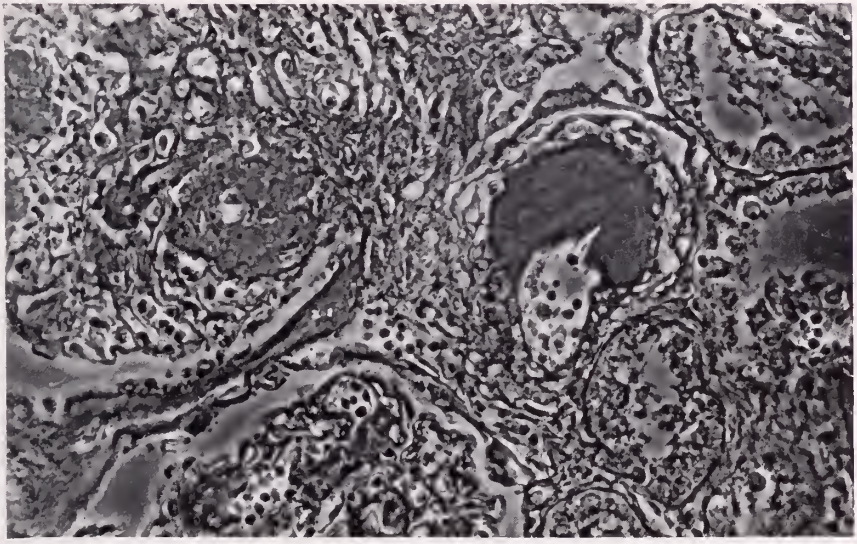

FIG. 4. Afferent arteriole of glomerulus showing hyaline sclerosis of its wall similar in appearance to the "hyaline-fibrinoid" material in the dilated capillaries of Figure 3. Thin section, phase microscopy, × 385.

classified as mild or severe with respect to the number of glomeruli involved and the degree of change of the individual glomeruli. Nine per cent were classified as mild, and 23 per cent displayed the full-blown pathologic picture.

No significant relationship to sex was observed, the same slight preponderance of females being noted as in the entire series of diabetics. Similarly, no relationship to age was found, with the exception of the slightly greater frequency of the lesion in diabetics dying below the age of fifty. Fifteen of these were included in our series, of which 7, or 47 per cent had ICG, practically all of severe degree.

The severity of diabetes as judged from the insulin requirement or the frequency of episodes of acidosis or coma, had no apparent statistical significance in the development of the kidney lesion. A definite relationship to the known duration of the diabetes was seen, however. In cases where diabetes was present over 10 years, the incidence of ICG was 51 per cent, and over 20 years, 67 per cent. Even in cases of diabetes of age less than 50 years, 6 of 7 cases of ICG gave a history of clinical diabetes longer than 5 years, and 4 longer than 15 years.

Hypertension, as estimated from the clinical record or from the gross weight of the heart at autopsy, in the absence of significant valvular lesions, was found in 76 per cent of the cases of ICG as compared to 57 per cent of the control diabetics, a difference of no statistical significance. Under the age of 50 years however, the presence of hypertension appears to have greater diagnostic import, since 86 per cent of these younger cases of ICG reveal elevated blood pressure in comparison to 38 per cent of the control series of the same age level.

Albuminuria, considered clinically significant in estimated quantities of 2 plus or more, was found in 71 per cent of cases of ICG and only in 33 per cent of diabetics without this kidney lesion. Here again this finding is of much greater significance in the younger diabetic, where all of the cases of ICG below 50 years of age displayed albuminuria in contrast to only 14 per cent of the control diabetics of the same age group.

The importance of renal insufficiency as a diagnostic feature of ICG could not be established in this series, since some degree of blood urea nitrogen elevation was recorded in a high percentage of the entire group of diabetics. This was not considered unusual, since so many factors, both renal and extrarenal contributed to this abnormality in this group of patients who came to necropsy. The more severe degrees of renal insufficiency however, were associated with ICG and again appeared of greater significance in the younger diabetic.

Edema was also a completely unreliable clinical feature, being noted in 34 per cent of the cases of ICG, but by far the greater number were dependent in type and associated with congestive heart failure.

Retinopathy was similarly not recorded frequently enough clinically, especially with detail as to type, to be of diagnostic significance.

An attempt at correlation of the pathologically proven cases of ICG with the classical triad of hypertension, albuminuria, and edema, with the added findings of retinopathy and renal insufficiency was made. With these strict clinical criteria, only 9 of the 35 cases of ICG or 26 per cent, were recognized, leaving 74 per cent undiagnosed. Some of these undiagnosed cases were of even greater

pathologic severity than those which could be established clinically. Of even greater significance was the finding of 3 cases displaying the classical triad of symptoms among the control series of diabetics, a false positive error of 4 per cent.

We have therefore tentatively concluded that no specific clinical syndrome could be attributed (with any reasonable degree of certainty) to the presence of this renal lesion, but the duration of the diabetes, and the presence of hypertension, and especially albuminuria, were the most closely related clinical findings (6). However, in the younger diabetic, (below the age of 50 years) these findings appear to have much greater diagnostic value for the presence of ICG (7).

PATHOLOGIC FINDINGS

In a consideration of the pathology of the kidney in diabetes mellitus, gross examination as expected, usually reveals no significant differences of weight or appearance which can serve to distinguish those involved by ICG from uninvolved organs.

One of the most striking microscopic findings in the kidneys of patients with diabetes mellitus, is the moderate to severe degree of hyalinization of the afferent arteriole. This change appears as a bright red homogenous smudging of the wall of the vessel by the Aniline blue-Chromotrope method, very different from the fibrillar purple-red staining of the characteristic nodule of ICG. It is well known that this change is accelerated in diabetes and in severe degree is almost pathognomonic (8). This lesion was found in over 70 per cent of our total series and was present in all cases of ICG. However, such a high incidence tends to detract from any hypotheses about its relationship to ICG except possibly as a contributory factor. Numerous severe cases of afferent arteriolosclerosis in diabetics of this entire group were completely free of the nodular lesion.

Of interest also was the finding of many examples of similar sclerosis of the efferent arteriole. This change appears to be more closely related to, and specific for diabetes mellitus (5,8). However, its true incidence and relation to ICG cannot be evaluated without the use of serial sections, since the efferent arterioles are so difficult to identify in the random section. This change may also act as a contributory factor in the formation of the nodular lesion, possibly by elevating the pressure in the glomerular capillary loop.

A large proportion of the glomeruli showed a diffuse thickening and hyalinization of the intercapillary space similar to the change described by Bell (7) and by Laipply et al (9). This has a fibrillar blue-staining uniform appearance with the Aniline blue-Chromotrope method. Over 50 per cent of the cases of diabetes mellitus showed this change. All of the cases of ICG were associated with some degree of diffuse glomerular sclerosis, but it was also found without nodular thickenings in other kidneys of this group. It is felt that this alteration is not as specific for diabetes as is the nodular lesion, since it is seen frequently in the benign nephrosclerosis of non-diabetics and in chronic glomerulonephritis. It may therefore be only an expression of the severe arteriolosclerosis so prevalent in diabetes.

The true nodular lesions which are pathognomonic of ICG vary in size from 20–120 microns and in distribution from a single well formed nodule in a microscopic section, to 3–4 in every glomerulus. The smaller lesions appear homogeneous, but the larger ones display a definite fibrillar or lamellar architecture, which is accentuated by the silver staining method (5). With the Aniline blue-Chromotrope technique, the smaller lesions appear as purplish-red areas in the intercapillary spaces of the peripheral capillary loops of the glomerulus. As the lesions increase in size, they pass thru a mottled reddish-blue stage, ending in the final large fibrillar blue mass. All of these nodules, large or small, have a peripheral ring or halo of patent capillaries, some of these being dilated to aneurysmal proportions.

With the progression to the more severe degrees of involvement by nodular masses, varying numbers of the glomeruli apparently undergo complete hyalinization and obliteration. In the end stages, practically all the glomeruli may be obliterated, with only a few remaining sufficiently recognizable to show the characteristic hyaline ball of ICG. Even the hyalinized glomeruli however, remain of large size and in some the outlines of previous nodules can still be made out. This is in marked contrast to the process of glomerular obliteration and shrinkage occurring in nephrosclerosis or chronic pyelonephritis. Sommers and Warren have also shown by newer methods of ultraviolet microscopy, that the hyaline glomerulus in diabetic glomerulosclerosis differs markedly in ultraviolet absorption behaviour and probably therefore in chemical composition, from those in other conditions. (10).

In many of the partially obliterated glomeruli, brightly eosinophilic masses or lakes of hyaline material were noted. These stain bright red with the Aniline blue-Chromotrope 2R method, and appear almost identical in tinctorial reaction to the smudged wall of the sclerotic afferent arteriole. They sometimes display red blood cells, or vacuoles trapped in their midst and are highly positive for fat on frozen section. Closer study, made possible with the thin section techniques, special stains and phase microscopy, appears to demonstrate that these represent precipitated or agglutinated substances within the intact but aneurysmally dilated capillaries of the glomerular tuft, probably as a result of obstruction to blood flow and stasis in these capillaries. This is evidently an intermediate step in the progressive hyalinization of the glomerulus involved in ICG, and is the lesion variously referred to as exudative glomerulosclerosis or the hyaline-fibrinoid lesion described by Koss (11).

It is our feeling that the nodular lesion of ICG is reasonably specific for diabetes mellitus (6). It is thought to develop as a result of some abnormal permeability of the capillary wall, possibly due to a metabolic change in the basement membrane. There is some evidence that diabetes mellitus affects the metabolism not only of glucose, but possibly of all the more complex structural mucopolysaccharides and mucoproteins, of which the capillary basement membrane is only an example (12). The formation of microaneurysms in the capillaries of the retina in diabetics may be analogous to this change (13).

As a result of this abnormal permeability, some of the constituents of blood plasma may escape into the intercapillary tissues or mesangium, and deposit

there in increasing amounts to form the nodular lesions of intercapillary glomerulosclerosis. These then undergo progressive alteration in chemical composition and colloidal state with the final stage being represented as the hyalinization of the nodule produced, as illustrated by the tinctorial changes of the Aniline blue-Chromotrope stain. Obstruction to capillary outflow is produced by the mass, with capillary dilatation and stasis, precipitation of the contents leading to eventual obliteration of the lumen, and complete glomerular hyalinization as described above.

In correlating the clinical and pathologic findings in this series, it appears that some of the earlier and more constant symptoms such as albuminuria may be found associated with the nodular lesions, and capillary stasis. The more advanced degrees of renal insufficiency, and more severe signs and symptoms of diabetic nephropathy are evidently a result of the end stages of this process, when glomerular stasis and hyalinization become prominent, and few of the individual nodular lesions remain visible. This may account for some of the discrepancies hitherto reported, in the attempts at establishing a definite clinical pattern as an expression of the pathologic lesions of intercapillary glomerulosclerosis.

SUMMARY

1. One hundred and nine postmortem cases of diabetes mellitus occurring in 1,454 consecutive necropsies, an incidence of 13.3 per cent were reviewed. The clinical and pathologic features of these cases were studied independently, and an attempt was then made at clinico-pathologic correlation.

2. Thirty-five cases of intercapillary glomerulosclerosis or 32 per cent were encountered in this group of diabetic patients.

3. The presence of intercapillary glomerulosclerosis does not appear related to age or sex and is not proportional to the clinical severity of the diabetes. However, there is a direct relationship to the duration of the diabetic symptoms, a greater incidence being found in those whose clinical course is of long duration, even among the younger diabetics.

4. From the clinical standpoint, only nine of the 35 cases, or 26 per cent, displayed the classical triad of hypertension, albuminuria, and edema. Three patients who had the triad were among the diabetics without the specific pathologic lesions in the kidney.

5. Hypertension, and especially albuminuria in the younger diabetic, (i.e., below the age of fifty, are much more diagnostic of the Kimmelstiel-Wilson lesion, when other specific renal disease such as glomerulonephritis can be ruled out.

6. A morphologic study of the development of the diabetic renal lesions was undertaken, employing the newer staining methods associated with thin section techniques and phase microscopy.

7. The Kimmelstiel-Wilson lesion is specific for diabetes mellitus. It is thought to occur as a result of metabolic changes in the basement membrane permitting transudation and accumulation of materials in the intercapillary space or mesangium with progressive glomerular damage and final obliteration.

ACKNOWLEDGMENT

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Note: Illustrations reprinted from Churg, J. and Grishman E. *Amer. Jour. Path.* 29: 199, 1953, by the courtesy of Drs. Churg and Grishman, and the *American Journal of Pathology*.

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THE KIMMELSTIEL-WILSON SYNDROME

Pathological Considerations

JAMES BERKMAN, M.D.*

In the twenty years which have elapsed since intercapillary glomerulosclerosis in diabetic patients was described by Kimmelstiel and Wilson (1), diverse opinions have been expressed regarding the nature and significance of this lesion (2). From the viewpoint of the clinician, the questions of whether a specific renal lesion is found in association with diabetes mellitus and whether its presence can be recognized clinically are chronically recurrent. Critical review of Kimmelstiel and Wilson's original description and illustrations of the glomerular lesion makes it clear by comparison with other reports that certain of the differences of opinion, and the confusion, originated in the failure of some subsequent observers to delineate the morphological lesion in terms as precise as those originally proposed. When meticulous histological criteria are applied, it becomes quickly evident that there are specific glomerular capillary alterations in patients with long-term diabetes, the morphological characteristics of which distinguish them for all practical purposes from simulating lesions in nondiabetic individuals, and from nonspecific glomerular alterations in diabetic kidneys (3).

This lesion, the nodular form of glomerular hyalinization, is now generally accepted as pathognomonic for diabetes. Its essential feature is a focal clumping of hyaline material which appears to intervene between the lumens of glomerular capillaries in an axial distribution. Very few to almost all glomeruli may be involved, and those affected are usually of average size to somewhat larger than usual. When fully developed, the distinctive lesion is nodular and fairly well circumscribed. It is composed of acidophilic hyaline material which occupies the center of a glomerular lobule, and consistently spares that side of the capillary wall on the outer surface of the loop. This axial distribution is striking and constant, and almost certainly reflects factors of histogenetic significance (4). Nodular lesions may be homogeneous, vacuolated, fibrillated, or lamellated. Overdistended capillaries are commonly seen marginally. Adjacent capillaries may be normal with intact capillary walls and lumens of normal patency, or their walls may be diffusely hyalinized to varying degrees, with corresponding narrowing of lumens, at times to the point of obliteration.

It is with regard to, and on account of, the so-called diffuse type of intercapillary glomerulosclerosis (5) that variations of opinion have arisen regarding the existence and incidence of a distinctive glomerular lesion in diabetic patients. These differences do not involve the question of the occurrence of a diffuse form of glomerulosclerosis, but its definition, recognition and specificity. This type of disease is actually more common than the nodular form, and may be found alone or in association with the pathognomonic lesions. Unfortunately, when found alone, the histological features are simply not sufficiently characteristic

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to allow differentiation from alterations which may simulate them in diabetic and nondiabetic individuals, whereas the presence of the nodular lesion is an almost unmistakable anatomical landmark of diabetes. In those cases in which it is found in patients said to have been nondiabetic, the adequacy of the clinical diagnosis is to be questioned.

Thus, twenty years after the description of the nodular Kimmelstiel-Wilson lesion, there is practically complete acceptance of its specificity as an anatomical vascular lesion of diabetic patients. It is not found in all patients with diabetes, nor is every glomerular alteration in the kidney of a diabetic individual a specific one. Nodular lesions are found in about one-third of long-term diabetics, and represent but one aspect of renal vascular disease in diabetes mellitus. Sparse classical lesions may be found in the absence of symptoms reflecting their presence. They rarely, if ever, occur as isolated lesions but as a rule are found in association with various degrees of arterial and arteriolar sclerosis. Not uncommonly, when the correlation between clinical and pathological findings is made, the striking feature is the extensive renal arteriolar sclerosis and its concomitants. In such cases one may be impressed by the apparent relative unimportance of the hyaline glomerular nodules as compared to the effects of disease of arteries and arterioles (6).

The clinical patterns associated with severe renal vascular disease in diabetic patients vary correspondingly (7), and in some instances, occur in patients in whom nodular lesions may be absent or appear unimportant. The point to be made is that there is no single anatomical lesion which accounts for the clinical "Kimmelstiel-Wilson syndrome." Nevertheless, there is a relatively simple laboratory procedure which has allowed the selection, during life, of those patients in whom one can with a reasonable degree of assurance expect to find nodular glomerular hyalinization histologically (6). This is the finding in the urinary sediment of doubly refractile intracellular lipids containing cholesterol as well as Sudanophilic fat. It has been emphasized that this laboratory finding in itself is a nonspecific one, characterizing the urinary sediment of patients with a nephrotic syndrome of any cause. It should also be emphasized that while relatively simple to perform, this laboratory procedure is subject to errors as is any other. However, if properly correlated with accurate clinical data, and if every refractile body in the urinary sediment is not interpreted as intracellular, birefringent, and lipoid in nature, this procedure is an extremely useful diagnostic aid. In our experience, doubly refractile lipids are absent from the urinary sediment of patients with even severe renal arterial and arteriolar sclerosis alone, in the absence of diabetic glomerulosclerosis, and it is almost always in such cases that diagnostic problems are raised.

While the clinical and morphological features of the renal vascular lesions in diabetes have become well recognized, much remains to be known about the pathogenesis of the glomerular capillary lesion. Certain data pertinent to this question have been uncovered. The argyrophilic trypsin resistant material which composes the fully developed nodular lesion has the staining characteristics of collagen (8), sometimes contains Sudanophilic fat (9), and is rich in carbohydrate

(10). It has a specific ultraviolet absorption pattern (11). The application of recent advances in histochemical and microscopic techniques seems to favor the initial localization of this material to the capillary wall rather than to an intercapillary space, but has not resolved this question (2). The axial distribution of nodular lesions is striking and constant and must have histogenetic implications, which in the present state of knowledge are best related to the existence of an axial space. From time to time, reports have appeared of various experimental glomerular lesions in animals, resembling human diabetic glomerulosclerosis. Of great current interest is the "cortisone" lesion in rabbits (12). None of these appear to represent the counterpart of the human nodular Kimmelstiel-Wilson lesion. Similarly, the role of adrenal cortical hyperfunction (13), and the significance of disturbances of serum polysaccharide concentrations in patients with diabetic glomerulosclerosis (14) remains to be determined. It may be said in summary that the available data at least point out certain directions for the pursuit of further understanding of a syndrome which now ranks among the foremost as a cause of death in diabetic patients.

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THE KIMMELSTIEL-WILSON SYNDROME: CLINICAL ASPECTS

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The clinical manifestations and significance of the capillary vascular lesions in diabetes mellitus have been the subject of many recent publications. The specificity of the clinical syndrome has been questioned. There is little doubt that a fully developed clinical syndrome characterized by diabetes, edema, hypertension, proteinuria, azotemia and diabetic retinopathy is noted in approximately 10–15 per cent of the patients with the specific nodular lesion of the glomerulus (1–6). Unfortunately, a number of other situations may give rise to a similar sequence of symptoms and signs. This includes diabetic patients who happen to have arteriosclerotic heart disease, hypertensive cardiovascular disease or chronic pyelonephritis with superimposed congestive heart failure; or patients, who in addition to their diabetes develop other etiologic bases for a nephrotic syndrome, such as renal amyloidosis, or nephrotic glomerulonephritis, or the rare case of co-existing diabetes mellitus and renal vein thrombosis or diffuse collagen disease.

The problem of the accuracy of the clinical-pathologic correlation has been a subject for discussion in almost all of the reports subsequent to Dr. Kimmelstiel's now famous paper. There is no doubt that the pathologist frequently cannot show us characteristic nodular glomerular lesions in patients who, during life, had been clinically diagnosed as having a typical Kimmelstiel-Wilson syndrome. This is well illustrated in a recent paper published three years ago by Drs. Rogers and Robbins on material analysed at the Boston City Hospital (Fig. I) (6). A probable diagnosis was made on the presence of a triad of physical findings—namely, edema, proteinuria and hypertension. A possible diagnosis was considered in the presence of proteinuria and hypertension, but without edema. One is impressed by the relatively high percentage of incorrect diagnoses in terms of positive clinical impressions and lack of histologic confirmation of the specific lesion. This was essentially our experience more than ten years ago when we first began to study this disease, and it was felt then that more objective criteria were needed. We have already described the value of doubly refractile lipoid cells and casts in the urinary sediment in helping to further establish the diagnosis (7). It is true that this finding is relatively non-specific in the sense that they are found in the urine of almost any case of nephrotic syndrome, regardless of the etiology. However, if properly correlated with other clinical data, this simple tool can be a most valuable diagnostic aid. We have had many visitors from other diabetic clinics and hospitals who seem to have found these cells in almost any type of urine. With a little care and interpretation, however, and simple instruction in technique, much confusion has been dissipated.

Another objective method for confirmation of diagnosis during life appears to be the recently introduced renal biopsy (8). A positive finding is most rewarding;

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Results in Cases Listed as "Probable"

Clinical Findings:

Albuminuria	Hypertension	Edema	No. of Cases	No. Correct	No. Incorrect	Per cent Error
2–4+	Minimal to marked	Generalized	4	3	1	
3–4+	Minimal to marked	Dependent	22	17	5	
Total			26	20	6	24

Results in Cases Listed as "Possible"

Clinical Findings:

Albuminuria	Hypertension	Edema	No. of Cases	No. Correct	No. Incorrect	Per cent Error
3+	Moderate to marked	None	6	2	4	
4+	Minimal to moderate	None	9	6	3	
Total			15	8	7	47

From Rogers, J. and Robbins, S. L. (6)

FIG. I

a negative one, however, does not exclude the diagnosis since the fragment of tissue obtained on biopsy may not be representative of the kidney parenchyma.

The reverse problem, namely, the existence of anatomically proven cases which are not identified during life, presumably because of the paucity or lack of clinical findings, is a well known observation. The reasons for this are manifold. First, it is possible that insufficient attention is paid to relatively insignificant abnormalities, namely, a trace of albumin or a borderline hypertension. Second, edema may not be present, since its rate of accumulation may be impeded by marked restriction of salt intake. Third, perhaps insufficient anatomic involvement is present, and this may be insufficient to produce increased permeability

to protein. And finally, perhaps a reappraisal is in order of this so-called lack of association between clinical and pathological findings by closer attention of the clinician during the life of the patient with careful follow-up at the autopsy table—since almost all the reports which stress this negative correlation are based on study of autopsy protocols and clinical charts in retrospect.

A most important problem facing the clinician is a determination of what constitutes the earliest clinical signs of the disease. This is particularly significant since any future medical or surgical regime may already be too late to affect already irreversible lesions. Perhaps, repeated use of the ophthalmoscope may give us valuable information, since it has been repeatedly stated that patients with retinal micro-aneurysms already have renal involvement morphologically in spite of the absence of any clinical or laboratory findings pointing to glomerular disease. The studies of Ashton (9) in England and our own late Doctor Jonas Friedenwald (10) have indicated that although all patients with diabetic glomerulosclerosis have retinal micro-aneurysms, the reverse situation does not exist, since only 58 per cent of patients who microscopically demonstrate retinal micro-aneurysms have characteristic nodular diabetic glomerulosclerosis. The findings of Wilens and associates (11, 12) on human material, and the recent demonstration of Hartroft (13) in choline-deficient animals indicate that increased lipid deposits in the glomeruli may be etiologically related to the development of the characteristic lesion. Perhaps, then, a really orderly and systematic study by experienced and careful observers in a diabetic clinic, where many young diabetic patients are observed serially during the course of their lifetime, would disclose the presence of doubly refractile lipoid in the urine to be a relatively early finding, rather than a late manifestation of the disease as we have previously considered it to be. It might just be possible to find patients who have had their disease six or eight years with no other clinical stigmata, except possibly a tiny retinal microaneurysm or a small resorbing hemorrhage or residual exudate—these would be the ideal patients to observe for these lipoid droplets.

Perhaps serial renal biopsies may be helpful, since Iverson and his co-workers have shown the presence of so-called diffuse lesions co-existing with diabetic retinopathy, in the absence of the nodular lesion. It is questionable whether pathologists would agree that such diffuse lesions are conceivably the forerunners of the nodular lesion, which the Scandinavian workers as well as some of our own people have recently claimed.

The amelioration of diabetes as the renal lesion progresses, and the rarity of acidosis in the course of the diabetic patient's lifetime were first pointed out by Zubrod and his associates of the Johns Hopkins Hospital (14). This has since been challenged by many clinicians who have large numbers of such diabetic patients under their care. While it is true that many patients with diabetic glomerulosclerosis tend to develop a diminished insulin requirement as the disease progresses, similar findings can be observed with diabetics who develop a wide variety of other non-specific renal diseases. The more likely explanation would appear to be a marked diminution of caloric intake, rather than a specific metabolic disturbance. A report recently appeared from the Boston City Hos-

pital in which this problem was carefully re-investigated (15). The results indicated that the insulin requirement varied considerably in different patients with the Kimmelstiel-Wilson lesion, and further, that frequent episodes of diabetic acidosis had occurred in the past histories of these patients. No real differences existed between diabetic patients with and without the specific renal lesion. Essentially this has been our experience.

In terms of pathogenesis, the argument still continues to rage concerning the effects of control of diabetes on the development of renal and retinal lesions. This is a difficult task to really evaluate since definition of control varies so widely in diabetic circles. Granted that a high incidence of severe diabetic retinopathy and nephropathy is associated with poor levels of control, one must still be cognizant of the fact that a fair percentage of patients with good control defined even under the most rigid criteria, develop extensive vascular damage. A recent paper by Root and co-workers (16) indicates that while it is true that retinopathy was either absent or minimal in approximately 75 per cent of patients with long-standing diabetes who maintained a "good" level of control, it is nevertheless of interest that close to 25 per cent of patients with a similar "good" degree of control exhibited moderately severe, marked or extreme retinopathy. Furthermore, 33 per cent of patients with a "poor" degree of control had little or no evidence of retinopathy (Fig. II).

It has now been firmly established that the duration of diabetes is an important

RETINOPATHY IN 189 PATIENTS WITH DIABETES OF TWENTY TO TWENTY-NINE YEARS' DURATION

Degree of Control	Number of Cases	Per cent of Cases	
		No, or Slight, Retinopathy	Moderate, Marked or Extreme Retinopathy
Good	32	76	24
Fair	41	52	39
Poor	116	33	67

From Root, H. F., Pate, W. H., Jr., and Frehner, H. (16)

FIG. II

factor (17). The time factor, however, varies considerably from as little as six years to as long as 20 or 25 years. It is not surprising, therefore, that all short-term attempts at the experimental production of retinal and glomerular lesions have thus far failed to reproduce the typical lesions noted in human diabetes. I do not believe that most pathologists would be willing to accept the lesions which have been produced either by alloxan (18), partial pancreatectomy (19), various steroid combinations (20), homologous serum globulin (21), B12 or choline deficiency (12, 13), as representative of human diabetic glomerulosclerosis.

Some interesting biochemical alterations have been described by both our group at Montefiore Hospital as well as by other investigators (22–34). Because of the presence of both mucopolysaccharides and increased lipids in the retinal and glomerular lesions, studies of these substances, as well as of the various protein fractions, both in blood and urine, have been performed and have al-

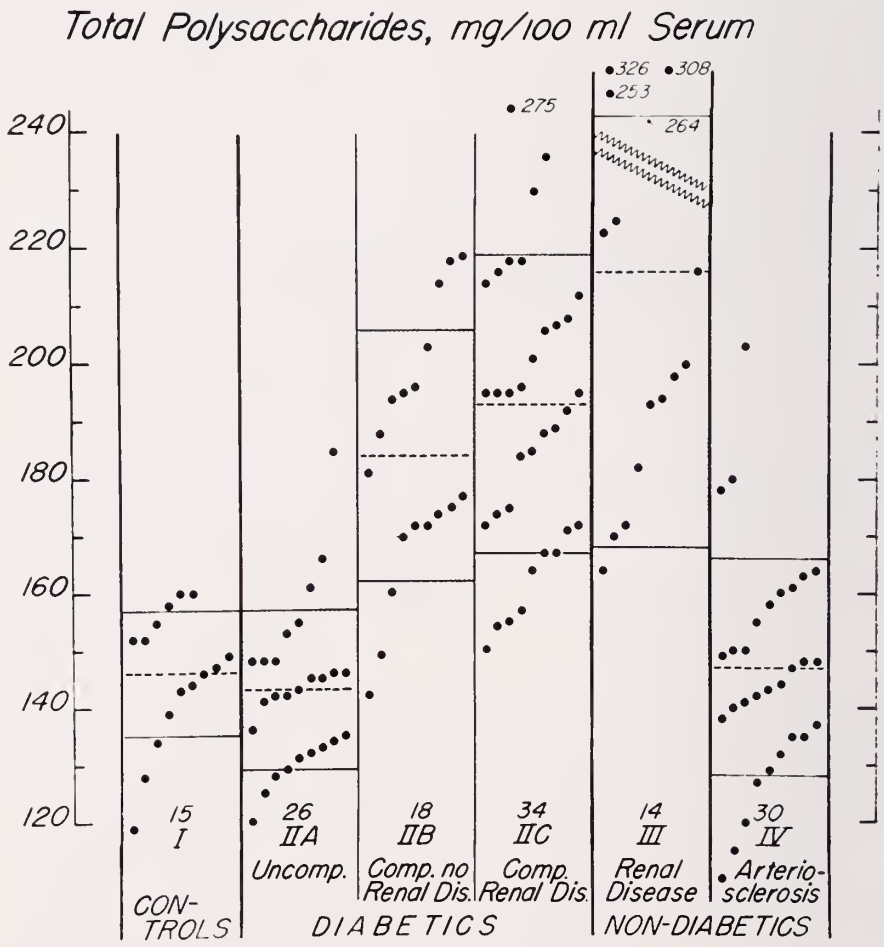

Fig. III

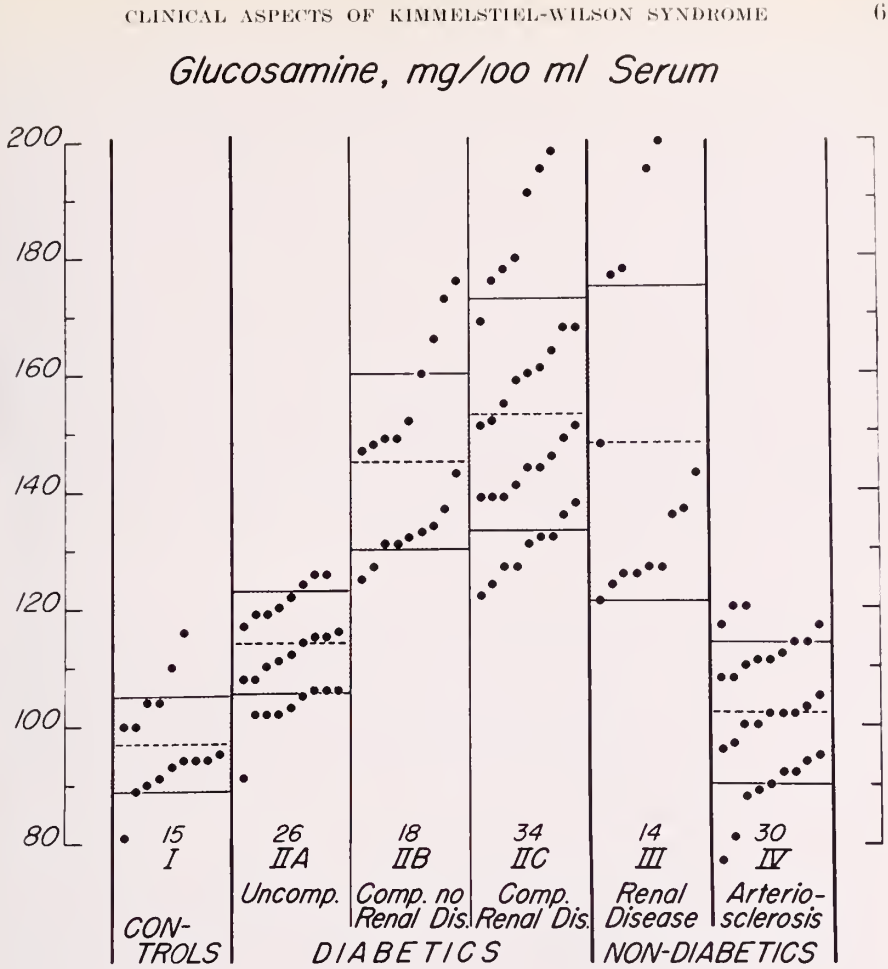

FIG. IV

ready been reported in the last five years. Serum glucosamine and protein-bound carbohydrates have been examined in the sera of diabetic patients with a variety of vascular lesions (22–26). Higher levels of these substances are noted in diabetic patients with retinopathy and nephropathy than in normal controls and uncomplicated diabetes (Figs. III, IV). The present evidence, however, is too fragmentary to allow a definite causal relationship of these substances to the renal and glomerular lesions. The knowledge that renal insufficiency per se, as well as tissue destruction and repair, leads to an elevation of these factors makes us cautious in interpreting these results. Serial studies in the course of the diabetic's progress, prior to the development of the specific vascular lesions, are necessary data before further conclusions can be drawn. Further studies, particularly in the purification and composition of these mucopolysaccharides, are clearly indicated.

Similarly, studies of the various serum lipid fractions and lipoproteins have been carefully studied (27–33). Conflicting data have appeared in the literature.

Recently we have made a correlative study of serum lipids and serum mucopolysaccharides in uncomplicated diabetic patients and diabetic patients with retinopathy and nephropathy (34). The serum cholesterol, lipid phosphorus and total lipids were usually elevated in patients with the fully developed Kimmelstiel-Wilson syndrome. In diabetic retinopathy, the serum cholesterol and lipid phosphorus, by and large, remained within the normal range, but the total lipids were elevated. The significance of these results is as yet unclear. There has been much speculation concerning the role of the lipoproteins and conflicting data appear in the literature. We have recently completed a study of these substances measured both by electrophoretic and ultra-centrifugal techniques. The Sf 12-50 class of lipoproteins are elevated in the fully developed Kimmelstiel-Wilson syndrome, but in patients with diabetic retinopathy there is a wide scatter of values ranging from normal to moderate increases. On the surface, this variation would appear to be related to the extent of associated renal insufficiency. This will be investigated with more subtle techniques in estimating renal function.

Finally, a word about the relationship of pituitary and adreno-cortical influences on these lesions, particularly since surgical procedures, such as hypophysectomy and bilateral adrenalectomy, are already being performed in an attempt to either ameliorate or halt the progress of these lesions (35–37). Much evidence from the clinical, experimental, and therapeutic standpoints has been marshalled to indicate that a possible relationship exists between increased pituitary-adrenal cortical activity and the development of the specific vascular lesions (38–40). Previous attempts to evaluate the level of adrenal cortical activity in diabetic patients, based on crude measurements of urinary ketosteroids or corticoids, have yielded discordant results; the outputs ranging from abnormally low to abnormally high values. It is conceivable that the methods employed by previous investigators for the estimation of the urinary metabolites of the adrenal hormones were inadequate for the detection of subtle evidences of adrenal-cortical hyperactivity. In association with Dr. Lieberman of Columbia University, we have and are continuing to measure the individual urinary metabolites arising from the secretory products of the adrenal cortex (41). Initially, we have measured the individual ketosteroids, but we are now in the process of studying the more abundant urinary corticoids, such as Compounds E, F, Tetrahydro E, Tetrahydro F, and the newer more highly oxygenated steroids, namely, Cortol and Cortalone.

Time does not allow for more than a brief summary of our findings. Diabetic patients with retinopathy and nephropathy have been found to excrete normal amounts of C 19-11 oxysteroids which are primarily derivatives of Compound F. When considered in the light of the impaired renal clearance of these patients, these so-called normal amounts may possibly be considered to be excessive. It is quite true that this observation may simply reflect a selective difference in the manner in which the kidney handles this class of steroids, although no such selective mechanism for the excretion of any group of steroids has ever been described. To obtain further possible evidence of adrenal hyperfunction, measurements of both free and conjugated corticoids were performed on plasma obtained from a number of these patients. No significant deviation from values

found in control subjects was noted. This finding, as is well known, is not incompatible with increased adrenal function. To test the responsiveness of the adrenal cortex in patients with Kimmelstiel-Wilson syndrome, ACTH was administered in 40 mgm. doses intravenously to several patients with diabetic retinopathy and nephropathy. The blood corticoids, the total identifiable ketosteroids, and the individual urinary ketosteroids rose in a manner quite indistinguishable from that observed with normal controls. It is much too early to come to any conclusions yet, but we hope to accumulate more data in the near future.

In conclusion, much remains to be learned. At present, no real therapeutic regime is available. One feels helpless and disturbed in the presence of these blind, bloated and uremic victims of long-standing diabetes. It is our hope that perhaps from meetings such as Dr. Dolger has arranged tonight, will come some glimmering of light which may ultimately lead to a fuller understanding of the physiologic and biochemical processes underlying this disease state—which Dr. Paul Kimmelstiel brought to our attention just 20 years ago.

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GASTROINTESTINAL AMYLOIDOSIS

Report of a Case and Review of the Clinical and Radiological Aspects

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Although the gastrointestinal tract is reported to be the second most commonly involved organ system in amyloidosis with primary type distribution, there are few descriptions of the clinical symptomatology and radiological appearance of this disorder. A case illustrating these aspects of gastrointestinal amyloidosis, in association with multiple myeloma, is described and the relevant experience of others is reviewed.

CASE REPORT

A 52 year old white single male was well until January, 1954, when he developed a yellow urethral discharge, dysuria and gross hematuria. These symptoms improved on antibiotic therapy. One month later he noted numbness of fingers, often radiating to the forearms, with intermittent "electric shock" sensations in the same distribution. In June, 1954, he developed tender reddish-white papular lesions on the peri-oral skin, and then on the lips, tongue and buccal mucosa. An early biopsy of one of these lesions was interpreted as lichen planus. The lesions spread to involve his eyelids, nose and the muco-cutaneous junction of the rectum. He then complained of weakness of voice, dryness and thickening of his tongue. A course of bismuth therapy and then cortisone were without relief. Exertional dyspnea soon followed. A second biopsy of a lip lesion now revealed the presence of amyloid, the amorphous material beneath the epithelium staining heavily with cresyl violet.

He was admitted to The Mount Sinai Hospital in March, 1955, after a weight loss of 20 pounds during the previous year. Three days prior to admission, he experienced sudden crampy mid-abdominal pain, followed by multiple formed stools. On physical examination his temperature was 99.6°F., pulse 80, respirations 14 and blood pressure 120/75. He appeared chronically ill. There were clusters of reddish-white dry and scaly papular lesions on his eyelids, lips, dorsum and frenulum of tongue, buccal mucosa and nasolabial folds, many ulcerated and tender. His tongue was enlarged and had a glazed waxy appearance; the lateral margins of the tongue retained the impressions cast by the adjoining teeth. Rhonchi and coarse rales were heard at the lung bases. The heart was not enlarged and there were no murmurs. A firm smooth liver edge was felt 3 inches below the right costal margin. The abdomen was slightly distended and tense. Several of the lesions described in the skin were also present at the rectal muco-cutaneous junction. Hyperesthesia was demonstrated along the left thumb and radial border of the left arm up to the elbow. There was significant sacral, pretibial and ankle edema.

Examination of the urine revealed a specific gravity of 1.010, with 2 plus albumin, no sugar and 5 white blood cells per high power field in the sediment. Occasional granular casts were seen. A 24 hour urine specimen contained 3.5 Gm. albumin. The hemoglobin was

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9.4 Gm. per cent, the hematocrit 32 per cent, and the red blood count 3.64 million. The white blood count was 13,500, with 12 per cent polymorphonuclear leukocytes, 51 per cent segmented neutrophils, 24 per cent lymphocytes, 11 per cent monocytes, 1 per cent basophils and 1 per cent myelocytes. The erythrocyte sedimentation rate was 11 mm. in the first hour (Westergren). The blood urea nitrogen was 11 mg. per cent and the fasting blood sugar was 93 mg. per cent. The total serum protein was 5.1 Gm. per cent with 3.1 Gm. albumin and 3.0 Gm. globulin. The serum bilirubin was 0.9 mg. per cent, alkaline phosphatase 14.7 King-Armstrong units, cephalin flocculation 0, and bromsulfalein retention 3.5 per cent in 45 minutes. The serum calcium was 9 mg. per cent, phosphorus 3.3 mg. per cent, sodium 139 mEq./L., potassium 5.2 mEq./L., and carbon dioxide 26.2 mEq./L. The stool occasionally gave a 3 plus guaiac reaction. An electrocardiogram showed left axis deviation. An x-ray of the chest was normal. The urine proved to be positive for Bence-Jones protein on two occasions. A bone marrow examination then revealed sheets of myeloma cells, a few with double nuclei. There was amorphous material about and between islands of cells which stained with methyl violet, revealing the presence of amyloid. Fractionation of the serum globulins showed increased alpha^2 and beta globulins and decreased gamma globulins. Electrophoresis of serum protein also showed decreased gamma globulins, and electrophoresis of urine showed an abnormal peak with the mobility of alpha^2 globulin.

In the course of workup, a skeletal survey showed diffuse demineralization of bones without distinct radiolucent lesions; the trabecular structure of the ribs and long bones had a somewhat ground-glass appearance. A cystogram and intravenous pyelogram were essentially normal but a biopsy of the trabeculated bladder showed edematous, acutely inflamed mucosal fragments with amyloid deposition in the blood vessel walls. A gingival biopsy, however, revealed only chronic inflammation.

FIG. 1

A flat film of the abdomen demonstrated gas in random fashion throughout the small intestine. A GI series revealed abnormal trapping of barium in the hypopharyngeal recesses. There was no evidence of intrinsic disease within the esophagus, stomach or bulb aside from suggested thickening of the antral folds along a short segment of the greater curvature. Peristalsis of the stomach was active. The small bowel series (fig. 1) demonstrated coarse generalized thickening of the mucosal pattern from the duodenum to the terminal ileum. At the end of 10 hours about 50 per cent of the barium column was still in the small bowel. A barium enema showed no organic lesion of the colon.

In evaluation of intestinal absorption a glucose tolerance test showed a mild diabetic pattern. In a vitamin A tolerance test, the control serum level was 48 gamma per cent, with values of 55 gamma per cent in four hours, 66 gamma per cent in six hours, and 68 gamma per cent in eight hours, interpreted as low normal absorption. A blood carotene level was 123 gamma per cent, a normal value. Serum phospholipids were 123 mg. per cent. Total cholesterol was 198 mg. per cent and cholesterol esters 144 mg. per cent.

During his hospital stay he was a problem in nutrition. He complained of soreness of the mouth and tongue which limited his choice of foods. He also suffered with upper abdominal crampy and sharp pains, increased in severity on deep inspiration. His electrocardiogram showed no evidence of myocardial damage and his venous pressure was well within normal limits. Nausea and vomiting became prominent; constipation was marked. His vomitus contained flecks of blood. Small amounts of food caused immediate discomfort. He was always bloated and his abdomen distended, but bowel sounds were always heard. Subcutaneous injections of 1 mg. of prostigmine were of temporary but definite benefit. His course was progressively down-hill. He continued to lose weight, the soreness of his mouth, abdominal pains and distention became more marked, and he died three months after admission. A second small bowel study (fig. 2) was obtained shortly before his demise revealing further accentuation and distortion of the mucosal pattern previously described.

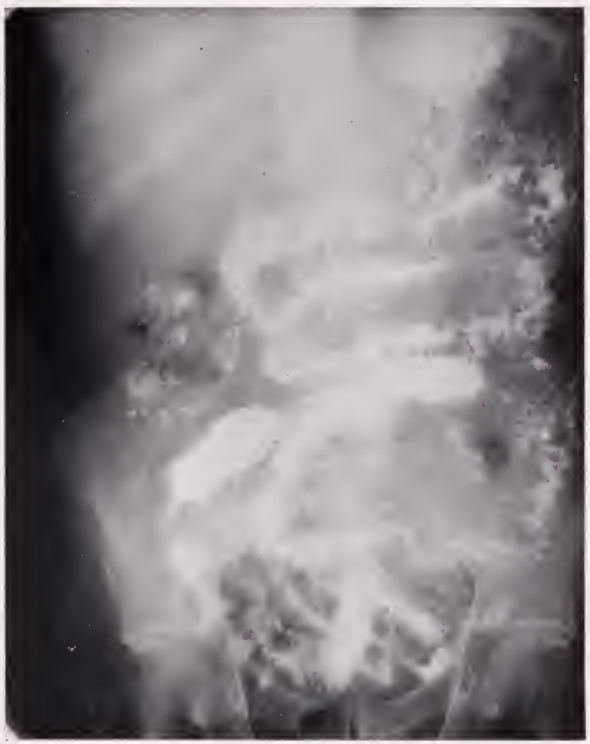

FIG. 2

Post mortem examination of the esophagus revealed pale, smooth mucosa. The cardio-esophageal junction was unremarkable, as was the pyloric ring. The entire small intestine was thickened and leathery. From the duodenum to the terminal ileum, the valvulae conniventes were shaggy, thick and very prominent, most marked in the jejunum. A reddish-brown material was easily scraped from the mucosal surface. On cut section of the thickened jejunum the muscularis was extremely pale. There were a few firm lymph nodes in the mesentery from one to 1.5 cm. thick which on section were reddish-brown. The colon and rectum were grossly unremarkable.

Microscopic examination of the small intestine revealed diffuse deposition of hyaline material, which took selective stains for amyloid in the submucosa extending into the valvulae conniventes. The muscularis and vascular walls were also diffusely involved. There was moderate amyloid deposition in the mucosa as well. Walls of serosal vessels were involved. Amyloid was present, though to a lesser degree, in the submucosa and muscularis of all other segments of the gastrointestinal tract.

Moderate amyloid infiltration of the epicardium, endocardium, myocardium, liver, spleen and thyroid was noted.

Grossly representative sections of the sternum, rib and lumbar vertebra revealed the trabecular patterns to be unremarkable. Microscopically the bony trabeculation was somewhat decreased. The marrow was somewhat hypercellular with a decrease in the fat spaces. Many of the arterioles showed an eosinophilic thickening of the interna. The cytology was one of almost exclusively plasma cells, the majority of which were mature. There was a decrease of cellular elements representing the other hematopoietic systems.

In this patient with the clinical picture of amyloidosis, multiple myeloma was discovered in the course of investigation. There was no symptomatology suggesting multiple myeloma; only the well known association of the two prompted the search. This secondary discovery of multiple myeloma duplicates the experience of others (1–3). Some authors report the fruitful search for amyloid after the diagnosis of multiple myeloma has been made (2, 4). King (5) reported the discovery of amyloidosis in 41 of 650 cases of multiple myeloma. In 1931 and 1933 Magnus-Levy (6, 7) reported 150 cases of multiple myeloma, in which significant amounts of amyloid were found in 29. Dahlin and Dockerty (2) added 21 found in literature, and in this total of 50 cases there were deposits of amyloid noted among myeloma cells in 22, as well as mild infiltration of various organs in most, a gross tumor of amyloid in 15, and general amyloidosis of the "primary" type in 11. These same authors resected 66 specimens of localized myeloma and found amyloid within the surgical specimen in 14. In two the amyloid was actually within the myeloma cell. Apitz, cited by Reimann et al. (8), suggested that multiple myeloma precedes all cases of "primary amyloidosis." Otani (9), and Reimann et al. (8) believe that multiple myeloma would be found much more frequently in patients with "primary amyloidosis" if a careful search were made. The vast majority of reports in the literature, however, concern cases in which the association with myeloma was not noted.

Involvement of the gastrointestinal tract in cases reported as secondary amyloidosis is quite uncommon. When (infrequently) gastrointestinal involvement is mentioned, it is quite insignificant compared to major involvement elsewhere. During the past twenty years at The Mount Sinai Hospital there have been twenty-one cases with predominantly secondary association and distribution (excluding cases with multiple myeloma). Of these 21, only three had symptoms

related to the gastrointestinal tract that could not be explained by associated pathology and unfortunately these three were not studied post mortem. There were four who had histological involvement of the gastrointestinal tract without previously associated symptomatology.

General Pathology. (10–12, 15, 19, 29, 30–32).

Only in the more advanced cases do the organs of the gastrointestinal tract show gross alteration. In the stomach the gastric arteries may be firm and prominent, and contain hard discrete nodules. Pinpoint granules may be seen on the gastric serosa and larger nodules scattered through the stomach wall. The muscle layers are often rigid and may appear orange in color. The mucosa may be atrophic. Similarly the small intestinal serosa is described as thickened, waxy, leathery, congested or spotted by tiny gray flecks resembling miliary granulomas; the mesenteric fat may appear gray and lusterless, suggesting fat necrosis. Tiny petechial hemorrhages can be seen. The muscle layers are usually thickened. In the most advanced the entire small bowel appears as a rigid tube possibly larger than the colon due to its thickness or dilatation. The muscle layers often contain visible gray nodules. Most commonly, only the muscle layer appears grossly involved while the serosa and mucosa are free. Submucosal hemorrhages may be prominent. The mucosal surface is occasionally interrupted by numerous transverse ridges with granular surfaces. Scattered nodules, often hemorrhagic, can be found beneath the valvulae conniventes making the folds firm and immobile. In some cases the mucosa is atrophic or edematous. In the colon the appendices epiploicae have been described as gray or of such resiliency that they project almost perpendicularly from the intestinal surface. The muscle layer may be thickened but far less frequently than that described in the small intestine. Mucosal and submucosal nodularity and transverse ridging similar to that in the small bowel have been described.

Microscopically, the most commonly described lesion is a deposition of amyloid in the medium sized blood vessels of the submucosa, less often in the adventitia, infrequently in the intima. These vessels are irregularly thickened by the pink staining nodular masses of amyloid. Giant cells are occasionally seen at the periphery of these amorphous collections. With greater involvement there may be extensive replacement of smooth muscle in the outer muscular wall and the muscularis mucosa. There are either scattered foci of amyloid, mainly in the circular but also in the longitudinal muscle coat, or the foci may be confluent and penetrate from serosa to submucosa. Nerve plexi in the submucosa have been seen to be completely replaced by amyloid. Infiltration of mucosa is usually minimal, but infrequently there is diffuse mucosal atrophy. Particularly in the stomach, necrosis of the glandular cells has been reported as well as focal atrophy with area of amyloid infiltration between gastric glands. Often subperitoneal masses of amyloid are described, as the gross pathology would indicate.

GASTROINTESTINAL INVOLVEMENT

In 1946, Eisen (10) reviewed 46 cases of "primary amyloidosis" and Matthews (11), in 1954, reviewed the same cases combined with an additional 50. Involve-

ment of the stomach was noted in 39 per cent, of the small intestine in 37 per cent, of the colon in 33 per cent, and of the esophagus in 23 per cent. As a total organ system the gastrointestinal tract was involved second in frequency (approximately 40 per cent) (10, 12); there was evidence of cardiac involvement in 53 per cent (10). Snapper et al. (13) found amyloidosis in 8 of 97 patients with multiple myeloma; all but one had gastrointestinal involvement.

We have reviewed 75 cases of "primary amyloidosis" and amyloidosis associated with multiple myeloma with significant deposition of amyloid in the esophagus, stomach, small intestine or colon. In no case was the gastrointestinal segment the only organ of involvement. In only about 30 per cent had the diagnosis of amyloidosis been made prior to autopsy. No effort was made to determine the exact percentage incidence of segmental involvement within the gastrointestinal tract, since this information was scanty when a particular segment was emphasized. Since more than half of the cases are the same as those reviewed by Eisen (10), the segmental incidence proved to be approximately the same. Symptoms also were often difficult to relate to a specific gastro-intestinal segment, occasionally to the entire gastrointestinal tract; this is understandable in that diffuse amyloidosis is usually manifest when gastrointestinal lesions are frankly demonstrable clinically or radiologically. In a significant number, however, there was little question as to the association.

Tongue. The tongue is one of the most common organs to be grossly involved in "primary" amyloidosis. Eisen (10) noted extensive involvement in 23 and moderate in 3 of 26 cases. Higgins and Higgins (32) found macroglossia in 25 of 71 patients (35 per cent); there was dysarthria associated in 18 (25 per cent). Matthews (11) reported involvement of the tongue in 37 of 98 cases, an incidence of 37 per cent.

When there is massive replacement of the musculature by diffuse or nodular masses of amyloid, the tongue enlarges and appears grey, yellow-grey, or pinkish-grey, either diffusely or in a patchy pattern. The tongue surface is usually smooth and pale but may be markedly atrophic with superficial ulcerations. The nodular protrusions on the surface are often seen. Particularly striking is the waxy consistency of the lateral margins which retain the impressions of the adjoining teeth. Infrequently, the tongue is so enlarged that the mouth cannot contain the entire mass.

Esophagus. The most frequently encountered symptom associated with amyloidosis of the esophagus was dysphagia, rarely the initial complaint. Its onset was always insidious and it progressed slowly, varying with the site and degree of involvement. In none was dysphagia the only complaint, nor was the later demonstrated esophageal deposition the only gastrointestinal lesion.

Hematemesis has not been noted in association with esophageal involvement. One case, reported by Pocock and Dickens (14), concerned a 57 year old diabetic colored male who was explored for recurrent hematemeses with the discovery of esophageal varices. The source of bleeding, however, proved to be multiple stomach erosions due to marked gastric infiltration with amyloid. This was one of the fairly common exceptions where amyloidosis of otherwise predominantly

mesenchymal distribution was sufficiently severe to cause marked hepatic involvement which was no doubt responsible for the varices. Iverson and Morrison (15) also reported a case with hematemesis in which there was found edema of the entire esophagus, atrophy of the mucosa, and complete loss of structure of the inner muscle layer of the lower third of the esophagus. There were, however, similar findings in the stomach and small intestine.

Bayrd and Bennett (16) reported a case in which ulceration was found at the esophago-gastric junction with irregular masses of amyloid deposited in the connective tissues of the muscular esophageal layers. There were no symptoms directly related to this. In the review of cases of amyloidosis at The Mount Sinai Hospital a similar case was found.

Recorded roentgen reports of esophageal amyloidosis are practically nonexistent. This may be explained partly by infrequent esophageal involvement, but more by the debilitated status caused by more generalized disease, usually present when esophageal symptoms become manifest, precluding roentgen evaluation. In the case presented here there was abnormal retention of barium in the valleculae and pyriform sinuses, with good distensibility upon performance of the Valsalva test. This finding is non-specific and considered only corroborative. The esophagus otherwise appeared normal. It is conceivable that ulcerations, tumor masses, rigidity, narrowing or a scleroderma-like picture might be seen, in view of the pathology described.

Stomach and *Duodenum*. Records of 30 cases of amyloidosis with significant stomach involvement have been found. Again, gastrointestinal amyloidosis limited to the stomach is most unusual, although radiographically the stomach may be the only demonstrable site of pathology.

Symptoms varied from vague digestive upsets to massive hematemesis and melena. The less specific complaints such as nausea, anorexia, vomiting, heartburn, belching and epigastric fullness often mimicked the symptomatology of peptic ulcer and gastric carcinoma, but they could not always be excepted from more generalized amyloid infiltration as their source. Epigastric pain was almost always associated with specific gastric pathology. Nausea and vomiting were present in 20 per cent of the 75 cases. In general, the responsible pathology was that prevalent in any area of the gastrointestinal tract, as described above.

Hematemesis occurred in 5 patients. Multiple fine gastric erosions were usually found. In the case presented by Pocock and Dickens (14), there were mucosal and submucosal ulcerations and severe hemorrhage extending between the layers of the muscular wall. Both the stomach and duodenum contained amyloid deposits in patchy masses in the lamina propria and sub-mucosa, particularly surrounding and replacing many of the Brunner and gastric glands. Radiological examination of the upper gastro-intestinal tract had demonstrated a deformed duodenal bulb and the esophageal varices only. In a second case of hematemesis, reported by Golden (17), a gastrointestinal series showed irregular narrowing of the antrum with retention. At autopsy there was a mass on the greater curvature of the pre-pyloric region with two superficial ulcers. The tumor mass was infiltrated with amyloid. A third case, reported by Steinhaus (18), also concerned

a narrowed antrum demonstrated radiologically; the pylorus was eroded and infiltrated with amyloid. The patient of Lubarsch, cited by Cooley (12), presented almost identical findings, radiologically and pathologically. The fifth report was that of Iverson and Morrison (15), where hemorrhagic edema of the stomach was noted on the basis of amyloid infiltration.

In 4 other cases, when the main complaint was epigastric pain without hematemesis, large gastric ulcers were found with amyloid deposition at the base. In the 2 with benefit of a gastrointestinal series, the ulcer was demonstrated. One was that reported by Lindsay and Knorp (19), in which a large crater 4 x 5 cm., at a distance of 4 cm. from the cardio-esophageal junction, was found. This case was also notable in that the small and large bowel were free of amyloid on microscopic examination. Radiologically and clinically the gastric lesion was thought to be a peptic ulcer. The patient improved on an ulcer regimen temporarily, but perforation occurred later and the amyloid basis of the ulcer was recognized.

The occurrence of tarry stools or massive rectal bleeding was infrequent without associated hematemesis.

Amyloidosis of the stomach is noted for mimicking carcinoma. Of the 30 cases of stomach lesions reviewed, 7 simulated malignancy radiographically and 4 still simulated carcinoma when the gross specimen was examined. In one (17) an epigastric mass was palpable. Schnider and Burka (20) described a patient who clinically had pyloric obstruction; x-ray examination of the stomach showed a narrowing of the antrum interpreted as an annular carcinoma, and at exploration an annular constriction was found. Histologically the amyloid nature of the mass was proven. Golden (17) described a case of a 66 year old colored female, the patient in whom the epigastric mass was palpable, whose x-ray examination of the stomach revealed irregular narrowing of the antrum and 50 per cent gastric retention. At exploration a white marble-like discoloration of the entire stomach was found, with a mass in the pre-pyloric region. A sub-total gastrectomy was performed. Ulcerations were noted within the mass and there was amyloid infiltration of all stomach layers.

An interesting case was that reported by Cooley (12) of a 59 year old white male with known amyloidosis for 15 years. While on ACTH therapy the patient developed post-prandial pain and abdominal distension. An x-ray of the stomach (fig. 3) showed deformity of the antrum with contraction or constriction of both the greater and lesser curvatures. A large ulcer crater 2 cm. in diameter was found on the lesser curvature. Peristaltic waves did pass through the area though sluggishly, and normal mucosal folds were present in the adjacent region of the stomach. A mass was thought to be associated and a carcinoma of the antrum was considered in spite of the known presence of amyloid elsewhere. Though five weeks after the cessation of ACTH therapy the ulcer was no longer demonstrated, the persistence of the antral distortion led to exploration which revealed a diffusely nodular stomach and nodules in the walls of the intestine and parietal peritoneum as well. The stomach was opened and a biopsy by way of the mucosa revealed infiltrating amyloid without neoplasm.

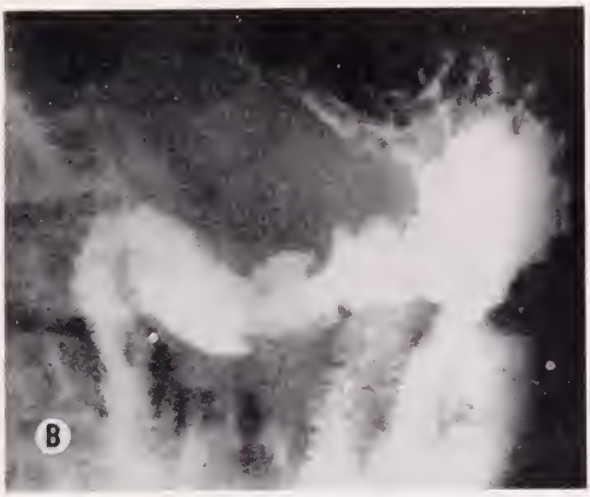

FIG. 3

Gastric amyloidosis simulating carcinoma has been found in the antral region in practically all cases; coincidentally, the antrum is also the site of greatest frequency of involvement with carcinoma. To further mislead clinically, infiltration of gastric glands with amyloid may prevent the secretion of hydrochloric acid. Amyloid infiltration does not, however, usually create the rigidity and lack of peristalsis that occurs with carcinomatous infiltration; definite abnormal radiological findings in gastric amyloidosis are probably infrequent for this reason. Relatively speaking, however, when an organic abnormality is certain on X-ray examination, the presence and degree of distensibility are considered of importance in differentiation from malignancy. This reasoning excludes lymphosarcoma, from which gastric amyloidosis is extremely difficult to differentiate.

X-ray examinations of the stomach infiltrated with amyloid have been descriptive of polypoid and nodular masses, atrophic and hypertrophic gastritis, and infiltrating and ulcerating lesions. In addition to the case of Pocock and Dickens (14), there was one other report of x-ray suggestion of duodenal ulcer which proved to be caused by amyloid (27).

Small Intestine. The frequency of amyloid infiltration of the small bowel is slightly less than that of the stomach. Occasionally it is the only segment of the gastrointestinal tract involved. The symptoms reported that are most likely associated with this specific involvement were constipation or diarrhea, distension, flatulence, crampy abdominal pain, vomiting, melena and weight loss. Progressively increasing constipation was one of the earliest symptoms. Marked abdominal distension and frank ileus were the usual late findings. All these symptoms except diarrhea and melena were prominent in the case presented here.

When amyloidosis of the small intestine becomes fairly far advanced, slowing of the transit time of the barium meal is apparent. Gottren (21) reported a case in 1932 in which the passage of the barium meal through the small intestine required five days. In the case presented here, about 50 per cent of the barium

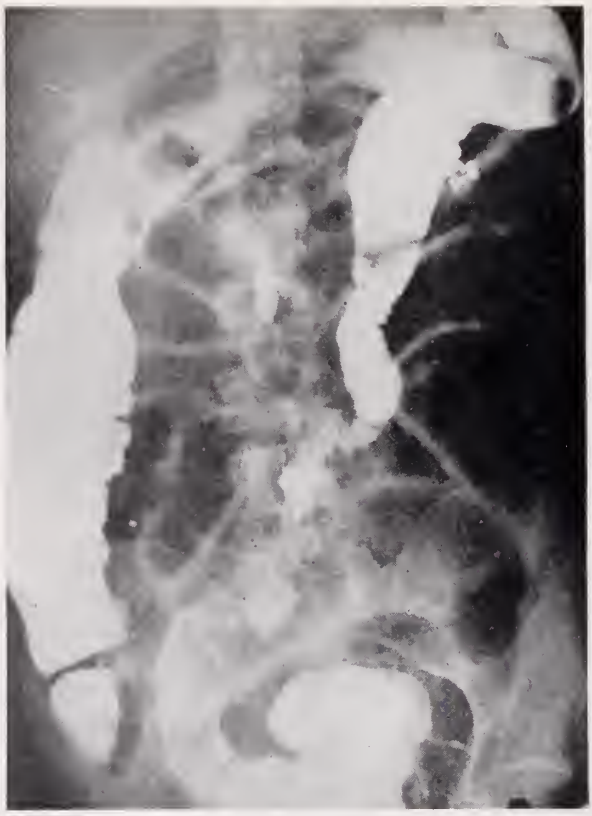

FIG. 4

was retained in the ileum at the end of ten hours. This slowing and, no doubt, the related constipation are due to the infiltration and replacement of smooth muscle with amyloid, to such a degree as to interfere with peristalsis. By the same process the muscular tone is compromised and ileus of varying degrees results.

Golden (22) cited one case of suspected mechanical obstruction of the small bowel; exploration revealed dilatation of the upper two thirds of the small intestine with no obvious cause of obstruction. Biopsy of the small intestine revealed extensive amyloid infiltration of all layers, with predominant involvement of blood vessels and nerve ganglia. Randall (23) described one patient with ileus where the small intestine was found to be larger than the colon. Large amounts of amyloid were found in the tunica muscularis, especially the circular muscle.

Gerstell (24) reported a case with successive symptoms of dysphagia, diarrhea and melena, then constipation and finally intestinal obstruction. At autopsy there was amyloid infiltration of the entire gastrointestinal tract. A portion of the small intestine measuring 80 cm. in length was striking; its walls were thickened and resembled a stiff tube. The mucosa was absent, replaced by a layer of granulation tissue which covered the muscularis mucosa infiltrated with amyloid. Pearson et al. (25) described one patient whose gastrointestinal tract was dif-

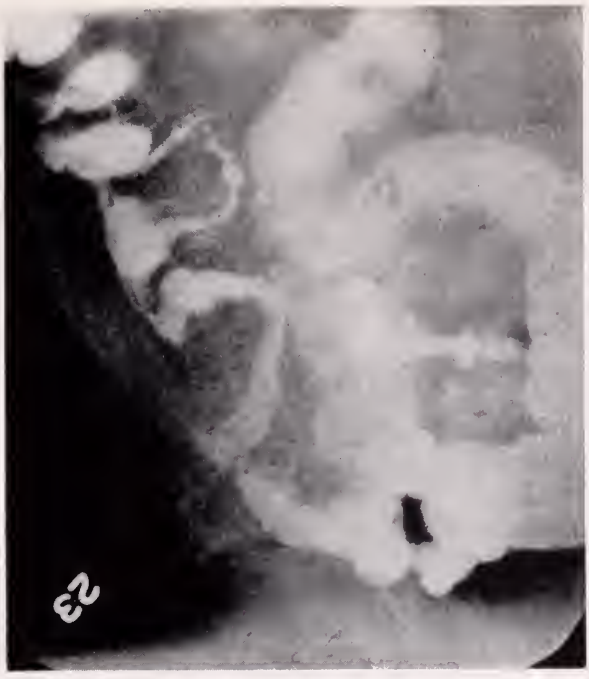

FIG. 5

fusely infiltrated with amyloid; the walls of the small intestine averaged 0.5 cm. in thickness, appearing as an irregular band of amyloid.

Golden (22) reported the case of a 42 year old man with a combination of symptoms and laboratory findings suggesting a collagen disease. Abdominal cramping pain, diarrhea and abdominal distension led to the performance of a barium enema (fig. 4), which disclosed no obstruction or abnormality in the colon but a small intestine which was dilated and distended with gas. The walls of the small intestine were thickened. These findings were again prominent in small intestinal x-ray. The patient was thought to have a paralytic ileus though small intestinal amyloidosis was considered because of the thickness of the walls. Post mortem examination revealed amyloidosis in mesenchymal distribution. The tunica muscularis of the small intestine was almost completely replaced by amyloid, especially in the upper ileum and lower jejunum. The walls were tremendously thickened. The mucosa was atrophic but intact.

An important case is another reported by Golden (22) of a 44 year old man with nausea, constipation, weight loss, anemia, albuminuria and red cells and white cells in the urine. Sigmoidoscopy revealed the picture of Grade II ulcerative colitis and x-ray studies of the kidneys showed an abnormality of the upper calyx on the right. A small intestinal study (fig. 5) disclosed both narrowed and slightly widened loops of ileum with the margins of the narrowed loops irregular and abnormal suggesting mucosal destruction. The transit time was slow. The picture was interpreted as regional ileitis. Amyloidosis in association with re-

gional ileitis was suspected clinically and confirmed by gum biopsy. Post mortem examination revealed fibrino-purulent peritonitis, a "clear" cell carcinoma of the upper lobe of the right kidney and generalized parenchymatous amyloidosis. There was involvement of the stomach, colon and ileum, however. The mucosa of the ileum was atrophic and edematous, the villi widened and reduced in height by irregular deposits of amyloid, maximum involvement occurring in the muscularis mucosae. This case is unique both in that the distribution and association of the amyloidosis would classify it as secondary type and in the radiological similarity to regional ileitis. Golden did note that the amount of amyloid in the intestinal wall was small compared to that in the case preceding where the distribution was more typical of the "primary" type. The abnormal margins of the barium shadows which were interpreted as evidence of mucosal destruction were probably the result of irregular atrophy and of irregular deposits of amyloid in the mucous membranes. Golden attributed the radiological areas of narrowing in the small intestine to spasm, since the intestine was of normal width at post mortem examination.

Golden (22) further described the concentric thickening of mucosal folds in the small intestinal amyloidosis as seen radiologically. This characteristic description was noted in Grotten's case (21). In the case presented here, the first of two small intestinal x-ray studies (fig. 1) revealed coarse symmetrical thickening of the mucosal folds, starting at the ligament of Treitz and extending to the distal ileum. A study performed two months later (fig. 2), shortly before death, showed proximal extension of the thickened folds toward the duodenum and further accentuation and irregular thickening of the folds, especially in the ileum. Slight segmentation in the ileum was also noted.

Recently we studied a patient with proven amyloidosis and multiple myeloma whose small bowel x-rays showed a deficiency pattern with occasional irregular segmentation and hypersecretion. The patient had been treated for sprue prior to confirmation of the true diagnosis.

In the few cases where melena was recorded, in addition to those with accompanying hematemesis, there was a demonstrable gastric lesion which was more likely responsible than the small intestinal lesion. In a 1949 Cabot Case (26), the pathological description of the small intestine of a patient with amyloidosis included subserosal hemorrhages and submucosal hemorrhages but normal mucosa. Frank bleeding from the small intestinal mucosa was rarely substantiated. In the case of Michelson and Lynch (3), ileus and fatal intestinal hemorrhage were described but the small intestine was not studied pathologically.

Colon. Infiltration of the colon with amyloid probably occurs as often as infiltration of the small intestine, but with rare exception it is to a much lesser degree and is infrequently responsible for symptoms. Mollow and Lebell (28) reported a case in which abdominal pain, meteorism, constipation and dysphagia were prominent. Autopsy revealed amyloid infiltration of the entire gastrointestinal tract, and very interestingly a stenosis of the sigmoid caused by local deposits of amyloid. Iverson and Morrison (15) described an extensive area of fresh necrosis and recent ulceration at the site of impacted fecal material in the lower rectum. The base of the ulcerating area was infiltrated with amyloid.

Reports of barium enema x-ray examinations revealing abnormalities of the colon or rectum due to amyloid are rare. Again no abnormality was found in the case reported here.

SUMMARY

1. Amyloidosis of predominantly mesenchymal distribution involves the gastrointestinal tract in about 40 per cent, and is second only to the heart in frequency.

2. Within the gastrointestinal tract itself, the stomach, small intestine, colon and esophagus are infiltrated with amyloid in that order of frequency.

3. Involvement of the esophagus often causes dysphagia—rarely bleeding. Pathologically, amyloid infiltration of the muscular wall is responsible. Reports of x-ray abnormalities due to esophageal amyloidosis are rare.

4. The stomach is the most frequent segment of the gastrointestinal tract to be involved in amyloidosis. Symptoms vary from vague digestive upsets to massive hematemesis and melena. A benign peptic ulcer is often suspected clinically and radiologically; the amyloid nature of the ulcer is frequently realized only at post mortem examination. The differential diagnosis of localized gastric amyloidosis and gastric malignancy is difficult though accurate observation of distensibility and peristalsis are helpful.

5. Involvement of the small intestines causes progressive constipation, distension, vomiting and ileus. The x-ray examination is characterized by delayed transit time and outstanding prominence of the mucosal folds. This picture is exemplified in the case presented. Gaseous distension, thickened bowel wall, narrowing and irregularity of lumen and segmentation with hypersecretion have been seen due to infiltration of different segments of the small intestine with amyloid.

6. Symptomatology due to colonic involvement is unlikely. Reports of barium enemata in gastrointestinal amyloidosis are rare.

7. Any defect in absorption from the small intestine infiltrated with amyloid is probably proportional to the degree of mechanical block.

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ROENTGEN FINDINGS IN DIVERTICULITIS OF THE RIGHT SIDE OF THE COLON

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The roentgen findings in diverticulitis, both acute and chronic, of the sigmoid and descending colon have been described in detail by several authors (1–3). Barium enema examinations demonstrating changes on the right side of the colon due to diverticulitis are uncommon and the possibility of making the diagnosis of diverticulitis in this area of the bowel has rarely been emphasized. It is a surprising fact that chronic diverticulitis, at any rate of clinical significance, on the right side of the colon is rare. Acute diverticulitis in this region is usually explored as a surgical emergency without prior roentgen examination. An occasional examination, however, is made in such an instance if the diagnosis is obscure or if, after exploration, confirmation or clarification of the diagnosis is desired. As a result, the changes to be described have been derived from a small group of cases. For the most part, the examinations were performed within one to two weeks after exploration. It might be noted that no complications occured as a result of barium enema examination which included not only the instillation of barium but the subsequent injection of air after evacuation. The purpose of the air injection in this group of cases was not to demonstrate small filling defects such as polyps but rather to produce as uniform distention of the involved area as possible.

In order to anticipate the nature of the roentgen findings, the pathologic anatomy of diverticulitis should be briefly mentioned. The course of events on the right side of the colon are presumably similar to those seen in the sigmoid, namely, (a) the production of the diverticulum which, in this group of cases, resembles the diverticula on the left side of the colon and appears at a point of weakness in the muscle wall. These diverticula are differentiated from larger congenital diverticula which may also lead to similar complications; (b) as a result of obstruction of the neck of the diverticulum, stasis occurs, followed by infection and a peridiverticulitis with intramural inflammatory changes which may go on to abscess formation. In other instances, when the diverticulum protrudes well beyond the wall of the bowel, perforation into the free peritoneal cavity is possible but localized abscess formation is more likely. Because the original infection is related to a single diverticulum, inflammatory changes are discrete and localized about the involved diverticulum. Inflammatory changes of a lesser degree occur in the adjacent bowel wall. The mucosal folds may be somewhat edematous and changed in their configuration as a result of the local rigidity of the wall and edematous changes but no significant ulceration or destruction of the mucosa occurs. As elsewhere in the gastrointestinal tract, in the presence of intramural inflammatory changes, irregular functional phenom-

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FIG. 1. J. K. 1A. Spot film of cecum and ascending colon in the right anterior oblique projection shows a finger-like indentation of a localized character on the postero-lateral wall at the level of the ileocecal valve. While a diverticulum may have been previously demonstrable in this area, none can be seen at this time.

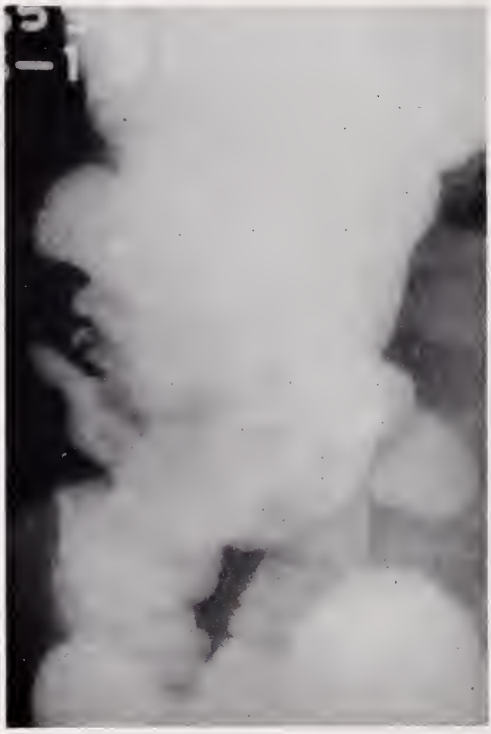

FIG. 1B. Spot film in postero-anterior projection shows that the lateral wall in this area has limited distensibility with multiple haustreola-like projections of variable size. The close spacing of these projections suggests that, in addition to limitation in distensibility of a circular nature, there is also failure to elongate normally.

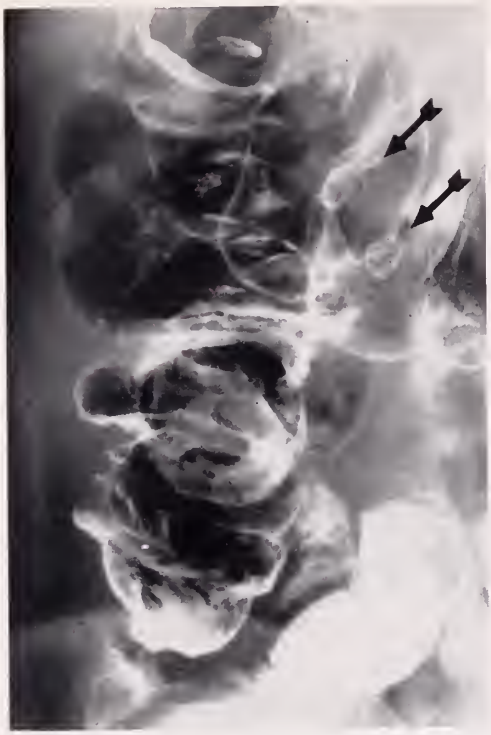

FIG. 1C. Double contrast view in the PA projection confirms the findings of Fig. 1B. The haustreola-like projections are duplicated. Typical diverticula are present in the proximal transverse colon.

ena, "spastic" changes, may be anticipated. In contrast to the sigmoid and descending colon which are of narrower caliber than the right side of the colon, circumferential or circular spasm in the cecum and ascending colon is less prominent and abnormal dynamic phenomena usually manifest themselves by irregularities in filling and emptying. Failure of the right side of the colon to elongate or to contract normally in a longitudinal direction are the most common findings. As a result of the pericolonic inflammatory changes, extrinsic fixation of the involved region would also be expected.

The most characteristic roentgen feature is the detection of a localized indentation in the distended bowel of a discrete character eccentrically located and intramural in location. (Figs. 1A, 2A, 3A, 4A and 4B). Because of the large circumference of this portion of the bowel, the optimum projection to determine the features of this defect must be found by spot radiography in various positions. The mucosal pattern over the defect is intact although the surface is often finely spiculated, the spicules corresponding to closely spaced crowded transverse folds. The defect does not have a lobulated or polypoid appearance and its base is wider than its apex directed towards the lumen. The margins of the defect join the overlapping adjacent haustra in a smoothly continuous fashion without any

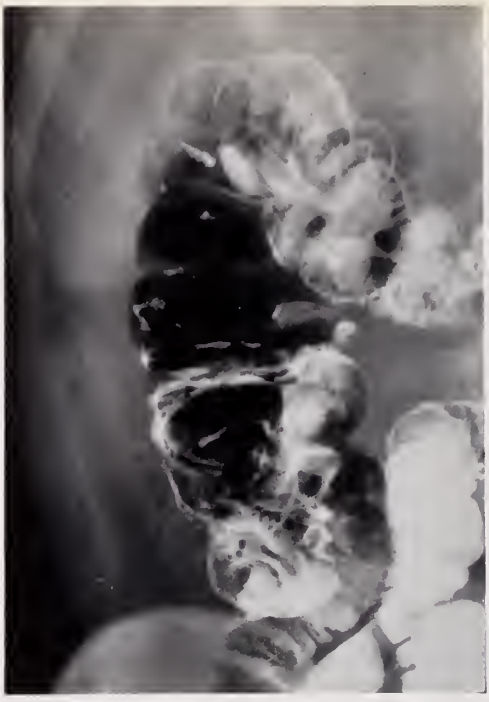

FIG. 1D. Double contrast. The lateral wall of the bowel appears considerably thickened and also somewhat mottled.

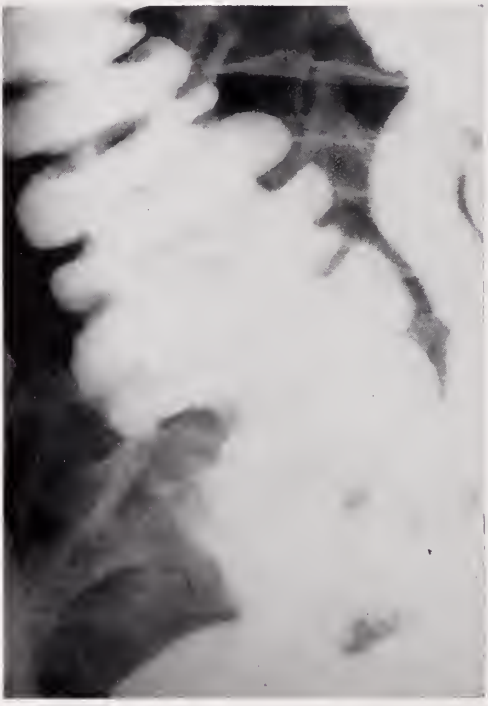

FIG. 2. D. G. Localized defect is present on the postero-lateral wall of the cecum at the level of the ileocecal valve. The luminal aspect of the defect shows a finely spiculated contour. Along the distal portion of the defect, there is a small, irregularly-shaped diverticulum with an elongated narrow neck.

FIG. 3A. G. S. Spot film shows a discrete defect on the lateral wall of the cecum with a small diverticulum immediately above it.

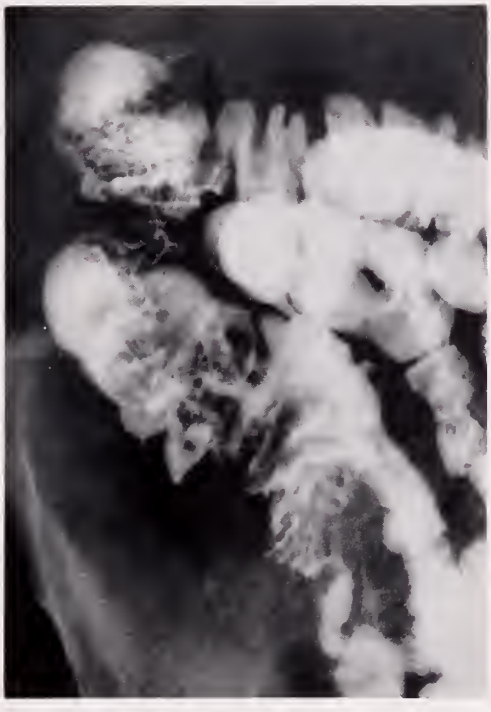

FIG. 3B. Evacuation film shows fixation of the involved area, coarse irregular folds in the region of the defect and a transverse mucosal pattern below it. The appendix is well filled.

FIG. 4A. L. S. Spot film shows limited distensibility of the lateral wall at the junction of the cecum and ascending colon. The jagged contour can be followed into closely spaced short transverse folds. (The defect in the hepatic flexure was a coincidental finding and has the appearance of a lipoma.)

sharp demarcation. A diverticulum within the center of the defect is not seen although diverticula may be seen adjacent to the defect or elsewhere in the right side of the colon. One of the spicules on its surface may suggest a closed off neck of the diverticulum which was the source of the intramural infection. The soft tissue shadow occupying the defect may have a somewhat mottled appearance and is continuous with soft tissue thickening of the adjacent wall. This thickening of the bowel wall may be well seen as a strip of water density between intraluminal barium or air and the lateral properitoneal fat of the abdominal wall (Fig. 1D). In addition to thickening of the adjacent wall, there may be limited distensibility of a rather diffuse character not sharply demarcated from adjacent normal bowel. This less involved area when maximally distended has an irregular coarsely jagged appearance with small haustreola of variable depth unusually close to each other (Figs. 1B, 4A). While the details of this involved contour may seem to vary in different films, this appearance is often the result of differences in projection and filling. In the same projection, there may be a surprising constancy of the contour both with barium and with air (Figs. 1C, 4C). Localized

FIG. 4B. With more complete distention, the lateral wall shows two rather discrete defects a short distance from each other. The ileocecal valve is prominent.

FIG. 4C. Double contrast, patient standing, confirms the double defect along the lateral contour and demonstrates thickening of the wall of the bowel in this region as well as the intact but vertically compressed haustral pattern.

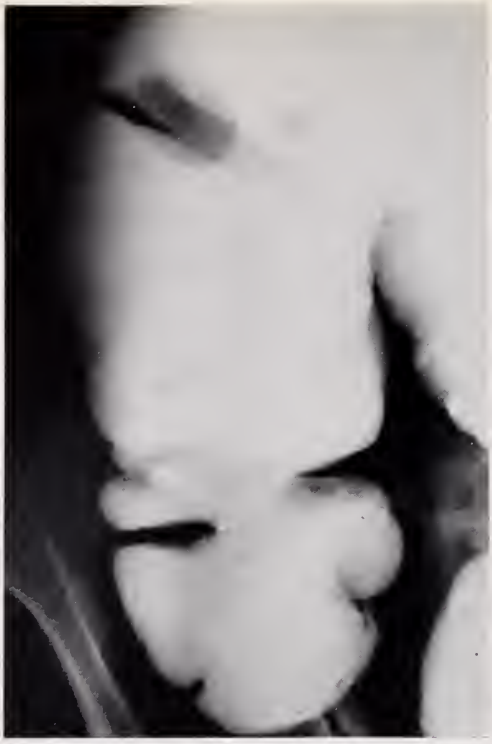

Fig. 4D. Spot film taken one month later appears to be within normal limits. At the site of the previous lower discrete defect, a deep haustral fold is present.

Fig. 5. C. K. Acute appendicitis with retrocecal inflammatory changes.
Fig. 5A. Spot film shows a local indentation on the inferior aspect of the caput.

Fig. 5B. Right anterior oblique projection demonstrates that the cecum and ascending colon appear to be displaced somewhat forward and medially without any localized indentation of the bowel.

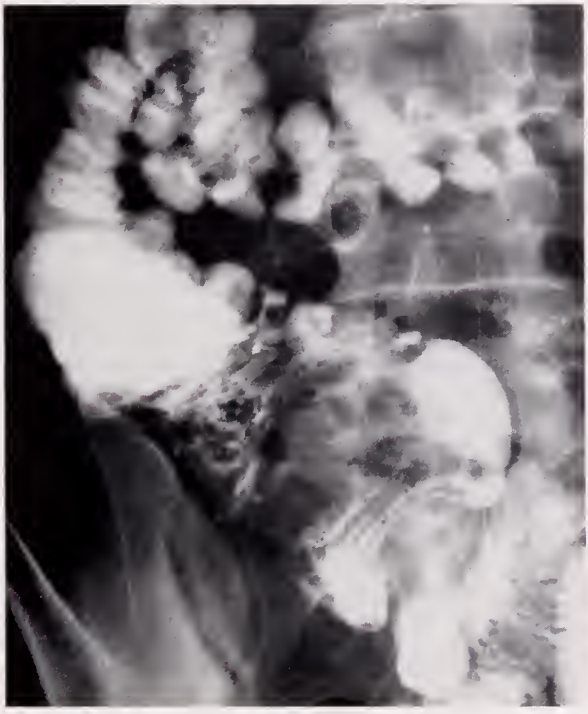

Fig. 5C. Bizarre appearance of the caput after evacuation suggests a large filling defect or extrinsic compression. This is not confirmed by other films and appears to be the result of the serosal inflammatory process interfering with normal contractility of the bowel.

thickening and irregularity of the mucosal folds may be seen after evacuation (Fig. 3B).

Other findings of significance are tenderness to deep palpation in the involved area, the presence of diverticula elsewhere in the bowel and the fact that the appendix may fill completely. If considerable time has elapsed from the onset of the acute infection, changes may be quite minimal and eventually appear to disappear (Fig. 4D). It is not certain that the bowel returns completely to normal but residual indentations or small irregularities may be obscured by the often exaggerated haustral pattern normally seen in this region.

From a roentgen point of view, diverticulitis of the right side of the colon must be differentiated from acute appendicitis, carcinoma, benign tumors, segmental ulcerative colitis, tuberculous colitis, foreign body perforation and so-called isolated ulcers of the cecum. Serosal implants and the normal ileocecal valve may create some question as well. In acute appendicitis, filling of the appendix is rare and any intramural inflammatory manifestations are located at the origin

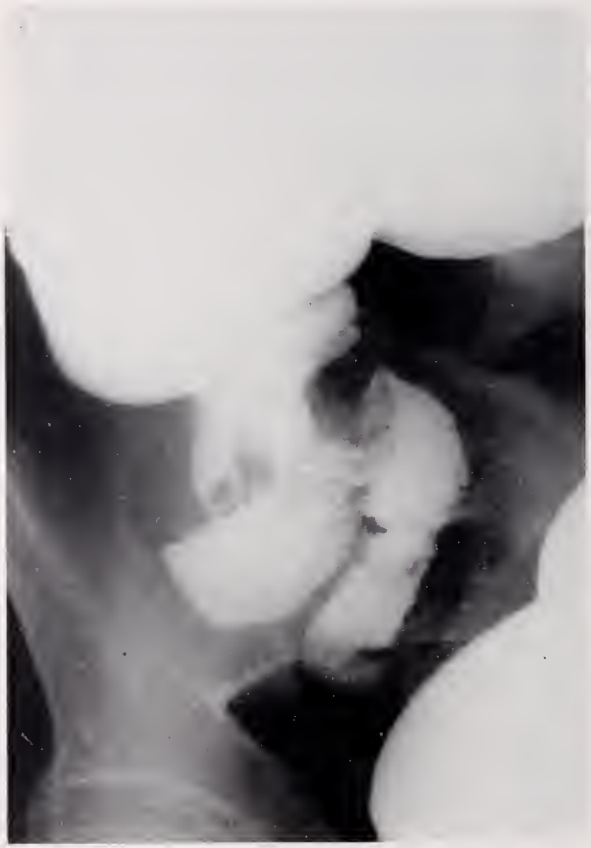

FIG. 6. C. C. Carcinoma at the level of the ileocecal valve of an infiltrating character with a rigid irregular filling defect and ulcerated surface.

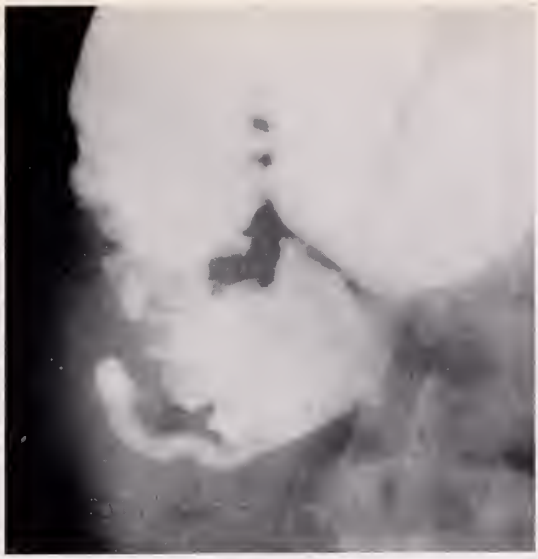

Fig. 7. M. E. Foreign body or diverticular perforation.

Fig. 7A. Spot film shows an irregular contour and apparently limited distensibility over a considerable portion of the lateral wall of the cecum and ascending colon. A localized indentation on the medial aspect has the appearance of the ileocecal valve.

Fig. 7B. After evacuation, a sinus tract arising in the region of the ileocecal valve is visualized. The mucosal pattern of the colon appears to be intact. This was a young male about 37 years of age. The resected specimen showed no evidence of a foreign body so that the possibility that this was a perforation of a cecal diverticulum could not be excluded.

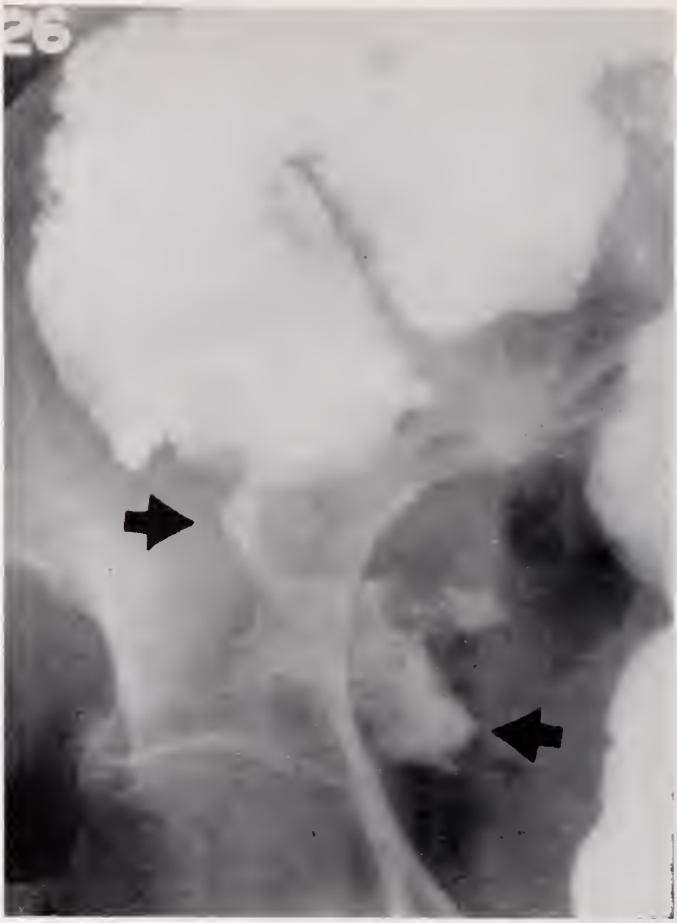

FIG. 8. S. S. S. Fig. 8A. Spot film taken during barium enema shows a very bizarre filling of the caput coli with no evidence of fold pattern and multiple scalloped contour irregularities.

of the appendix (Fig. 5A). With retrocecal inflammatory changes associated with acute appendicitis, evidence of extrinsic pressure on the cecum or displacement of the cecum may be demonstrated (Fig. 5B). Emptying of the caput is frequently quite bizarre (Fig. 5C). If a periappendiceal abscess is present in the usual location of the appendix, compression or eccentric involvement of the terminal ileum as well as extrinsic pressure on the most inferior aspect of the caput coli may be demonstrated. Differential diagnosis from carcinoma, if a satisfactory examination can be obtained, is usually not difficult since the absence of an irregular filling defect with destroyed mucosa can usually be established. In some instances, a carcinoma in this region may not be bulky but infiltrating or scirrhous in character producing a defect in contour which, however, is usually quite irregular and rigid with evidence of mucosal ulceration and

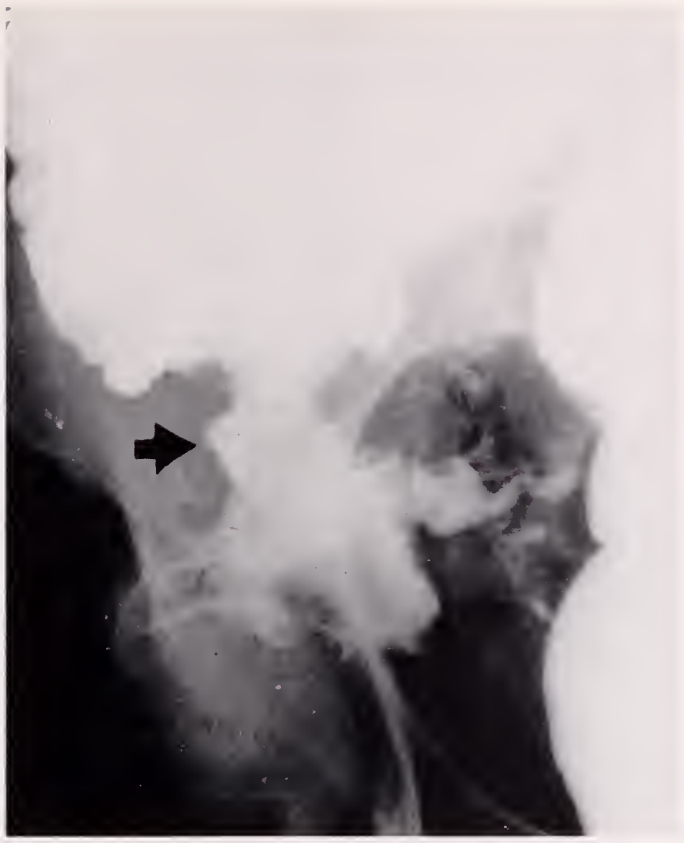

FIG. 8B. Spot film taken shortly after figure 8A shows somewhat better filling of the involved area. The upper arrows in this and the previous figure suggest areas where ulceration was found at operation. Air bubbles indicated by the lower arrows in these figures, were found in the mucosa and in the wall of the bowel. Histological examination indicated three gangrenous areas in the cecum.

unassociated with spastic phenomena (Fig. 5). Differentiation from a perforated carcinoma may be impossible if the examination is not satisfactory because of the associated inflammatory changes. In contrast to an intramural neoplasm, for example, a carcinoid, the fold pattern over a diverticulitis defect is exaggerated or crowded rather than stretched or effaced. The lipomas of the colon usually present themselves on a broad pedicle and their configuration (Fig. 4A) as well as change in shape after evacuation frequently suggest the correct diagnosis (4). Differentiation from a perforated foreign body may be quite difficult unless the foreign body is radio-opaque (Fig. 7). The absence of diverticula unfortunately does not permit this differential diagnosis since only a single diverticulum may have been present. Segmental colitis is usually relatively easy to identify because of its greater extent, the presence of mucosal changes, and a loss of haustral pattern. If the ileum is simultaneously involved, differentiation is simplified.

The same features are helpful in differentiating tuberculous involvement of the ileocecal region. The rare condition of isolated cecal ulceration (Fig. 8) may create quite irregular spastic phenomena within the caput coli and adjacent portion of the ascending colon and be difficult to differentiate unless the presence of ulceration can be demonstrated. In the case illustrated in figure 8, besides the suggestion of discrete ulceration within the irregularly contracted cecum and ascending colon, there was evidence of interstitial air bubbles in the wall of the bowel. The anatomical features of the ileocecal valve, namely the presence of an upper and inferior lip with the terminal ileum entering between the lips should be sufficient to permit recognition even when abnormal rotation of the cecum is present. A serosal implant may create a localized defect in the contour of the filled bowel but this is usually considerably flatter than the finger-like indentation associated with diverticulitis and appears quite fixed and rigid.

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STUDIES IN MYASTHENIA GRAVIS: NEONATAL AND JUVENILE TYPES[1]

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Myasthenia gravis in infants and children is not so rare as it has been considered to be. This disease in children was first recognized in 1877 by Wilks and in 1879 by Erb (1). In a history of myasthenia gravis to 1900 Veits (2) reported eight cases in children. Only eight cases were recorded in the literature from 1908 to 1930 (3–10). With the introduction of the Prostigmin test, the diagnosis was made more often. Thus in the decade of the thirties, there are four reports (11–14). Nevertheless, in 1940 (15) it was reported that myasthenia in children was both infrequent and dubious. In the decade of the forties, 16 reports were recorded in the literature (15–30). Since 1950, 50 reports dealing with myasthenia gravis in children have been published (31–79). To date, we have found 196 cases of myasthenia in infants and children in the literature.

Among the 180 patients diagnosed and treated at the Myasthenia Gravis Clinic at The Mount Sinai Hospital, New York City, from 1951 to 1955, 21 were children, an incidence of 11.2 per cent. This represents two neonatal and 19 juvenile cases whose symptomatology occurred from birth to 17 years. Thus, the total number of reviewed and reported cases is 217.

In 1942 (18) the first case of myasthenia gravis in a baby born to a myasthenic mother was reported in detail and subsequently the term "neonatal myasthenia gravis" was used to describe the transient type and "congenital myasthenia gravis" was used for the persistent form in children, the mother being non-myasthenic (25). The latter group was further subdivided into "congenital" and "acquired" types depending on age of onset (63). We now suggest the use of the term "juvenile myasthenia gravis" to clarify "congenital" whose symptoms may develop at birth or at any time during the growing years.

NEONATAL MYASTHENIA GRAVIS

Currently there are 27 cases of neonatal myasthenia gravis described in the medical literature including the two mentioned above (18, 22, 26–28, 30, 37–40, 44–46, 51, 52, 63–66, 79). The first reported case of a neonatal myasthenic infant (18) died of respiratory failure on the seventh day despite treatment with neostigmine. In 1944 (22) the birth of myasthenic infants in two successive pregnancies of a myasthenic woman was reported.

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A study of these cases showed that there was no correlation between the severity of the infant's symptoms and the duration of the mother's illness or the severity of the mother's myasthenia during pregnancy. The literature reveals three cases in which thymectomy performed on mothers prior to pregnancy did not prevent signs of myasthenia gravis from occurring in their three infants at birth (26, 28, 40).

Incidence

Babies with transient neonatal myasthenia gravis were born of mothers affected by the same disease. However, the majority of infants born to myasthenic mothers were not so affected. In 1951, 36 deliveries of myasthenic women were observed in which only three babies had transient myasthenia gravis of the neonatal form (37). In 1953, fourteen pregnant myasthenic women were observed. Six of these fourteen delivered with one set of twins, a total of seven babies. Six infants were normal and one was myasthenic (46). This infrequency has been pointed out recently (80).

Clinical Picture

The symptoms and signs of myasthenia gravis in children are different in their symmetry than those noted in adult patients. In newborn infants the clinical course and symptomatology, especially of the eyes, further differs from that observed in children. An analysis of these 27 cases showed that the onset of their disease occurred at birth in fourteen patients, the first day of life in six, the second day after birth in five, the third day in one, and one with no details available (Table I).

Symmetrical muscular weakness is a feature in infants affected by this disorder. These infants are described as being limp, motionless, or with feeble movements of the limbs. The muscles are atonic or markedly hypotonic. The Moro response is usually absent or very weak. Prominent symptoms are exhibited by muscles of bulbar innervation such as feeble or voiceless crying, inability to suck, difficulty in swallowing and breathing, and an expressionless face.

The extraocular muscles are rarely affected. Ptosis is also uncommon. This is in contrast to the symptoms in juvenile and adult patients in whom the involvement of the extraocular muscles is most common.

If there is inability to swallow, aspiration of formula and mucus may occur. This could further embarrass an already depressed respiration. In severe cases, if undiagnosed and untreated, death usually occurs in respiratory failure.

Natural Course

Neonatal myasthenia gravis is a disease of short duration. Its natural course usually lasts from a few hours to seven weeks. Recovery is complete. Cases have been followed up to five years and show no signs of recurrence. The transitory nature of this syndrome suggests the presence of a substance passing from the mother to the infant which is slowly excreted or destroyed during the neonatal period. There is no proof of this theory. One of our cases of juvenile myasthenia

TABLE I

Transient neonatal myasthenia gravis

Author	Sex	Onset	Therapy	Duration	Results and Remarks
Viets & Brown, 1939	?				3 cases, no detail; 2 of these quoted by Kibrick
Strickroot et al, 1942	F	3rd day	Prostigmin bromide, 2.5 to 5 mgm each feeding		Sudden death on 7th day, respiratory failure (?)
Wilson & Stoner, 1944	F	Birth	None		Died on 4th day
	M	Birth	None		Improved several weeks then complete recovery
Ford, 1949	?	2nd day	Neostigmine, no details	7 days	Complete recovery
Labranche & Jefferson, 1949	M	2nd day	Started on 7th day, Prostigmin bromide, 2 mgm q4h for 3 days, increased to 4 mgm.		Treatment maintained 4 months
Stone & Rider, 1949	F	No detail	Started on 3rd day, Prostigmin 0.07 mgm i.m.; neostigmine bromide 2 mgm q3h for 1 day, then 1 mgm q3h	13 days	Complete recovery
Nilsby, 1949	M	Birth	Prostigmin methylsulfate, 0.1 to 0.15 mgm t.i.d. to q.i.d.	21 days	Complete recovery
McKeever, 1951	M	22 hours	Neostigmine bromide 1 mgm each feeding; 2.5 mgm for one dose. From 8th day 1 mg every other feeding	14 days	Complete recovery
Holt & Hanson, 1951	F	1st day	Neostigmine bromide, 2-1 mgm q3h for 16 days	17 days	Complete recovery
Geddes & Kidd, 1951	F	2nd hour	Prostigmin methylsulfate 0.05 to 0.125 mgm q4h; ephedrine 1.66 mgm per rectum	36 days	Complete recovery
La Riche & Rosevar L., 1951	F	Birth	Prostigmin methylsulfate 1/20 mgm i.m. q4h for 10 days, then 1/8 mgm q4h	2 months	Complete recovery
Gans & Forsidic, 1953	M	Few hrs. after birth	Started 5th day neostigmine methylsulfate 0.05 mgm i.m., followed by 3 mgm bromide with each feeding increased to 3.75 mgm; atropine 1/200 q4h	11 days	Complete recovery

TABLE I—*Continued*

Author	Sex	Onset	Therapy	Duration	Results and Remarks
Fraser & Turner, 1953	M	2nd day	Neostigmine bromide q6h	12 days	Complete recovery
	?	No detail	None	21 to 28 days?	Complete recovery
Bryan, 1954	M	1st day	Prostigmin methylsulfate 0.25 mgm i.m., then 1 mgm t.i.d.	7 days	Complete recovery
Kibrick, 1954	F	Birth	Neostigmine bromide 3 mgm each feeding, then 1.5 mgm q3h	20 days	Complete recovery
	M	Birth	None	9 days	Complete recovery
	F	Birth	None		Died on 3rd day
	F	Birth	Neostigmine, no details	3 months?	Treatment maintained for 3 months, complete recovery
Moore, 1955	F	Birth	Neostigmine 0.125 to 0.5 mgm q4h. Changed to Mestinon bromide 1 to 1.75 mgm q4h on 10th day. Daily test with Tensilon	6 weeks	Complete recovery
Geddes, 1955	F	1st day	Prostigmin methylsulfate 0.05 to 0.15 mgm q4–6h	7 days	Complete recovery
Schotland, 1955	F	Birth	Prostigmin methylsulfate, 4th day 0.05 mgm test dose. 2 mgm Prostigmin bromide q4h	7 weeks	Complete recovery
Rowland, 1955	F	Birth	Prostigmin methylsulfate 0.5 mgm as test. 0.2 mgm q4h	7 days	Complete recovery
Tether, 1955	M	36 hours	Neostigmine, dose not given	10 days	Complete recovery
Teng & Osserman, 1956	M	1st day	Prostigmin bromide, 1 mgm t.i.d.	5 days	Complete recovery
	M	Birth	Mestinon bromide 0.25 mgm (H) p.r.n.	14 days	Complete recovery

born of a myasthenic mother may well have been a most unusual form of the transient type which has persisted. This will be more fully discussed in the section on juveniles.

Diagnosis

The diagnosis of transient neonatal myasthenia gravis is not difficult to establish bearing in mind that a myasthenic mother might give birth to an infant

affected by the same disease. Once this condition has been noted, the pregnancy should be particularly suspect and followed closely at term. A newborn infant of a myasthenic mother whose previous pregnancy had resulted in a neonatal death of undetermined etiology should be more closely observed for signs of this syndrome. It is the combined duty of the physician who treats the mother for her disorder, the obstetrician who delivers her, and the pediatrician who cares for the infant, to watch for the possible development of signs and symptoms of the disease in such newborns.

Whenever an infant born of a myasthenic mother develops bulbar symptoms, neonatal myasthenia gravis is first to be suspected rather than intracranial birth injury. These two conditions can be differentiated by an injection of 0.1 cc of Tensilon®[3] (81–85) either intramuscularly or subcutaneously. (Tensilon in this dosage has been administered without hazard.) If the baby responds to the test by almost immediate relief of symptoms, the diagnosis is established. Prior to the use of the Tensilon test, the diagnosis was made by subcutaneous or oral Prostigmin® as reported in 21 of the 27 cases (Table I).

Treatment

Once the diagnosis is established, the infant is treated with a maintenance dose of cholinergic drugs such as Prostigmin or Mestinon®[3] in order to relieve the symptoms. We prefer the use of Mestinon (86, 87) because it is less toxic, having fewer muscarinic (parasympathomimetic) side reactions. It has a more effective action on the musculature innervated from the bulb than Prostigmin and is superior in effect in one-half to two-thirds of the adult patients who have taken it (85–87). Mestinon is available as a 60 mgm scored tablet and is roughly equivalent to a 15 mgm Prostigmin tablet. A syrup can be made of Mestinon so that one drop equals 1 mgm of Mestinon bromide and this can be added to the feeding. In the injectable form we use from 0.1 to 0.2 cc yielding 0.2 to 0.4 mgm of Mestinon. Injectable Mestinon is thirty times as effective as the oral type. This is also true of Prostigmin.

Neonatal myasthenia gravis is comparatively uncommon and individual experience is limited in the treatment of such patients. Analysis of these 27 cases revealed that in the milder forms of this disease, the patient may recover completely without specific therapy with cholinergic drugs. However, this may be hazardous as five patients were so treated and two deaths resulted, one on the third and the other on the fourth day after birth. Eighteen patients were given Prostigmin and two Mestinon: one treated with Prostigmin died on the seventh day from sudden respiratory failure (cholinergic death?) (82).

This study indicates that cholinergic drugs should be given to patients whenever it is indicated by the presenting symptoms such as difficulty in breathing, swallowing or inability to suck. In the milder forms without bulbar symptoms medication can be withhold. Nevertheless, the infant should be closely watched

[3] The Tensilon (edrophonium chloride) and Mestinon (pyridostigmine bromide) used in this study was supplied by Dr. T. C. Fleming of Hoffman-LaRoche, Inc.

for the development of the aforementioned signs and therapy with cholinergic drugs should be instituted as soon as they are noted.

The dosage of Prostigmin which has been used in these patients varied from 0.05 mgm to 1.0 mgm of the injectable preparation and from 1.0 mgm to 5.0 mgm by mouth with each feeding. This range indicates that an adequate dose of cholinergic drug differs in each individual case. In the majority of cases a successful result has been accomplished with 1.0 to 2.0 mgm orally. Exceeding care should be taken in the adjustment of the proper dosage in the treatment of these patients. Our experience (84, 85) in myasthenic crisis has cautioned us that it is always safer to slightly undertreat rather than overtreat which may result in cholinergic crisis. If a small oral dose of 5 to 10 mgm of Mestinon or 1 to 2 mgm of Prostigmin every four hours with each feeding can effect a satisfactory sucking, swallowing ability and adequate respiration, then this dosage should be maintained without further increase for the purpose of achieving loud crying or better strength in limb movements. The latter conditions do not threaten the life of the patient. Moreover, since the disease is of short duration, there is no need to be over-vigorous in treatment.

After the first week of medication with cholinergic drugs an attempt at gradual withdrawal should be made. If this fails, the original dosage should be re-instituted and the procedure should be tried again two or three days later. During the course of treatment if weakness cannot be differentiated as being caused by too little or too much cholinergic therapy, the Tensilon test using 0.05 cc can be used to clarify the cause.

If undesirable side-reactions such as diarrhea, vomiting, excessive secretion of saliva or bradycardia occur, reduce cholinergic medication. These reactions may be controlled by the use of small amounts of atropine, which should not be used routinely (88). Supplementary therapy with incubators, oxygen, repeated suction of the oronasapharyngeal cavity, and antibiotics should be used as indicated. Careful, watchful, excellent nursing care is essential.

JUVENILE MYASTHENIA GRAVIS

Myasthenia gravis in children has been diagnosed more frequently in the past twenty years. One hundred seventy one cases have been reported in the literature. With the addition of our 19 cases the total to date is 190 children. These 19 cases are briefly summarized in Table II.

Age and Sex

Twelve patients are female and seven male. The ages range from 10 months to 17 years.

Onset

In our group, myasthenic symptoms were first noted at birth in five patients, 48 hours after birth in one patient, 1 to $1\frac{1}{2}$ years old in six patients, 2 years in two patients, 7 years in two patients, 12 to 17 years in three patients. Thus, six

could be defined as the so-called "congenital" type and twelve as the "acquired" type (63).

Family History

Myasthenia gravis is said not to be an hereditary disease. This is fairly well borne out in studies of the family history in the adult form. In our entire adult group we have only two incidences of sibling myasthenia, a brother and sister and two sisters.[4]

In the juvenile form the frequency of sibling incidence is much greater; in fact, seven of our 19 patients had some form of family history including brothers, sisters and first cousins. Only one mother of one juvenile patient is myasthenic. This patient had a history of difficulty in sucking, swallowing, and choking on feeding at birth. The mother stated that all symptoms disappeared in "several weeks" without specific medication. Later at the age of two to three years frequent stumblings and general muscular weakness were noted. The latter symptom became more marked at the age of nine years. Judging from the history this patient might have had the transient neonatal type which had disappeared in his early infancy and two years later was affected with the juvenile type.

All the others including those 163 cases reported in the literature were born of non-myasthenic mothers. This is in contrast to transient neonatal myasthenia which invariably occurs in infants born to myasthenic mothers.

Review of the literature as shown in Table III shows a similar high familial incidence (7, 12, 21, 24, 25). In spite of this frequency, a genetic basis of myasthenia gravis is difficult to accept.

Symptomatology

The symptoms and signs observed in children differ from those in adult patients. The distinguishing characteristic in children is the generalized bilateral and symmetrical distribution of weakness involving the eyes, face, neck, body and limbs. In adults weakness is usually asymmetric involving one part of the body more than the other.

Ptosis. Bilateral symmetrical ptosis was observed in 16 and unilateral ptosis in one of our 19 patients. In adult patients the incidence of ptosis is 47 per cent (85).

Ophthalmoplegia. A bilateral symmetrical ophthalmoplegia has been noted in eleven of our eighteen patients. Six children showed a complete form with their eyes at a centering position. The other five showed an incomplete form or symmetrically limited ocular movements, i.e., both eyes retained some degree of lateral and/or vertical movements. All these movements were in conjugation. In adult patients 43 per cent had extraocular muscle involvement and in all except four, the involvement was asymmetrical and disconjugated. All these adults had diplopia. This difference between children and adults has been noted previously (25).

[4] These sisters were recorded in 1943 as having their onset during adolescence (21).

TABLE II

Juvenile myasthenia gravis

Case #	Sex	Age	Onset	Chief Symptoms	Mestinon Bromide Therapy	Results, Remarks
1	M	13 yrs.	1–1½ yrs.	Bilateral ptosis and ophthalmoplegia, weakness in legs and arms	120 mgm t.i.d.	Weakness in limbs improved. Ophthalmoplegia slightly improved.
2	F	9 yrs.	Birth	Bilateral ptosis and ophthalmoplegia, weakness in limbs, difficulty in swallowing	120 mgm q3h daytime only	Partial improvement or ocular symptoms. Others markedly improved.
3	M	17 yrs.	Birth	Bilateral ptosis and ophthalmoplegia, weakness in limbs	120 mgm q4h daytime only	Partial improvement of ocular symptoms. Others markedly improved.
4	F	9 yrs.	7 yrs.	Bilateral ptosis, weakness in limbs and neck, slurred speech	60 mgm Mestinon bromide and 15 mgm Prostigmin q3h daytime only	Symptom-free except for ophthalmoplegia
5	F	26 months	1½ yrs.	Bilateral ptosis, ophthalmoplegia, difficulty breathing and swallowing, slurred speech, weakness in limbs and neck.	30 to 90 mgm q.i.d.	Symptom-free
6	F	2 yrs.	1½ yrs.	Bilateral ptosis, ophthalmoplegia, head to right, difficulty in swallowing, frequent falls, slurred speech, weakness in limbs	30 to 40 mgm q4h q.i.d.	Died from bronchopneumonia
7	M	10 months	Birth	Bilateral ptosis, ophthalmoplegia, weakness in limbs, weak cry	35 drops syrup* each feeding	Symptom-free
8	F	3 yrs.	Birth	Bilateral ptosis, ophthalmoplegia, weakness in limbs, sleepy look	60 mgm t.i.d.	Symptom-free
9	M	38 weeks	48 hrs. after birth	Bilateral ptosis, general weakness, poor sucking	10 mgm q4h daytime only	Symptom-free
10	F	12 yrs.	12 yrs.	Bilateral ptosis, ophthalmoplegia, weakness in limbs	50 to 90 mgm q5h daytime only	Remission

11	M	8 yrs.	2 yrs.	General weakness, sleepy, weakness in limbs	30 mgm q.i.d.	Symptom-free
12	F	13 yrs.	7 yrs.	Bilateral ptosis, ophthalmoplegia, weakness in limbs, slurred speech	120 mgm t.i.d.	Ptosis improved, ophthalmoplegia slightly improved. Marked improvement in limb strength.
13	F	17 yrs.	16 yrs.	Crisis, difficulty in swallowing and breathing, marked general weakness, ophthalmoplegia, later became disassociated	17.5 mgm i.m. q2½h, 240 mgm (oral) b.i.d. to t.i.d.	Improved after thymectomy
14	F	14 yrs.	14 yrs.	Diplopia only	90 to 120 mgm t.i.d.	Remission
15	M	6 yrs.	1 yr.	Bilateral ptosis, ophthalmoplegia, inability to walk, difficulty in swallowing, chewing, speech	360 mgm q3h Changed to 60 mgm Mestinon with 10 mgm Mytelase q4h	Improved
16	F	2½ yrs.	2 yrs.	Bilateral ptosis, weakness in lateral movement O.S., generalized weakness.	120 mgm q4h (Tried on Mytelase 15 mgm, preferred Mestinon)	Residual ptosis
17	F	2 yrs.	1 yr.	O.D. ptosis, generalized weakness	30 mgm t.i.d.	Symptom-free
18	M	4½ yrs.	Birth	Bilateral ptosis, trunk and extremity weakness, slurred speech, slow learning, frequent choking. Tracheotomy at 3 months	30 mgm t.i.d.	Improved
19	F	5½ yrs.	10½ months	Bilateral ptosis, difficulty in swallowing, trunk and extremity weakness, some respiratory weakness	60 mgm t.i.d.	Symptom-free

* Syrup Mestinon—Pharmacy prepared syrup so that 1 drop equals 1 mg.

TABLE III

Bilateral Ophthalmoplegia

Author	First Examined	Sex	Onset	Relationship	Description
Hart, 1927	17 yrs.	F	9 yrs.	Sisters	Complete ophthalmoplegia
	19 yrs.	F	14 yrs.		Complete ophthalmoplegia
Rothhart, 1937	9 yrs.	M	6 weeks	Brothers	Partial ophthalmoplegia
	15 yrs.	M	3 yrs.		Partial ophthalmoplegia
Riley & Frocht, 1943	26 yrs.	F	11 yrs.	Sisters	Complete ophthalmoplegia
	19 yrs.	F	14 yrs.		Complete ophthalmoplegia
Heinzen, 1955	13 yrs.	M	Birth		Complete ophthalmoplegia
Schilf, 1955	22 yrs.	F	Birth		Partial ophthalmoplegia
Bowman, 1948	3 7/12 yrs.	M	Birth	Cousins	Practical absence of ocular movement
	4 6/12 yrs.	M	3 2/12 yrs.		Practical absence of ocular movement
	8 2/12 yrs.	F	4 yrs.		Marked diminished ocular movement in all directions
Levin, 1949	4 yrs.	F	Birth	Sisters	Partial ophthalmoplegia
	1 yr.	F	Birth		Partial ophthalmoplegia
Walsh, 1949	3 yrs.	F			Complete ophthalmoplegia
	5 yrs.	M			Complete ophthalmoplegia
Macrae, 1954	3 yrs.	M	Birth		Virtually no ocular movements
Wyllie, et al, 1951	9 yrs.	F	8 yrs.		Restricted ocular movements
Mackay, 1951	9 yrs.	F	Birth	A binovular twin, normal	Complete ophthalmoplegia
Teng and Osserman, 1956	13 yrs.	F	7 yrs.	A first cousin 23 yrs. old has myasthenia gravis since childhood	Complete ophthalmoplegia
	13 yrs.	M	1–1½ yrs.	First cousin to the next 2 patients	Complete ophthalmoplegia
	9 yrs.	F	Birth	A normal binovular twin	Complete ophthalmoplegia
	17 yrs.	M	Birth	Brother and sister	Almost complete ophthalmoplegia

TABLE III—*Continued*

Author	First Examined	Sex	Onset	Relationship	Description
	3 yrs.	F	Birth	Sister	Partial ophthalmoplegia
	10 months	M	Birth	Brother	Partial ophthalmoplegia
	2 yrs.	F	1½ yr.		Almost complete ophthalmoplegia
	17 yrs.	F	Acute onset at 16 yrs.		Complete ophthalmoplegia
	2 yrs.	F	1½ yrs.		Complete ophthalmoplegia
	12 yrs.	F	12 yrs.		Partial ophthalmoplegia
	6 yrs.	M	Infancy		Incomplete ophthalmoplegia

Eighteen of the thoroughly reported cases had ophthalmoplegia. Ten of these eighteen patients had a complete bilateral type and the others had a symmetrical incomplete form. Invariably all these patients had bilateral symmetrical ptosis. The two sisters mentioned above retained their ophthalmoplegia and ptosis into adult life.

Bilateral complete ophthalmoplegia is one of the prominent features in adult patients in crisis and was observed in eight of our patients who were in such a state.

Other types of abnormal eye movement in symmetrical fashion such as convergence strabismus, difficulty in convergence and disconjugation of eye movement of the adult type also have been noted in children.

Diplopia. Diplopia is uncommon in children. Three of our 19 patients had occasional transient diplopia.

Weakness in Facial Muscles. Involvement of the facial muscles in children is frequent and symmetrical. In 17 of our 19 patients facial weakness was noted before treatment. They showed an expressionless face which has been frequently described in the literature as "myasthenic face": long drawn, sad looking with lack of animation.

Difficulty in Swallowing, Speech and Respiration. Difficulty in swallowing was observed in 10 of these 19 patients. Four children also had respiratory distress. Slurred speech or weak crying was noted in seven. These symptoms were more frequently observed in children below the age of two years. The presenting symptoms in this age group were similar to those displayed by the neonatal group as described above.

Weakness in Skeletal Muscles. The involvement of the skeletal muscles in children is generalized and symmetrical: this has been observed in all 19 cases. Younger children manifested delayed or weak walking, frequent stumbling, awkward gait or limp limbs with muscular hypotonia. Older children tired easily,

had sagging shoulders, sleepy appearance and were incapable of sustained activity.

Diagnosis

If the physician is aware of the myasthenic syndrome, the diagnosis of juvenile myasthenia gravis is not difficult to establish. In the newborn, especially in the presence of a family history of this disease, the differential diagnosis between intracranial injury and myasthenia gravis must be determined. In children with myasthenia gravis, the bulbar symptoms often simulate poliomyelitis. Nevertheless, this can be differentiated by the subcutaneous or intramuscular injection of 0.2 cc of Tensilon which relieves the presenting symptoms *only* in myasthenia gravis. In the newborn the dosage is 0.1 cc. The positive Tensilon test should be followed by a successful therapeutic trial with cholinergic drugs such as Mestinon or Prostigmin.

Treatment

All our patients were treated with Mestinon including one with a combination of Mestinon and Prostigmin and two with Mestinon and Mytelase[5]. The dosage used varied in each individual case according to the age and severity of the disease. In infants and young children a trial dose of 10 mgm of Mestinon orally was first used. If no significant signs of improvement were observed the dose was increased by 5 mgm increments until a satisfactory result was obtained. The use of a syrup so that 1 teaspoon equals 1 Mestinon (60 mgm) tablet yielding 1 mgm per drop is very helpful in estimating the amount used. In older children we use ¼ scored tablets starting usually with ½ tablet and increasing by ¼ tablet until satisfactory results are obtained. Tensilon was frequently resorted to in the management of these cases.

Under Mestinon treatment 17 of the 19 patients exhibited marked improvement of their general muscular status with no sign of weakness of the skeletal musculature. Ten patients became symptom-free under treatment. Six still showed a partial bilateral ophthalmoplegia. One patient, a 17 year old girl with an explosive onset, showed only transient slight improvement with 300 mgm of Mestinon every 2½ to 3 hours. She went into crisis and was put in a respirator. When her condition permitted, a thymectomy was performed. Immediately following the thymectomy the required amount of Mestinon was reduced to one-third of the pre-operative dosage. She is now six months post-operative and showing slow improvement which had not been achieved prior to the operation. One patient died from bronchopneumonia.

Toxic side effects of Mestinon, manifested as diarrhea, abdominal cramps and excessive salivary secretion, has been observed in three of those patients. In two cases these side effects were counteracted with the administration of atropine.

The indications for thymectomy in adults as a means of producing remission is slowly being resolved. Recent papers (59, 89, 90) advocate the operation for

[5] The Mytelase (ambenonium chloride) used in this study was supplied by Winthrop Laboratories, Inc.

females under thirty-five; others (90) say females under fifty years of age who have had myasthenia gravis for less than two to three years and have no thymoma. There are those who do not agree with this procedure (91–93), observing that medical management yields similar remissions. Nevertheless, the trend is to thymectomize the young female who fulfills the requirements stated above.

Keynes (59) continues to thymectomize both sexes and reports fifteen remissions of type A and B in twenty-one children who have had the operation. Other clinics are beginning to thymectomize children. Until more cases are operated upon and evaluated and much more knowledge obtained, this procedure in children must be undertaken with great selection. Our case (# 15 in Table II) was thymectomized two years prior to our seeing him without any relief of his myasthenic symptoms.

Prognosis

The prognosis in juvenile myasthenia gravis is better than in the adult form. The mortality rate of adult patients varies from 15 to 28 per cent (89). Our own incidence in adult patients is 12.5 per cent (85). Of the 182 reported cases of the juvenile form, seven died (4.0 per cent).

This disorder in children responds well to treatment. Crisis occurs very infrequently as compared to adults. The literature reveals few spontaneous remissions; however, two of our patients are in complete remission. Juvenile patients have to be treated continuously with an adequate amount of cholinergic drugs.

Systemic and upper respiratory infection almost always aggravates the symptoms. Under such circumstances patients require a higher dose of medication with cholinergic drugs. At times, in spite of the increased medication, symptoms are not satisfactorily controlled during the course of infection.

SUMMARY

1. An analysis is made of 217 cases of myasthenia gravis in children, 196 from the literature and 21 from the Myasthenia Gravis Clinic of The Mount Sinai Hospital. Myasthenia Gravis in infants and children is classified in two distinct types: (a) transient neonatal (27 cases); (b) juvenile (190 cases).

2. Transient neonatal myasthenia gravis affects newborns of myasthenic mothers. The disease is of short duration lasting up to seven weeks. Its symptomatology, diagnosis and treatment are discussed and the literature reviewed.

3. Juvenile myasthenia gravis affects children or infants of non-myasthenic mothers except one case in our series. The disease is lasting.

4. In the juvenile type the symptomatology differs from that of the adult, particularly the ocular manifestation of bilateral symmetrical ophthalmoplegia, a characteristic sign of myasthenia gravis in children.

5. The use of Mestinon in the treatment of myasthenia gravis in children is discussed. The dosage of Tensilon as a diagnostic test and its use in management is described.

6. Myasthenia gravis in infants and children responds well to treatment with cholinergic drugs. The prognosis is better in children and infants than in adults.

7. Thymectomy in children is discussed.

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THE HISTORICAL DEVELOPMENT OF THE CONCEPT OF METASTASIS

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Most pathology texts and dictionaries define metastasis as "the transfer of disease from one organ or part to another not directly connected to it. It may be due either to the transfer of pathogenic organisms, or to the transfer of cells, as in malignant tumors" (1). We are here specifically concerned with metastasis as related to malignant tumors.

In order to trace the steps in the development of the concept of metastasis we go back to ancient times. Cancer was well known by the Ancients. It is recognizably described by the Egyptians in the various papyri, and descriptions of malignant tumors have also been found in Babylonian and Indian writings. Study of ancient skeletons has given evidence of the occurrence of bone tumors. In the Ebers Papyrus, there is an entire chapter devoted to tumors. In most instances, it was recommended that the tumor not be treated, but in a passage concerning the fat tumors which we know as the lipomas, the Ebers Papyrus says, "When thou meetest a fat tumour in any part of the body of a person and thou findest that it comes and goes under thy fingers while it also trembles when thy hand stands still, then say thou: 'It is a fat tumour, I will treat the disease.' Treat it with the knife as one heals an open wound" (2). Thus in 1500 B.C. some tumors were treated surgically. During this time, however, and as long as physicians did not practice dissection of cadavers, only the superficial tumors were seen and only the superficial spread of these tumors was seen.

Probably the first description of local and metastatic spread of cancer was recorded by Herodotus (3). He wrote as follows: "Atossa, daughter of Cyrus, wife of Darius, about 520 B.C. had a tumour on her breast. After some time it burst and spread considerably. As long as it was small she concealed it and from delicacy informed no one of it. When it became dangerous she sent for Democedes and showed it to him." Hippocrates in the 4th century B.C. classified tumors as malignant and benign. If a tumor spread and if the patient died, it was a malignant tumor. Otherwise he called it benign. Celsus (30 B.C.–38 A.D.) went on to distinguish several carcinomas, and advised excision of breast tumors, stressing involvement of the axillary glands. However, he advised against removal of the pectoralis major (4).

In the first century A. D. Galen (131–203 A.D.), the founder of experimental physiology and pathology, failed to make any significant advances in the comprehension of cancer but in his writings he did present us with the humoral doctrine of "Atra Bilis", which influenced medical thought for more than a thousand years (5). According to Galen the body was composed of solid parts and fluids

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of which there were four: the blood, the phlegm, the yellow bile and the black bile. Health implied that the fluids were in balance. A disturbance in the balance meant disease. The concentration of black bile was responsible for cancer and where it gravitated the cancer appeared. Suppression of hemorrhoidal and menstrual bleeding was thought to be an important factor in preventing the discharge of the black bile. This was one of the first scientific attempts to explain the cause of cancer, and the theory found firm entrenchments. Galen also gave us a good description of the local spread of breast cancer. He compared it to a crab as follows: "In the breast we often find tumor in size and shape closely resembling the animal known as the crab. Whereas in the latter the limbs protrude from either side, so in the tumor the swollen veins radiate from its edges and give a perfect picture of a crab" (5). Galen advised purging the evil tumor and then excising the diseased part allowing drainage of the black bile to take place.

Up to this time the word metastasis had not yet been used and the concept was not understood. During the next 1500 years little progress was made in the comprehension of cancer. Although the Arabs in the Renaissance added to the symptomatology, diagnosis and treatment of malignant tumors, no new fundamental ideas on the nature of cancer were brought forth. Surgeons, however, continued to treat the disease. Guy De Chauliac (1300–1368) advocated the wide removal of the disease and what he called all the "rests" of the disease. Fabricius (1537–1619) separated many inflammatory swellings from cancer and warned rigidly against incomplete removal. Marcus Aurelius Severinus (1580–1656) extirpated the axillary nodes. Ambroise Paré, (1510–1590) a confirmed Galenist advised total excision of the tumor. The German surgeon Guilielmus Hildanus, carried out extensive dissections, including axillary node dissections. Paracelsus (1413–1541) stands out as the first successful opponent of Galen's theories. He claimed that cancer was due to mineral salts in the blood, and that cancer developed where these salts became concentrated and sought an outlet.

The Renaissance (1500–1700) brought forth a great many new discoveries and investigative techniques: the circulation of the blood by Harvey (1628), the discovery of the lymph vessels by Olens (1652), and the development of the microscope by Leeuwenhoek (1673). Post mortem examinations became more frequent. Still we find evidence that metastasis was not well understood. Giovanni Battista Morgagni, who compiled about 700 autopsy cases, recognized cancer but did not recognize metastasis. He describes a case of carcinoma of the pylorus of the stomach with massive spread to the liver, however he does not relate the pyloric lesion to the lesions which were found in the liver (16).

By the 18th century, the influence of Galenical thinking had receded and a great many new theories had come into vogue concerning the etiology of cancer (7). These ranged from the "Sour Lymph" theory of Descartes to "Acidosis versus Alkalosis" as expressed by Sylvius. Henry Francois LeDran early in the 18th century wrote that cancer is a local disease in its early stages, and that it is spread by lymphatics to regional nodes and then to the general circulation. The concept that cancer began as a local disease was an important advance. Many, however, continued to think of cancer as a systemic disease. LeDran was further supported

by Bernard Peyrilhe (1735–1804) who wrote that cancer begins as a local process which later becomes generalized through propagation via the lymphatics. Both John Hunter (1728–1793) in England, and the French school felt that alterations in the lymph might be responsible for cancer and they formulated the "coagulated lymph" theory. Thus in their eyes, cancer was more of a systemic disease coming from the lymph and arising wherever the lymph coagulated. All who discussed cancer now, no matter what theory they ascribed to, recognized the eventual spread or secondary growth of the disease and the surgical necessity of wide excision with all the lymph glands and tissue involved. A word of caution, however, was forthcoming from John Hunter who said, "Lymphatic glands which often appear movable, when exploration is performed, a chain of them is found to run far beyond our reach, which would render the operation unsuccessful. As this is not easily known, I would, in most cases, where the lymphatic glands are considerably enlarged, advise that the case should be let alone" (8).

At the beginning of the 19th century, Raspail (1826) showed that the growth of tissues resulted from the multiplication of cells. Schwann (1838) established the doctrine of a cellular structure as a universal principle. Müller published his classical study of malignant tumors in 1838. Tumor cells were thought to come from germ cells scattered between the tissue elements, or from a blastema, an unknown rudimentary substance from which cells and tissues were formed. It is during this period that the term metastasis was first used by Joseph Claude Récamier, who in 1829 recorded secondary growths in the brain occurring in mammary carcinoma and applied to them the specific term metastasis as follows: "Le fait de M. Parent, en montrant la résolution spontanée d'un engorgement carcinomateux, suivie d'un autre engorgement de même nature, peut conduire à admettre des métastases cancéreuses" (9). Récamier also described the local infiltration of cancer and the invasion of veins by cancer. Then, while medical science still labored under the blastema theory as to the origin of tumors, Virchow (1821–1902) founded cellular pathology on the doctrine of "omnis cellula e cellula" or all cells from cells. Thus he stated that cells arise from other cells and applied this not only to normal tissue as Schwann and others had already done, but also to pathological tissues and tumors. He took tumors out of the realm of humoral disturbances manifesting themselves in various parts of the body. In stating that tumor cells must arise from pre-existing cells he provided impetus for surgeons to attempt to eradicate the disease.

The concept of metastasis, however, was not completely understood by Virchow. In his text on "Cellular Pathology" (1863) Virchow says," The propagation of malignant tumors is considered to be that the malignancy has its root in the blood which gives rise to the local affections, and yet it is in these processes that it is easy to show the mode of propagation both in the immediate neighborhood of the diseased part, and in remote organs; and it is in them we find that there is one circumstance which especially favours the extension of such processes, namely the abundance of parenchymatous juices in the pathological formations. The drier a new formation is, the less are its powers of infecting both nearer and more distant parts" (10). Virchow thus ascribed to the belief

that tumors contain a fluid which carries the disease to more distant parts. He further states that the fluid is carried in the lymphatics or that the cancer may encroach upon the walls of a vein and the fluid then travel via the blood stream. Virchow continues, "The manner in which metastatic diffusion takes place seems to render it probable that the transference takes place by means of certain fluids and these possess the power of producing an infection which disposes different parts to a reproduction of a mass of the same nature as the one which originally existed." He discusses the possibility of cells travelling in the blood stream and in the lymphatics but doubts that this occurs. Virchow also mentions that the infecting juices may pass from cancerous tumors through the lungs without producing a change in them and yet at a more remote point excite changes of a malignant nature. He states, "Where there is breast cancer, disease of the liver takes place frequently, whereas the lung is sometimes unaffected." He used this observation as well as the fact that certain cancers appear to advance in direction contrary to the current of the lymph, to argue against the dissemination of cancer cells as the means by which cancer spreads, and to support his theory of parenchymatous juices. Virchow further claimed that malignant cells arise from connective tissue cells.

Virchow's concepts, both that tumors arise from connective tissue cells and that metastatic disease is spread by a parenchymatous juice, were quickly attacked. Alfred Hannover had stated, even before Virchow had published his book, that cancer cells circulated in the blood stream and were responsible for metastasis. Because of Virchow's authority, however, his concepts of the connective tissue origin of cancer and of metastasis held sway until Thiersch (1822–1895) by painfully taking serial sections, traced the growth of several epithelial carcinomas from the malpighian layer of skin (11). He thereby presented convincing evidence of the invariable derivation of epithelium from epithelium, thus disproving Virchow's theory that all tumors arise from connective tissue cells. As for metastases, Thiersch advocated the embolic phenomenon as the cause of secondary deposits. He argued that if one finds epithelium in lymph nodes, how may it have gotten there? How could it arise from a cell when there is no epithelium in a lymph node? Therefore it must have gotten there by a process of embolism or by direct extension. He went on to state that toxic substances or products of metabolism may go into the lymph and blood but he believed that it is cancer cells that travel in the body and produce metastases. He supported this view with many observations. For example, he said one frequently finds cancerous growths breaking into veins and cancer elements in the blood stream. He quoted a case observed by Camile Bourell in 1859—a 34 year old woman died of epithelial carcinoma of the uterus which had metastasized to the pelvis, the lumbar nerves, the right ovary, and both external iliac veins. In the lymph of the thoracic duct epithelial cells were found identical with those in the lymph nodes, those of the thrombosed veins, and those of the primary tumor itself. Thiersch went on to support the concept of cancer as a local process which spreads and becomes systemic by the embolic phenomenon. Waldeyer, shortly thereafter (1872), extended Thiersch's proof. He studied the origin of carcinoma of the

internal organs. He traced the origin of cancer of the stomach, the liver and kidneys to the epithelial cells of these organs. He continued to support the idea that the dissemination of metastases occurred via the blood and lymph vessels by continuous growth and by cell emboli. It was his writings (12) and those of Thiersch that finally led to the rejection of Virchow's view on metastasis.

Immediately following Thiersch's and Waldeyer's work, a great many investigators in the late 19th century came to the support of the mechanical theory. The mechanical theory implied that tumor cells travel in the blood, in the lymph and cause secondary growths wherever they lodge. George Hoggan before the London Pathological Society in 1878, wrote "On Cancer and its Relationship to the Lymphatic Vessels" (13). He supported the idea of the embolic, mechanical phenomenon. Stevens (1907) supported the mechanical theory (14). Goldmann in 1906 states, "Purely mechanical conditions are also at the bottom of the peculiarities prevailing in primary and secondary growths of lymphatic glands, liver, lungs and kidneys (15). Stiles upheld the embolic origin of gland deposits (16) because he said that microscopically he found no growth in the main lymphatics between the breast and the axilla, and because secondary growths did not appear at intermediate points. Also in support of the mechanical theory was Von Recklinghausen's work in 1885 which stressed the retrograde flow in lymphatics caused by obstruction and collateral channels, explaining some of the peculiarities in the location of metastases. This mechanical theory, however, was not accepted by all. Langenbeck and Billroth asked, "What is it that decides what organ shall suffer in a case of disseminated cancer?" Stephen Paget, in an article called "The Distribution of Secondary Growth in Cancer of the Breast", (1889) reviewed the problem (17). He pointed out that although in cancer the distribution of embolism is necessarily an impartial process, the distribution of metastases in the various organs is by no means impartial. He felt therefore, that certain organs form a favorable site for these emboli which lodge in them while in other organs the particles are destroyed. This recalls Virchow's statement that parenchymatous juices pass through the lung without producing tumors and then produce tumors in more remote organs. To support his view, Paget collected some 735 cases of breast cancer. Out of these, 241 had metastases in the liver and 17 had metastases in the spleen. He also collected 340 cases of pyaemia and found that in the liver there were 66 cases of abscesses, whereas in the spleen there were 39 cases of abscesses. If this were an impartial process, he wondered why there should not be more metastases in the spleen, which has a rich blood supply. He offered this observation as one reason for stating that some organs form a favorable site for the growth of metastatic cells. Another important contribution was made by Martin Schmidt who in 1903 by painstaking histological study came to the following conclusions, "In carcinoma of abdominal organs cancerous embolism of small arteries of the lungs occurs with unlooked for frequency and often repeatedly. Only a small portion of these emboli give rise to metastatic tumors or break through the arterial wall into the perivascular lymphatics. Most of them are either destroyed by organization of their ensheathing thrombus, or while retaining the power of growth, are encapsulated and rendered

harmless. They may, however, push forward through the organizing thrombus which surrounds them, into the capillaries and small pulmonary veins and may so give rise to growths in the course of the systemic circulation. All this may happen while to the naked eye the lung remains unaltered" (18). Armstrong and Oretil in 1919 also supported this observation stating that the site of the secondary tumor depends on a great many other things beside the mechanical theory. They attributed much importance to the effect of the metabolic process of tumor cells in weakening physiological resistance, to the biogenetic relationship of tumor cells, to the tissue soil, and to the quantity of tumor elements (19).

Thus far the concept of metastatic disease has been explained basically on the mechanical theory with possibly some modification due to the theory of "soil selection". In the beginning of the 20th century, a third thought was handed down, fostered and expressed by William Handley whose chief interest was in the breast. Handley attributed metastasis to a process of continuous permeation in the lymphatics (20). He felt that the embolic theory was untenable, and after reviewing Schmidt's and Paget's work writes, "In showing that cancer cells in blood excite thrombosis and that the thrombus as it organizes usually destroys or renders them harmless, Goldmann and Schmidt seem to have established a fact of primary importance and one which is strongly opposed to the embolic theory as applied to carcinoma. Cancer in lymphatic vessels, as far as I have seen, excites no such thrombosis, a fact to which Schmidt himself draws attention. Hence it is no doubt that although carcinoma often obtains access to the blood almost as early as to the lymph its dissemination takes place almost entirely by the lymphatics and not by the blood vessels." To explain the fact that tumor may be found in a lymph gland without the lymph vessels to that gland being involved Handley postulated that perilymphocytic fibrosis destroys the continuous line of cancer cells so that they are not discernible. His theory, although not generally accepted today, greatly influenced surgery, for he advocated a more extensive removal of lymphatic tissue and the fascia which contained the lymphatic channels.

Recently J. H. Gray (1938) reviewed the relationship of lymphatic vessels to cancer and concluded that the mode of spread to the lymph glands is by lymphatic emboli; that cancer affects lymphatics only in a mechanical way; and that cancer cells do not remain for any length of time within the lumen of the lymphatic vessel. He was unable to confirm the permeation theory of Handley although some cases of skin tumors revealed lymphatic vessels with long chains of cancer cells (21).

SUMMARY

We began with the early descriptions of cancer and cancerous spread, the teachings of Galen and the humoral doctrine, and the earliest surgical treatment of cancer and its metastases. All this occurred even before the disease was understood and the term metastasis applied. Then came the first use of the term metastasis by Récamier in 1826; Virchow's contribution; and finally the refutation of Virchow's concept of metastasis, and the presentation of our present day

ideas by Thiersch and Waldeyer. The controversial issues of the early 20th century were propounded by Paget, Schmidt and Handley. Today most pathologists believe that the mechanism of the circulation can doubtlessly explain the spread of tumors and the peculiarity of the location of metastases; and that lymphatic emboli play a most important role. Yet many contemporary investigators as exemplified by Willis and Ewing state that there are probably chemical and "soil" factors which determine whether or not a transplanted particle will germinate to produce a metastasis. For a metastasis is not merely a cell that travels in the blood or lymph; the cell must lodge someplace and produce a growth histologically similar to the growth from which it came.

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Radiological Notes

"CONTRACTION RINGS" ASSOCIATED WITH GROSS HIATAL HERNIATION

A Roentgen Method for the Detection and Measurement of Minimal Esophageal Structures

A "contraction ring" in the distal esophagus as a cause of dysphagia has been described by Schatzki and Gary (1) and by Ingelfinger and Kramer (2). Characteristically, the ring is located a short distance above the diaphragm and appears as a thin, sharply demarcated projecting shelf encircling the lumen when the area is distended. A solid bolus may actually displace the edges of the shelf distally in an arcuate fashion. The exact location and nature of this contraction ring are not known with certainty but it is assumed that it is related to the physiological rings which may be seen in the distal esophagus at the level of the inferior esophageal sphincter or of the cardiac sphincter. These physiological rings are always wider than those associated with dysphagia. Patients with contraction rings give a history of chronic or recurrent dysphagia for large boluses of food which, however, rarely interferes with their general nutrition.

It is likely that "contraction rings" are always associated with hiatus hernias of the sliding or pulsion variety. In the cases first described, this was not particularly evident because the associated herniation appeared to be minimal. However, there is another group of cases with obvious gross herniation who also show a similar appearance in the distal esophagus. Figures 1A and 1B illustrate such a case. Figure 2 is a diagrammatic representation of the appearance of the distal esophagus in the same patient with different degrees of distention demonstrating dynamic changes in this region.

The group of cases with gross hiatal herniation and contraction rings have presumably been described in the past as examples of spasm of the cardia associated with herniation. It is possible that this phenomenon is a response to regurgitation of acid gastric juice and evidence of minimal esophagitis. The appearance, however, is considerably different from the usual case of peptic esophagitis in which narrowing and diffuse spastic changes occur over a considerable distance in the distal esophagus. The characteristic shelf-like appearance of the contraction ring serves to differentiate it from organic strictures which occur in the same area but are associated with marginal esophagogastric ulceration or peptic or chemical esophagitis.

It is of practical and prognostic interest to estimate the caliber of a "contraction ring" or other esophageal stenosis. For this purpose, Schatzki and Gary (1) have utilized gelatin capsules filled with radio-opaque material. We have found it convenient to have prepared a round compressed barium sulfate tablet one-half inch (12.5 millimeters) in diameter.* The tablet or pellet is flattened

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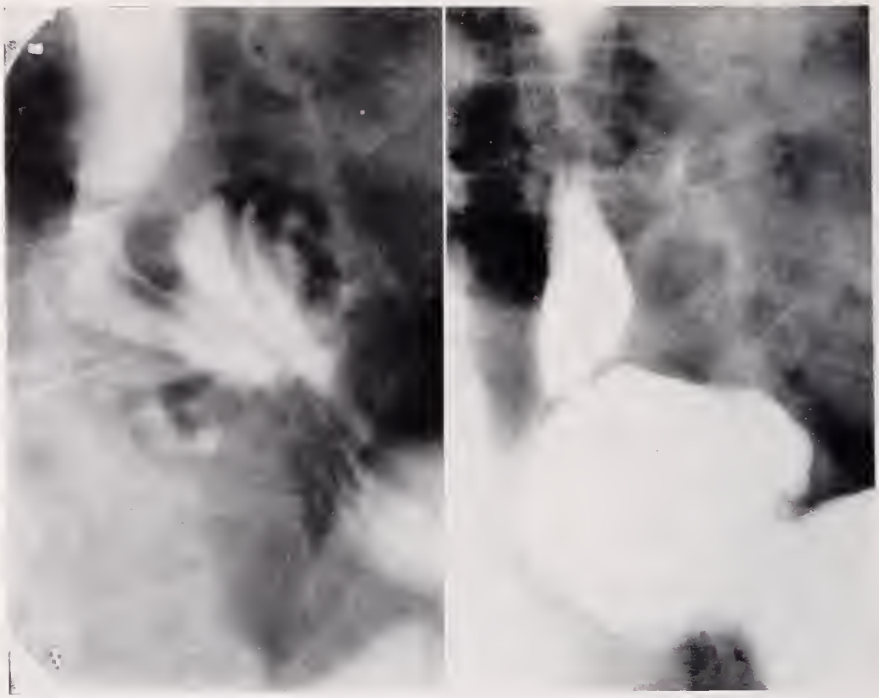
* Made by the Vitarine Co., Inc. Manufacturing Chemists, 625 West 55th Street, New York 19, N. Y.



A B

FIG. 1 Sixty-five year old woman with dysphagia for large boluses of solid food for many years. Typical sliding or pulsion type of hiatus hernia with the cardia about 6 cm. above the hiatus. Free reflux of barium from the stomach into the hernial sac and into the esophagus was present on roentgen examination. In addition, the esophago-gastric region showed a constant lack of normal distensibility and, when maximally distended, had the typical appearance of a "contraction ring." *A*. "Double Contrast" view demonstrates rugae extending proximally to site of constriction. *B*. Demonstrates characteristic features of contraction ring.

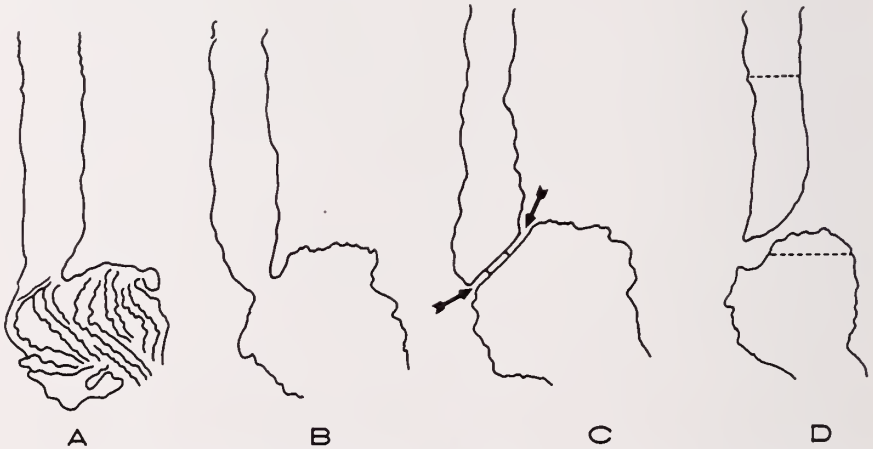
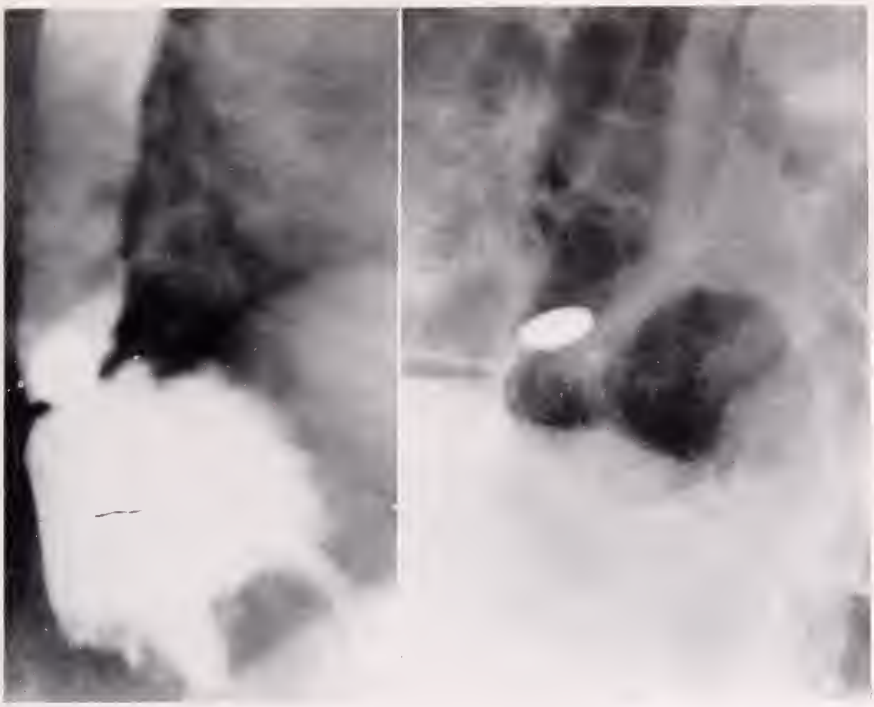


FIG. 2. Same case. Diagrammatic representations of varying appearances of esophago-gastric region. The level of the diaphragm is at the lowermost margin of each figure. *A*. Demonstrates proximal extent of fold pattern. *B*. Incomplete distention of distal esophagus. *C*. Complete distention of distal esophagus but contraction ring (arrows) of limited distensibility persists. *D*. In erect position, temporary cut-off in distal esophagus. Fluid levels in esophagus and hernial sac indicated by dashed lines.



A B

FIG. 3. *A*. Same case. Barium sulfate pill held up proximal to contraction ring. Size of contraction ring (9 mm.) is calculated by comparison with the known size of the tablet. *B*. Barium sulfate pill held up proximal to contraction ring; patient erect (contours accentuated in reproduction).

from side to side in order that patients may swallow it without difficulty. These tablets are easily kept on hand and used whenever indicated. If retained proximal to a stricture, they disintegrate in about a half hour. Because of its shape, the pill does not insinuate itself into a stricture but is retained proximal to it and does not increase the degree of obstruction. Other sizes of tablets may be prepared if desired. A diameter of half an inch, however, corresponds to the external diameter of a 36 French esophagoscope, the size in routine use for esophagoscopy for many years. If a barium tablet of this diameter passes through the esophagus without difficulty, dysphagia on an obstructive basis is unlikely. Transient delay above the arch of the aorta or above the hiatus is often seen but a sip or two of fluid barium causes the tablet to pass along freely, distending the walls of the esophagus as it is carried distally. When an obstruction is met, the progress of the tablet is interrupted although fluid barium easily passes around the tablet. The simultaneous visualization of the tablet of known size and the constricted site make calculation of the diameter of the constriction very simple since the magnification factor is directly determined from the width of the tablet on the film. In inches, the true diameter of a stricture is simply one-half of the ratio of its measured value on the film to the measured value of the tablet. In a patient who will take only small amounts or in a patient

with a rapid transit of barium through the esophagus, the administration of an opaque tablet is particularly useful in excluding a stenotic lesion.

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A METHOD FOR THE ROENTGEN DEMONSTRATION OF MINIMAL HIATAL HERNIATION

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Various positions and maneuvers have been recommended for the roentgen demonstration of hiatus hernias (1). In the majority of instances of gross herniation, a film taken with the patient prone, left side elevated about 45 degrees swallowing continuously the routine fluid barium mixture, suffices. With the casette in the Bucky tray, this position is a prone right anterior oblique view. In this projection, the esophagus and pulsion hernias are well shown unobscured by the spine or heart. In these instances, it is of greater surgical significance to demonstrate, if possible, that the hernia is reducible than to demonstrate its maximum size. The erect position is helpful in this respect but identification of the esophagogastric junction is most equivocal in this position. The demonstration of minor degrees of hiatal herniation associated with "hiatal insufficiency" is considerably more difficult. Maneuvers designed to demonstrate regurgitation (2) may succeed in visualizing small hernial sacs provided reflux of barium from the stomach into the hernial sac can be induced. We have been most successful in demonstrating small hernias by a simple modification of the routine prone right anterior oblique position with the patient drinking continuously. A radiolucent mat is rolled up and placed underneath the abdomen of the patient (Fig. 1). The mat serves to increase intra-abdominal pressure and also places the patient in a moderate Trendelenburg position. The central ray is directed approximately perpendicular to the plane of the thoracic spine. Since the flow of barium is somewhat slower than in the straight horizontal position, films taken in Trendelenburg position often demonstrate excellent esophageal filling (Figs. 2, 3). Figures 4 and 5 illustrate the demon-

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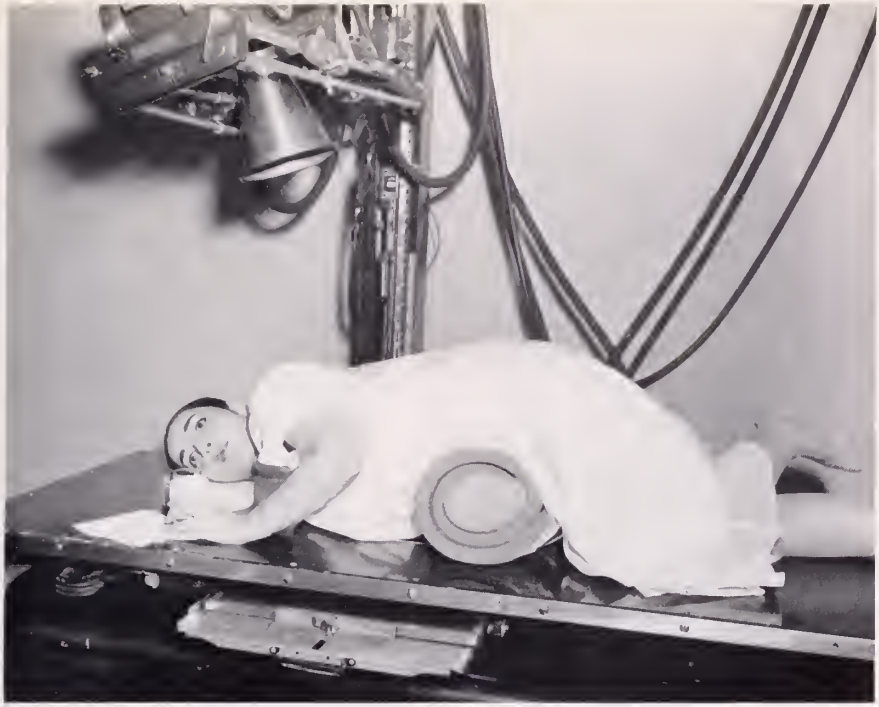
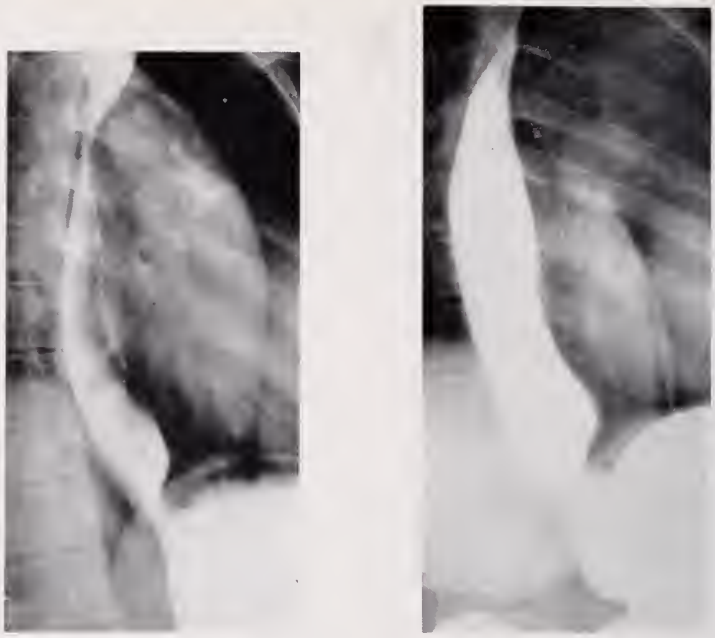


FIG. 1. Photograph of patient in "pressure prone, right anterior oblique, Trendelenburg position". Radiographic table is horizontal; rolled-up radiolucent mat under abdomen; central ray is tilted, perpendicular to thoracic spine; patient drinks routine fluid barium mixture continuously as rapidly as possible during exposure.

FIG. 2. Normal. The maximum width of the hiatal channel is demonstrated as well as a slight bulge above the hiatus in the distal esophagus. Widening of the hiatal channel greater than this is abnormal.



A B

FIG. 3. *A*. Normal. Conventional prone right anterior oblique view of esophagus without pressure or elevation of abdomen. *B*. prone pressure view illustrates better filling and maximum distention of esophagus and hiatal channel.

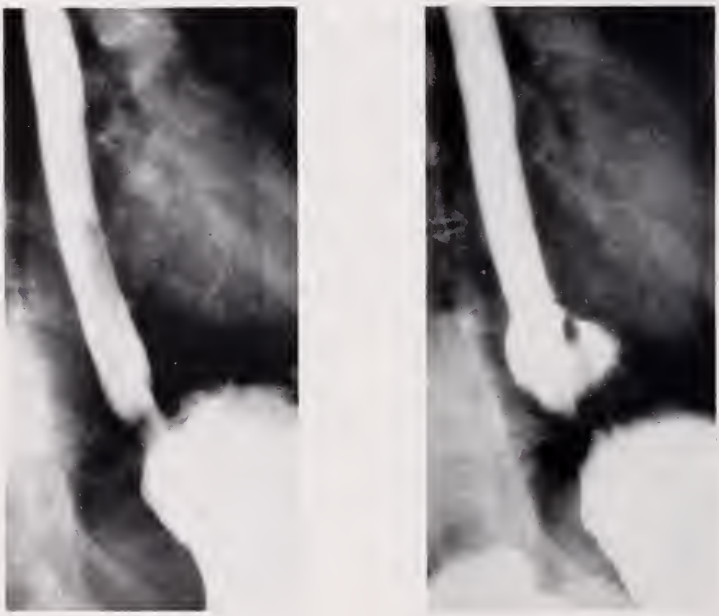


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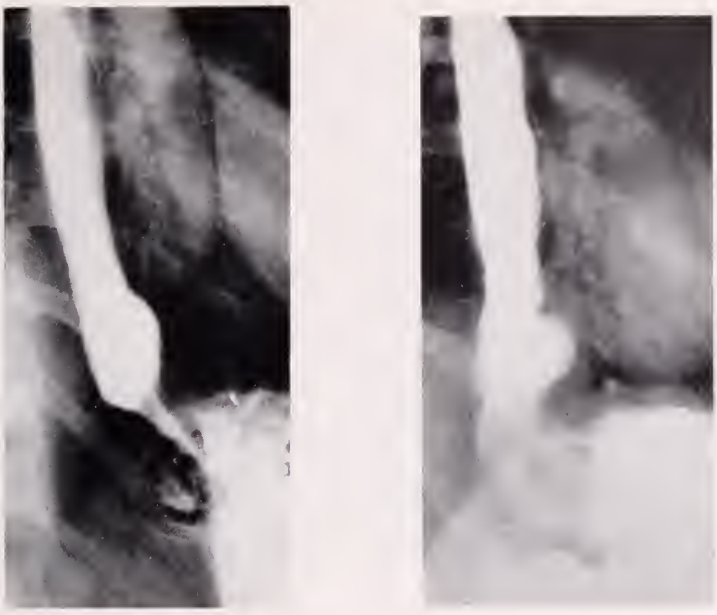
FIG. 4. *A*. Conventional prone right anterior oblique view does not appear remarkable. *B*. Pressure prone view reveals a small hernial sac.



A B

FIG. 5. *A*. Conventional prone right anterior oblique view is within normal limits. *B*. Pressure prone view shows marked widening of hiatus and small hernia.

stration of small hernias by this method. It should be noted that simple tilting of the radiographic table to place the patient in the Trendelenburg position does not increase intra-abdominal pressure and is therefore not equivalent to the position described. It also should be emphasized that the presence of small hiatus hernias without reflux is frequently of little clinical significance and the borderline between the normal and abnormal is uncertain (2).

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CASE OF VOLVULUS OF THE SPLENIC FLEXURE

M. S., a 58 year old female, had a subtotal gastrectomy in 1945 for lymphosarcoma of the stomach. No involved lymph nodes were found. Radiotherapy was administered post-operatively. She was readmitted to The Mount Sinai Hospital in 1956 because of abdominal pain and occasional vomiting for five weeks prior to admission. In the interval since operation, multiple x-ray examinations of the gastrointestinal tract had been done because of recurrent

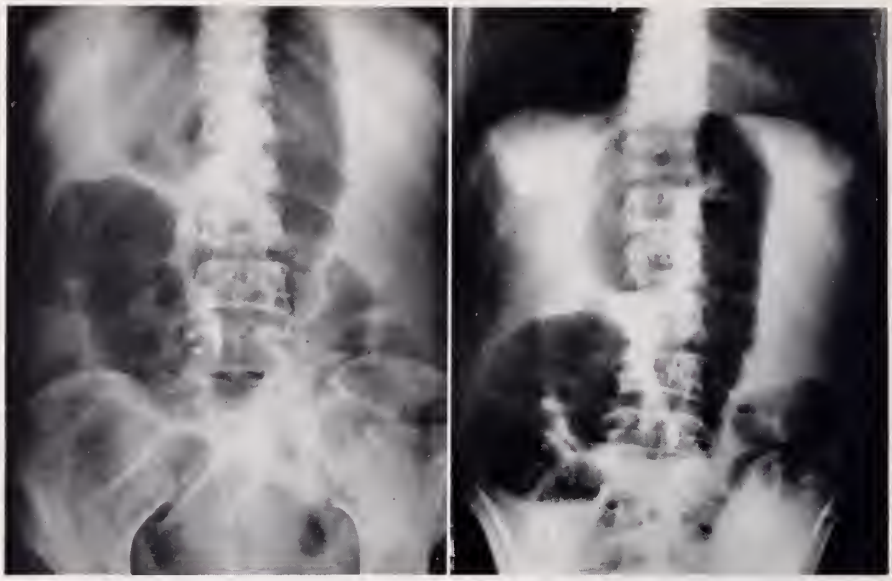

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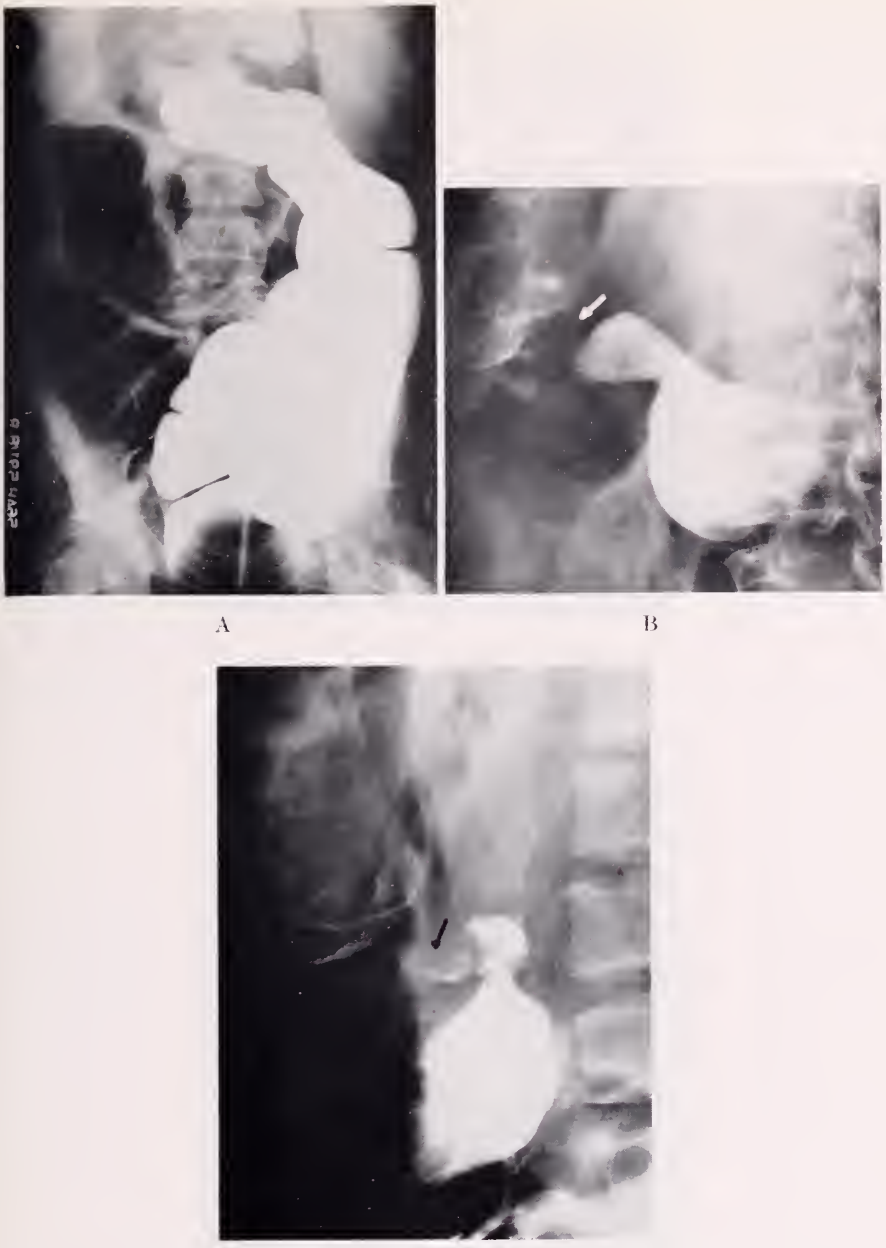
FIG. 1. *A*. Supine film of abdomen shows markedly dilated proximal colon with reversal of splenic flexure; abrupt termination of air column to right of spine in the *distal* transverse colon. Homogeneous density in left upper quadrant is due to enlarged spleen. Air filled loops in left iliac fossa have the appearance of small bowel. *B*. Erect film confirms findings of supine film and demonstrates lack of mobility of colon; fluid level in dilated cecum.

upper abdominal discomfort and pain in the left upper quadrant. There had been no remarkable loss of weight. Except for the subtotally resected stomach, findings were repeatedly negative and the patient was considered to have a "dumping" syndrome. One year prior to admission, bilateral cervical adenopathy, an enlarged spleen extending five finger breadths below the costal margin and an enlarged liver extending two finger breadths below the costal margin were discovered. A moderately severe secondary anemia was present. Investigation in the hospital, including lymph node biopsy and repeat gastrointestinal series, were not contributory. Two weeks after admission, in the afternoon, the patient complained of bloating and diffuse abdominal pain, and her abdomen became markedly distended. No stool or flatus had been passed for twenty-four hours. There was diffuse abdominal tenderness and rebound tenderness. High pitched bowel sounds were audible. Emergency roentgen examination for intestinal obstruction was requested (Figs. 1A, 1B) and was followed by a barium enema (Figs. 2A, 2B, 2C). The diagnosis of volvulus of the splenic flexure, suspected from the preliminary films, was confirmed. The patient refused operation. With the use of an indwelling Cantor tube, intravenous fluids and the knee-chest position, the patient improved within twenty-four hours. Repeat films of the abdomen demonstrated considerably less distention of the colon although the reversed course of the splenic flexure was still present. Twenty-four hours later, re-examination showed complete relief of



A B

C

FIG. 2. *A*. Barium enema demonstrates practically complete obstruction in distal limb of reversed splenic flexure. The site of obstruction corresponds to the abrupt termination of the air column seen on the preliminary films. *B*. Cause of obstruction is demonstrated in oblique projection to be due to a narrowed segment (arrow) about 3 cm. in length; the barium filled bowel distal to it has a "beak shaped" appearance and there is a nipple-like projection proximal to it. *C*. Site of obstruction in lateral projection shows intact folds in narrowed segment (arrow) with curvilinear course; beak-shaped appearance of distal segment seen in profile.

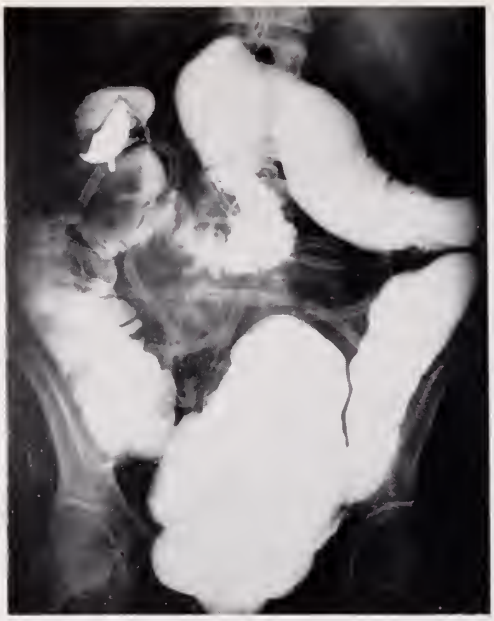


FIG. 3. Barium enema reexamination four days after fig. 2 shows normal course of splenic flexure except for depression and indentation by the enlarged spleen. Obstruction has been relieved. Irregular distensibility and coarse mucosal folds in mid-transverse colon suggest post-congestive changes are present.

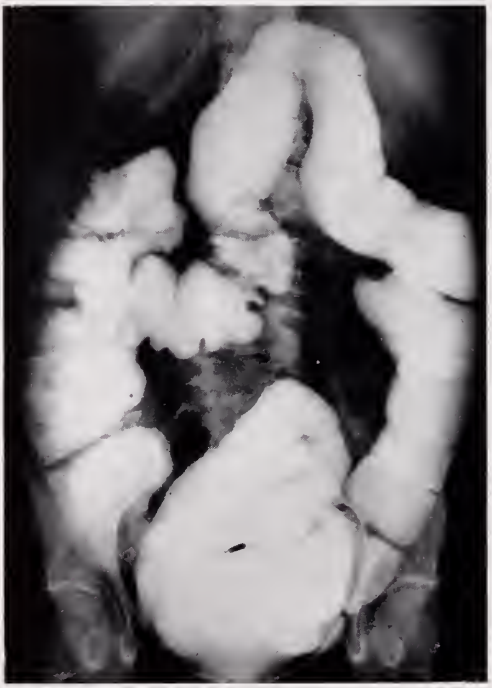


FIG. 4. Third barium enema examination twenty-five days after Fig. 3 shows normal distensibility and mucosal pattern throughout the colon.

distention and the colon was empty of gas. The tip of the Cantor tube was located in the ascending colon. Barium enema was repeated two days later (Fig. 3) and again twenty-five days later (Fig. 4) and showed no evidence of volvulus or obstruction.

Comment

Volvulus of the splenic flexure is a rare cause of intestinal obstruction (1). It is likely that, in addition to redundancy of the colon in this region, adhesions which serve effectively to narrow the posterior attachments and furnish a fixed base for rotation are required. In general, these adhesions are likely to follow a previous laparotomy. In the present case, there is little doubt that adhesions resulting from the previous gastrectomy are present and played a rôle in the production of the volvulus.

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CONTENTS

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In Memorian

LEONARD J. DRUCKERMAN, M.D.

July 29, 1907–July 30, 1956

Dr. Leonard J. Druckerman was born in Brooklyn, New York, July 29, 1907. He attended the public and high schools there and received his B.A. degree at Cornell University, and graduated from its medical college in 1931 with honors, receiving the first prize in gynecology and the Alpha Omega Alpha key. He was a surgical interne at The Mount Sinai Hospital for two years and spent a year as Resident in its Private Pavilion. In 1938, he was appointed an Adjunct Surgeon and simultaneously received a similar rank at Gouverneur Hospital, New York. After 1941, he devoted all his efforts to The Mount Sinai Hospital to enable him to work in the Department of Physiology on problems of gastrointestinal

LEONARD J. DRUCKERMAN
1907–1956

ulceration. On the basis of these efforts many valuable papers were published. He married his beloved wife, the former Jane Hochstadter, in 1942.

He was a Diplomate of The American Board of Surgery, a Fellow of the New York Academy of Medicine, the American College of Surgeons and the New York Surgical Society.

It was my privilege to serve with Leonard Druckerman during his service as surgical interne, resident, adjunct and associate. With pride, which was almost paternal, I watched him progress from an inexperienced wardsman to master surgeon and a clinical teacher greatly esteemed by the house staff. I knew his hopes, his ambitions, his aspirations. I was ever cognizant of his intellectual honesty and moral integrity. I marveled at his constant bubbling enthusiasm and effervescent joy of life. He bore the pain and agony of chronic illness with equanimity and resignation, realizing full well that his days would be shortened. Yet undaunted and asking no quarter, he worked unselfishly and without restraint, giving his all to rich and poor alike, finishing his last operation a few hours before his death. His untimely loss will be keenly felt by his colleagues and friends who will honor and respect his memory.

It may not be our lot to wield
The sickle in the ripened field;
Not ours to hear, on summer eves,
The reaper's song among the sheaves.
Yet where our duty's task is wrought
In unison with God's great thought,
The near and future blend in one,
And whatsoe'er is willed is done.
And were this life the utmost span,
The only end and aim of man,
Better the toil of fields like these
Than waking dreams and slothful ease.
But life, though falling like our grain,
Like that survives and springs again;
And, early called, how blest are they
Who wait in heaven their harvest day.

Ralph Colp, M.D.
For the Editorial Board

THE USE OF VECTORCARDIOGRAPHIC LEADS TO REPRESENT ELECTRIC AXIS AS A POINT ON THE SURFACE OF A SPHERE

LOUIS BRINBERG, L.R.C.P. Ed.

New York, N. Y.

Electric axis, as determined on the Einthoven triangle does not take into account the sagittal component of ventricular electrical activity. As it is the projection on the frontal plane of a spatial vector, its significance is limited. In a recent study a method was advanced by which the spherical coordinates, magnitude (M°), azimuth (H°), and elevation (V°), of a vector in space may be determined (1). It is our purpose to demonstrate that the terms, azimuth and elevation, may be supplanted by the geographical coordinates, longitude and latitude, respectively, and an axis therefore represented as a point on the surface of a sphere.

METHOD

In orthographic projection, the frontal (F) and the horizontal (H) planes are considered transparent and intersect at a ground-line (GL). F and H form by their intersection four dihedral angles, or quadrants, as in Figure Ia.

A point in space may be represented by its projections on the F and H planes. Each projection lies at the foot of a perpendicular from the point to its respective plane. In Figure Ia, a^F and a^H are the respective frontal and horizontal projections of point A. To represent A on a single surface, the H plane is rotated about GL as an axis until it is superimposed on the F plane, the portion of the H plane in front of GL falling down and that part in back of GL moving up. In this new position all of the plane of the paper above GL represents that part of the H plane behind GL as well as the F plane above GL; the part below GL represents that portion of the H plane anterior to GL as well as the F plane below GL. Figure Ib is the orthographic representation of Figure Ia; a^F has not been affected by rotation of the H plane, but a^H has been brought below the ground-line. Between them is the line of recall. It is perpendicular to GL.

It can be deduced from Figure I that in orthographic representation:

A point in I has its F projection above and its H projection below GL.

A point in II has both projections above GL.

A point in III has its F projection below and its H projection above GL.

A point in IV has both projections below GL.

Several vectorcardiographic systems of electrode placement are in use today (2–8). Each derives spatial information from three components: X, the transverse (side-to-side); Y, the vertical (up-down); Z, the sagittal (back-forth). If the area of QRS be measured algebraically in each of these components, the rectilinear, or Cartesian, coordinates of the vector of QRS are obtained. From

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Submitted for publication July 6, 1956.

these the two projections are derived, as the frontal is the resultant of X and Y, and the horizontal, of X and Z.

Let us assume that this has been performed and that the projections obtained are those of Figure 2a. The null-point, O, lies on the ground-line. Om^F and Om^H are the frontal and horizontal projections of vector $\overline{OM}$, which here represents the time-integral of the electromotive forces generated during activation of the ventricles. The problem is to determine its true length (magnitude) and orientation in space. If we pass a plane between the vector and its horizontal projection, this plane will be perpendicular to the horizontal plane and is called a horizontal projecting plane. This has been performed in Figure 2b. The plane, OMm^H,

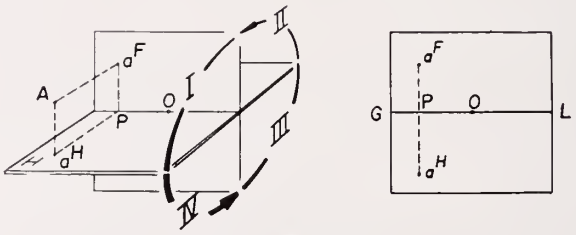
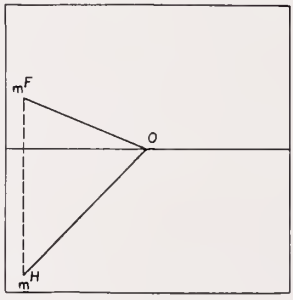


Fig. 1.—a and b



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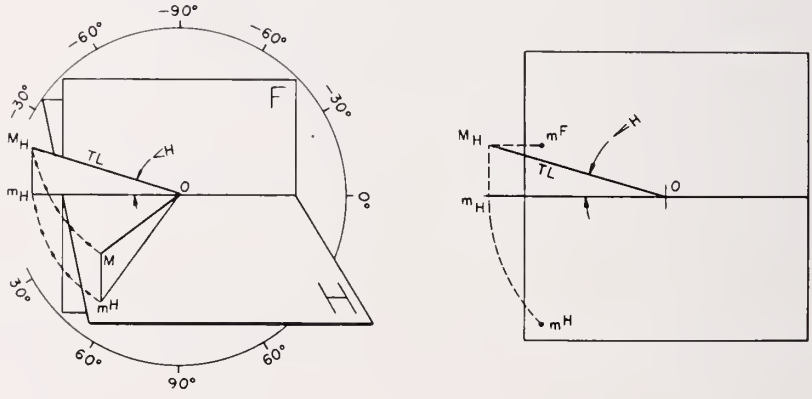

b c

Fig. 2.—a, b and c

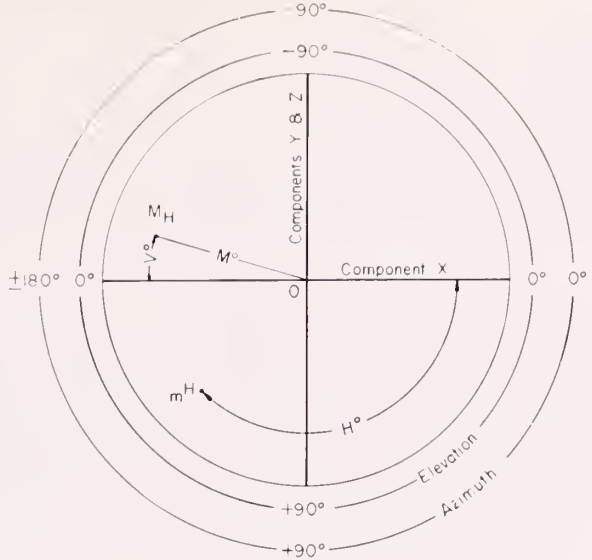

FIG. 3.

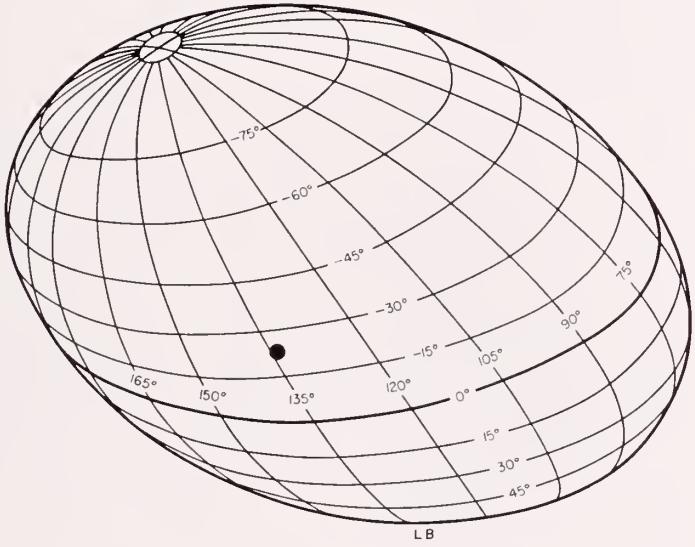

FIG. 4.

can then be revolved about O, remaining perpendicular to H, until it is superimposed on the frontal plane. The new positions of m^H and M are now m_H and M_H. OM_H is TL, the true length, or magnitude, of the vector, and $<M_HOm_H$ is the angle subtended with the horizontal plane by $\overline{OM}$, these having been unaffected by the revolution. Measurements here will not give us the true dimensions, but if the revolution be performed orthographically, as in figure 2c, these

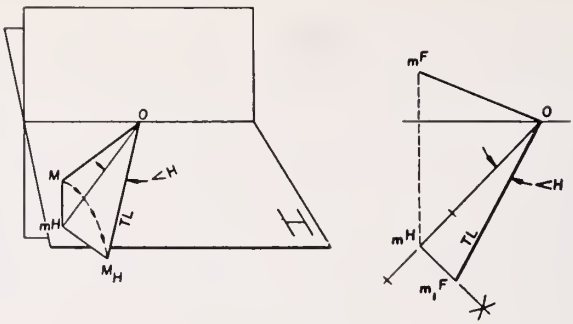

FIG. 5.—a and b

are obtained. An arc of radius Om^H is drawn to the ground-line, and a perpendicular, m_HM_H, erected to the altitude of m^F. OM_H is then the true length of $\overline{OM}$, and $<M_HOm_H$ is the angle $\overline{OM}$ subtends with H. This may be designated $<H$. It is the angular distance of $\overline{OM}$ from the horizontal plane, or its elevation. As M_H has been obtained by revolution of a horizontal projecting plane and gives us the angle with the horizontal plane, it has been termed the horizontal revolute (1). Magnitude and elevation are the polar coordinates of the vector terminus, M, on the horizontal projecting plane. The position of the plane is its azimuth. This is the angle it subtends with the left half of the frontal plane and equals the angular distance between the horizontal projection and the left half of the ground-line.

Azimuth ranges from 0° to ±180°. Angular distances anterior to the frontal plane are considered positive; those posterior, negative. Elevation ranges from 0° to ±90°. Angles below the horizontal plane are positive; those above, negative. This is illustrated in the modified polar coordinate chart of Figure 3 on which the manoeuver can be conveniently carried out. The XYZ components are laid off on their respective axes, the projections derived, the revolution performed, and magnitude, azimuth, and elevation read on the chart. In this case the last two coordinates are 134° and −23°, respectively.

Let us imagine that the null-point lies at the center of a sphere and that vector $\overline{OM}$ pierces its surface at a single point. It is divided into superior and inferior hemispheres by the horizontal plane and into anterior and posterior hemispheres by the frontal plane. The surface is graticulated with meridians of longitude and parallels of latitude as in Figure 4. Longitude is measured from the left side and ranges from 0° to ±180° in the same distribution as azimuth. Meridians anterior to the frontal plane are positive; those posterior negative. Latitude ranges from 0° to ±90°. Parallels below the equator are positive; those above, negative.

Each meridian circumscribes a plane which passes through the null-point and is perpendicular to the plane of the equator. As this is the horizontal plane, the planes of the meridians are then horizontal projecting planes. Vector $\overline{OM}$ lies on a horizontal projecting plane whose azimuth is 134°. It therefore pierces the surface of the sphere on the 134° meridian of longitude.

Latitude is the angular distance of a point from the equator and equals the elevation of a radius to that point. As the elevation of $\overline{OM}$ was found to be −23°, $\overline{OM}$ pierces the surface of the sphere on the −23° parallel of latitude.

The axis of OM may then be represented on an actual sphere by a point positioned at 134° longitude and −23° latitude, as in Figure 4, and its orientation in space visualized by these coordinates. If the point be enlarged to a spot whose radius is proportionate to the magnitude of OM, this coordinate may also be represented on the sphere. The same may be done for instantaneous vectors. If the axes of QRS and T be so marked on a sphere, the QRS-T angle may be determined by measuring the arc distance between QRS and T with a moveable meridian or compass. This is amplified in a forthcoming publication (9).

Elevation, or latitude, and magnitude may also be obtained by rotating the horizontal projecting plane into the horizontal plane, as in Figure 5. Here $m^H m^F$ equals the distance of M from the horizontal plane, and therefore of m^F from the ground-line. As this is equal to component Y, the construction amounts simply to the drawing of a hypothenuse to two sides, one of which is the length of the horizontal projection, the other of Y. It is readily calculated that $<H$, the elevation, equals

$$\tan^{-1} \frac{Y}{\sqrt{X^2 + Z^2}}.$$

SUMMARY

A method of representing vectors as spots on the surface of a sphere is suggested.

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TREATMENT OF CHALAZIA WITH SYSTEMIC PREDNISONE

SYLVAN BLOOMFIELD, M.D.

New York, N. Y.

Chalazia are among the commonest pathological conditions encountered in the practice of ophthalmology. They are probably the most frequent reason for the performance of surgery on the eyelids. It is remarkable therefore that despite the notable therapeutic advances achieved in recent years there is still no satisfactory medical treatment for this condition and surgical extirpation continues to be the main recourse.

Typically, a chalazion gradually forms in an eyelid as a firm, circumscribed mass varying in size from that of a pin-head to that of a large pea. They may be single or multiple and may occur in one or more eyelids at a time. Chalazia may appear at any age, though more commonly in adults, and they occur about equally in both sexes. Occasionally they develop in successive crops; a disturbing tendency for which there is no satisfactory prophylaxis.

A chalazion is generally painless but is often associated with heaviness of the affected eyelids and local conjunctival irritation. Since it arises in the tarsus, a chalazion of appreciable size generally protrudes under the skin of the eyelid as a marked cosmetic blemish, and may also press backward on the globe causing some blurring of vision due to an induced and reversible refractive error. Superimposed infection may also cause suppuration and acute inflammatory symptoms.

When a chalazion is small, a simple regime of warm compresses, antiseptic ointment and massage may be tried but its beneficial effect is questionable. The medical cure of a chalazion is very infrequent and spontaneous regression of the mass is equally uncommon. Once they occur, the large majority of chalazia persist and slowly enlarge, and for these the traditional treatment for over a century has been surgical excision. Although such an operation is generally considered to be a minor one, it does require careful local anesthesia, or general anesthesia in children, and painstaking technique to ensure complete removal of the mass in order to avoid recurrence. Postoperatively, some local swelling, ecchymoses and tenderness may be present for several days.

Pathologically, a chalazion is a granuloma caused by a chronic inflammation of a Meibomian gland in the tarsus of the eyelid. There is evidence of proliferation and degeneration of the glandular epithelium resulting in a core of fatty droplets and cellular debris. The surrounding tarsal and connective tissues show dense proliferation and infiltration by leucocytes, plasma cells, epitheloid cells and numerous giant cells. The peripheral fibrous tissue is often compressed into a dense capsule-like layer. The entire mass may become densely fibrotic and hyalinization may occur. Often, central necrosis results in a cyst-like gelatinous fluid mass surrounded by a dense fibrous coat. Most frequently an intermediate state between these two extremes exists.

The pathogenesis of chalazia has been the subject of long dispute. In view of

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the pathological picture it presents, the early opinion that it occurs as a simple retention cyst of a Meibomian gland is not tenable. For many years its etiology was considered to be a low grade infection, and various organisms have been implicated as causative agents at different times. However such claims are now generally considered invalid. The theory most widely accepted at present is that the granuloma is the result of the proliferative reaction of surrounding mesenchymal tissue to retained Meibomian secretions and degeneration. This concept is supported by the fact that similar lesions can be produced experimentally in animals by the injection of certain lipoid substances (1).

The theory that a chalazion is essentially the result of tissue reaction to a toxic agent suggested to us that treatment aimed at inhibiting or even reversing such tissue response might prove beneficial. Such a therapeutic approach is in line with the widening medical interest in altering bodily responses to abnormal stimuli. With the introduction of corticotropin and the adrenal corticosteroids, therapeutic agents have become available whose beneficial effects derive, in part at least, from their inhibitory action on tissue reactivity. Recently, the range of usefulness of these substances has been widened by the synthesis of the more potent and less toxic derivatives prednisone and prednisilone, which permit systemic administration of these agents in effective dosage with greater safety. In view of these considerations, the possible therapeutic effect of prednisone on chalazia seemed worthy of investigation.

The general indications and contraindications as well as dosages, and physiologic effects of prednisone have been described by many authors (2, 3). A review of current literature, and personal communications indicate that 30 milligrams of prednisone daily, administered orally in three doses of 10 milligrams each, would prove an effective and safe dosage for the adults under investigation. In three patients this quantity was reduced to 20 milligrams administered as 5 milligrams four times a day to assess the therapeutic effect of this lesser and therefore presumably even safer dosage. No patient with known hypertension, diabetes mellitus or peptic ulcer was included because of possible aggravation of these conditions by prednisone. No other treatment of the chalazia was prescribed except in the few instances which will be later detailed. In no case was treatment continued beyond eight days, and thereafter the medication was discontinued gradually by reduction of dosage by 10 milligrams daily.

Seventeen chalazia in eleven patients have been treated with prednisone up to this time. Aside from the elimination of patients with hypertension, diabetes mellitus or peptic ulcer, no selection of cases was made. The ages of these patients varied from 22 to 68 years, and they included eight males and three females. No appreciable difference in results attributable to age or sex was apparent nor could they have been considered significant in so small a series. The chalazia were present in about equal numbers in the four eyelids, and two of the 17, in different patients, were marginal. The size of the chalazia varied from 3 to 6 millimeters in diameter. Three of the chalazia had been present for at least three months, five had been apparent for two or three weeks, and the remaining nine were less than two weeks old. Four of the seventeen chalazia were moder-

ately tender and painful suggesting a superimposed infection and inflammation. The others presented the picture of asymptomatic masses in the lids characteristic of chalazia. Before prednisone therapy was begun, twelve of these chalazia already had been unsuccessfully treated locally with warm compresses and antiseptic or antibiotic ointments.

Sixteen of these 17 chalazia showed a very significant reduction in size within five to eight days after the initiation of oral prednisone therapy. In nine instances the mass seemed to have disappeared entirely, and in four others the size was reduced to a degree where only a slight asymptomatic induration of the tissue was present. Three chalazia which decreased in size to lesser degree were operated upon as described below. One of the two marginal chalazia, a 3 millimeter wide granuloma present for three months was not improved by this treatment.

The four chalazia which appeared inflamed were treated as the others, with oral prednisone, but in addition, warm wet compresses were applied locally three times daily. In one of these cases spontaneous drainage of a small amount of pus was reported by the patient after three days of therapy, and when seen four days later, after continued treatment, the entire mass had disappeared. Another patient, with a recurrent and inflamed chalazion, showed a small point of fluid presenting under the skin surface of the chalazion after four days of oral prednisone treatment. A small incision at this site released a slight amount of thin purulent fluid. Four more days of treatment with prednisone and warm compresses resulted in reduction of the previous mass to a small flat induration requiring no further therapy. The two other inflamed chalazia diminished in size uneventfully with this medical regime and required no further treatment.

In one patient with two chalazia and another with a single one, oral prednisone resulted in a definite reduction in size of each mass within one week. However, for cosmetic reasons, both patients preferred surgical excision of the residual chalazia at that time. After discontinuing prednisone administration, the usual operation for chalazia was performed through the conjunctival surface. It was noted that on incision into each of these three chalazia a quantity of thin, grayish, granular fluid oozed forth, leaving an unusually thin-walled cystic cavity behind. On curetting the lining of this cavity in each case, much less resistance and roughness of the wall was encountered than is customary in this procedure. In both these patients healing of the surgical wounds was uneventful and postoperative reaction minimal.

Before the institution of treatment many of these patients, particularly the four with evidence of infection of their chalazia, had complained of local symptoms. Within a few days after prednisone had been prescribed, in almost all cases, the symptoms attributable to the chalazia had been relieved. In no patient was any adverse effect of the drug noted either systemically or locally within this period of administration.

The patients in this study have been followed for from three weeks to three months. Intermittent observation of eight of the eleven patients has been possible since the termination of therapy. The subsequent course of eleven chalazia im-

proved by systemic prednisone without surgery has thus been observed. Only one of these has shown any evidence of recurrence during the follow-up period. The others continue to appear clinically cured.

COMMENT

Although this series of cases is small, the frequency with which reduction in size of the chalazia occurred following oral prednisone therapy seems to be significant. This is particularly so in view of the static, or slowly growing course which these granulomata generally maintain.

At present one can only speculate about the local tissue changes induced by systemically administered prednisone which resulted in the decrease in size of these chalazia. It is known that granulation tissue formation about chemically induced necrosis is markedly reduced and that collagen synthesis is generally inhibited by adrenal corticosteroids (4, 5). It is not surprising therefore that a potent member of this group of drugs should exert a regressive effect on so essentially a granulomatous lesion as a chalazion. It is possible that with the thinning of the isolating fibrous layer about it, the central gelatinous core of degenerated Meibomian material, if still present, may become more susceptible to phagocytosis, lysis, and ultimate resorption. Similarly, any superimposed infection may become more vulnerable to normal healing processes. The relatively small amount of dense fibrous tissue and the unusually thin fluid found in the three chalazia operated upon after short courses of prednisone therapy, lend some clinical support to such a theory. Further information will be sought from pathological examination of tissue excised from chalazia during such treatment.

The dosage of prednisone administered during this study was generally 30 mg. daily, as previously described. In three cases, only 20 mg. daily was prescribed. In these latter patients reduction in size of their chalazia occurred apparently as satisfactorily as in patients receiving the greater dosage. Further investigation will be necessary to establish clearly the amount of prednisone which will afford the greatest therapeutic efficacy and least toxicity in the treatment of chalazia. More study also will be necessary to decide the optimum period during which treatment should be continued.

SUMMARY

Seventeen chalazia in eleven adults were treated by oral administration of prednisone.

In 16 of these chalazia significant reduction in size occurred and in 13 surgery previously indicated became unnecessary.

In a follow-up period of three weeks to three months, evidence of recurrence has been observed in only one of eleven chalazia apparently successfully treated with systemic prednisone without recourse to surgery.

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CATHETERIZATION OF THE LEFT SIDE OF THE DOG'S HEART

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In order to perfect a technique for retrograde arterial catheterization of the left side of the heart in man, we first performed the procedure in a series of 20 dogs. Once standardized, the method proved relatively safe and simple to perform, and the chambers of the left side of the heart were entered in a large proportion of the animals. The chief object of this communication is to report the technical details and the main complications that were encountered.

Retrograde arterial catheterization of the left side of the heart is not a new procedure in either animals or man. Hellems et al. used the carotid artery to pass ℳ8F catheters through the aortic valve into the left ventricle and left atrium, in six dogs (1). Post-mortem studies revealed small hemorrhagic areas in the mitral and aortic valves in four of the dogs, and in one a small subendocardial hemorrhage was present in the wall of the left ventricle.

Right and left-sided catheterization was performed by Haddy et al. using ℳ10F catheters, without electrocardiographic control (2). For arterial catheterization, they utilized the carotid artery, which was subsequently ligated. The mortality in left-sided catheterization was ten per cent in that series of 71 dogs. Deaths were predominantly due to traumatic rupture of cardiovascular structures.

Sodi-Pallares (3) used a technique similar to, but not identical with that of Limon (4) in obtaining intracavitary electrocardiograms from the left ventricle of man by retrograde catheterization of a peripheral artery. Of the 25 cases in which the left ventricle was entered, one fatality occurred—a patient with luetic aortitis and aortic insufficiency, who died suddenly on the third day after the procedure, without preliminary symptoms. Post-mortem examination was not carried out, and the cause of death was not determined.

In 1950 Zimmerman, Scott and Becker reported that they entered the left ventricle in 11 patients with aortic insufficiency, by catheterization of the ulnar artery (5). These authors usually used a ℳ6F catheter stiffened by a steel stylet. In five normal subjects they were unable to pass the catheter through the aortic valve. In one patient with aortic insufficiency fatal ventricular fibrillation developed as the catheter was being manipulated in the aortic valve region.

Seventeen retrograde arterial catheterizations were successfully performed by Limon Lason, Rubio Alvarez and Bouchard without untoward incident (4). They had no difficulty in passing the aortic valve with a catheter provided with a J-shaped tip. It is Limon's technique which we have adopted.

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METHODS

The techniques were in great part modifications of routine right-sided cardiac catheterization methods employed in patients at The Mount Sinai Hospital and the equipment was of the same type.

Twenty large mongrel dogs served as subjects. They ranged in weight from 12 to 32 kilograms. Intravenous Nembutal anesthesia was used (30 mg. per Kg.) and respiration with 100 per cent oxygen was maintained by a positive pressure demand valve (Pneophore). The animal was placed on a fluoroscopy table, and the electrocardiogram was constantly monitored on the oscilloscopic screen of a four channel oscilloscopic-photographic recorder. This required the presence of at least one individual in addition to the operator.

The femoral artery was selected at its most superficial point in the inguinal area, as determined by palpation. Sterile technique was used throughout. An incision was made parallel to the vessel, the artery isolated and tied distally. An assistant elevated the artery into the wound by means of another proximal ligature, which was not tied but used as a sling. This prevented bleeding while the artery was incised by a sharp pointed scalpel. The catheter was introduced with the aid of a fine-pointed curved forceps. The proximal tie was relaxed as the catheter passed up into the aorta. At this point, in most cases, there occurred moderate bleeding around the catheter, which was easily controlled by a silk ligature tied about the vessel with the catheter in it. After a little experience it was possible to make this ligature tight enough to prevent bleeding but not to impede the movement of the catheter. Arterial spasm was not encountered. The catheter was of the Cournand type, with birds-eye openings, ⅞6F, 125 centimeters long. A J-shaped tip was produced by inserting a steel stylet of the proper shape into the end of the catheter prior to autoclaving. The stylet was removed before using the catheter.

The catheter was kept patent by flushing with a heparinized saline infusion under a pressure of 200 mm Hg. This pressure was maintained by means of a five gallon metal drum acting as a pressure reservoir. The drum was connected by heavy rubber tubing to a standard infusion bottle* fitted with a specially-built screw-on metal adaptor†. The air intake tube of the adaptor opened above the level of the fluid in the inverted bottle. The fluid outlet of the metal adaptor was connected to the catheter by means of specially-designed disposable plastic tubing* incorporating a drip device for gauging rate of flow. This assembly for maintaining an infusion under high pressure has been used in the Catheterization Laboratory of The Mount Sinai Hospital for some years.

The left anterior oblique position was found to be most suitable for fluoroscopy. In this projection the descending aorta was distinct from the heart shadow and the left ventricle and atrium were not superimposed. There was usually no difficulty in passing the catheter to the region of the aortic valve. If the catheter was seen to enter one of the brachio-cephalic arteries, it was withdrawn, re-directed and advanced. When the catheter was in the aorta its tip was partially curved,

* Abbott Laboratories, North Chicago, Ill.

† Geo. Pilling & Son, Philadelphia, Pa.

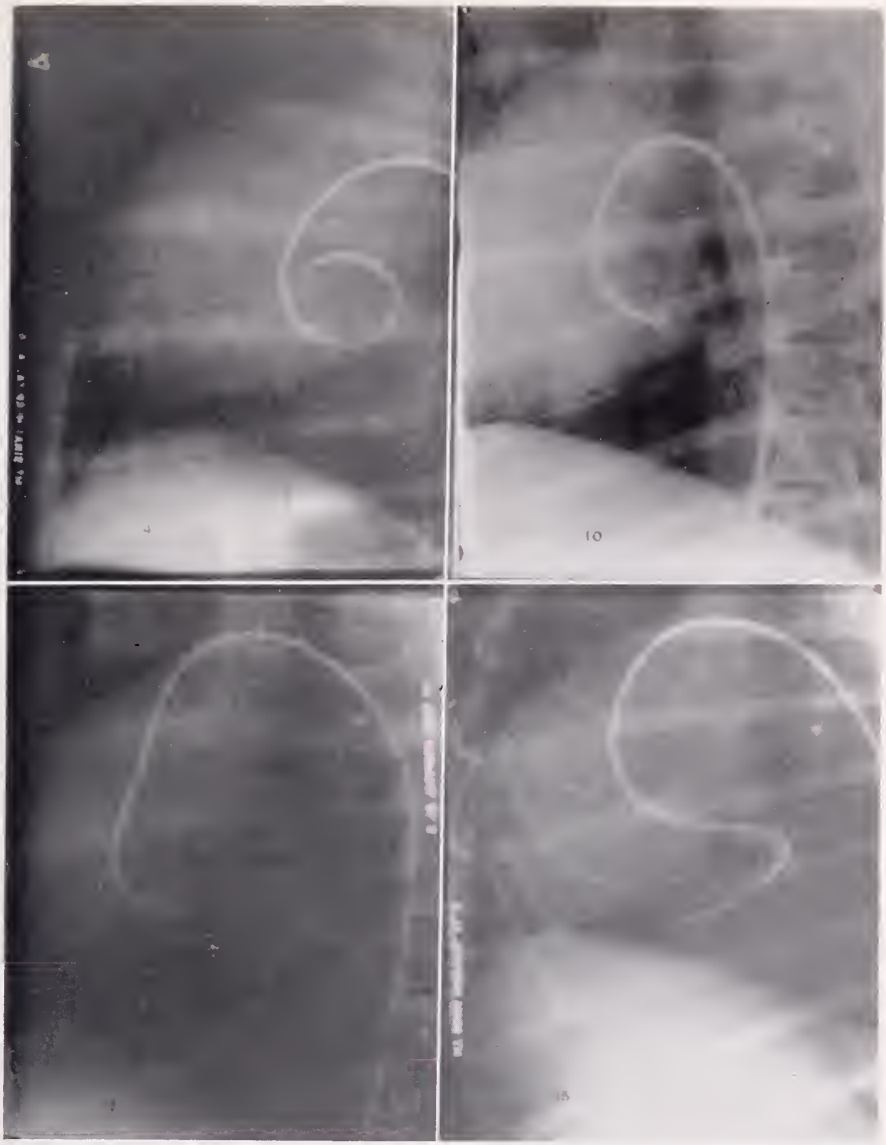

FIG. 1. Representative x-ray films taken in the left anterior oblique projection during catheterization in four different dogs. (#4—catheter tip in left atrium; #10—left atrium; #11—in left ventricle at mitral valve; #15—in a left lower pulmonary vein.)

but the complete J-shape was usually not assumed until the ventricle was entered.

The aortic valve was usually passed without difficulty. Care was exercised not to use force. If resistance was met, the catheter was promptly withdrawn and re-advanced. With one exception, it was possible to pass the catheter repeatedly back and forth across the aortic valve. The only untoward effects noted were short runs of ventricular premature contractions. The exception occurred in one instance when the catheter with J-shaped tip became contaminated and had to

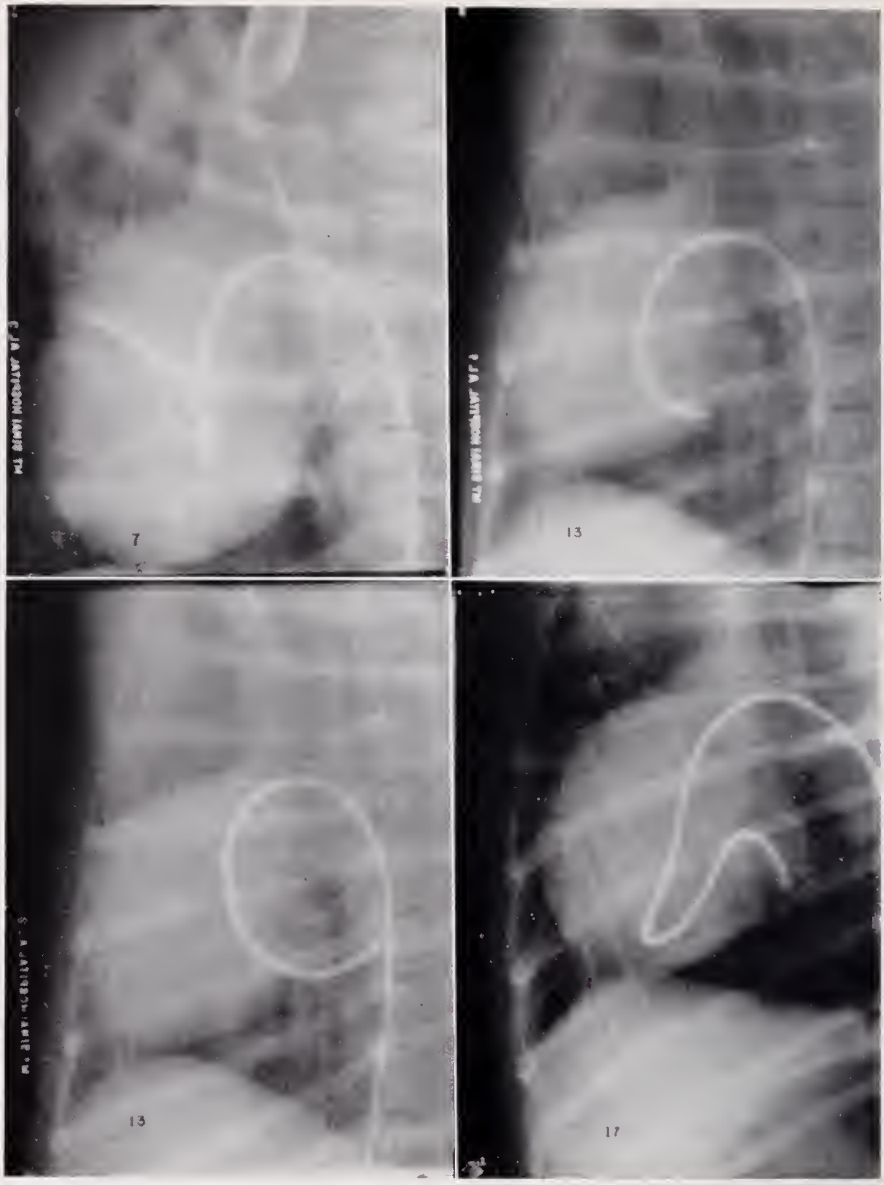

FIG. 2. Four other "spot" x-ray films. (#7—catheter tip probably in a right pulmonary vein; #13 (upper)—left atrium; #13 (lower)—pulmonary vein; #17—left atrium or pulmonary vein.)

be discarded in favor of one with the slight curve ordinarily used for catheterization of the right side of the heart. With this relatively straight tip, passage through the aortic valve proved difficult.

When the ventricle was entered a pressure curve was registered on the oscilloscopic screen by connecting the catheter by means of a three-way stopcock to

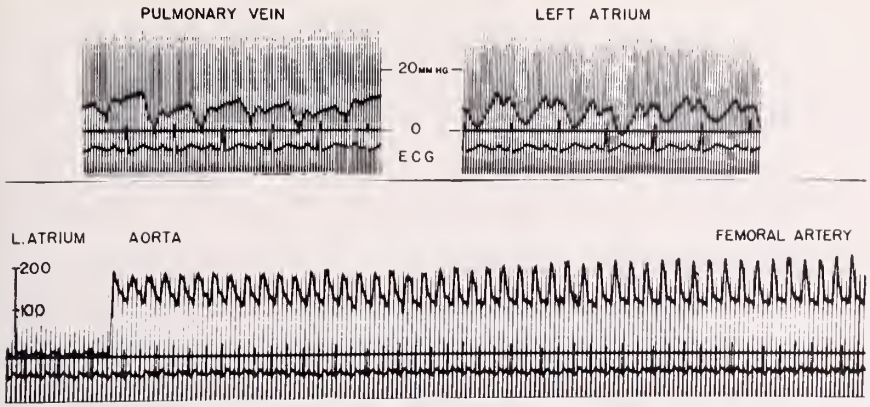

FIG. 3. Pressure pulses in a pulmonary vein and left atrium (above) and continuous tracing during withdrawal of catheter from left atrium to femoral artery (below). In the two top tracings the paper speed was 75 mm. per second, and time lines 0.02 seconds apart; in the lower, paper speed was 25 mm. per second, and time lines 0.1 seconds apart.

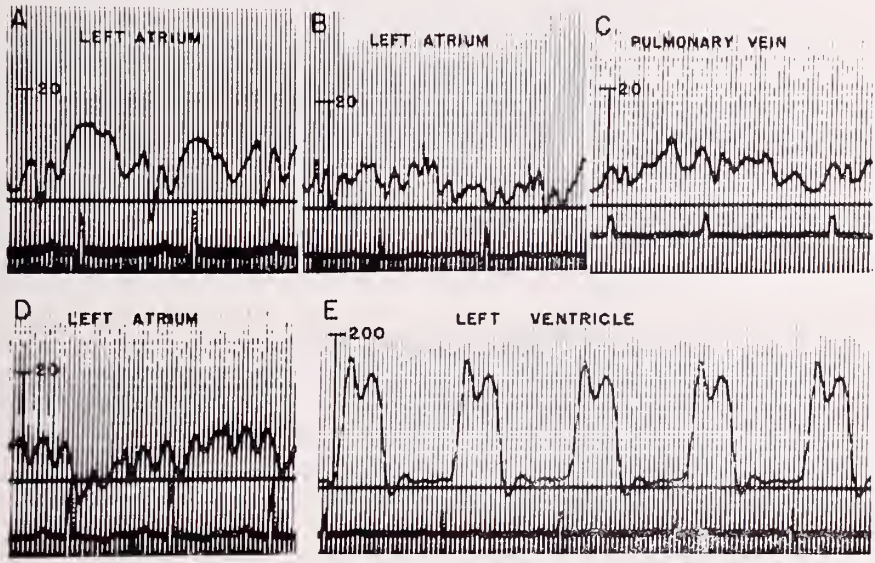

FIG. 4. Representative tracings of pulmonary venous, left atrial and left ventricular pressure pulses. (Paper speed—75 mm. per sec., and time lines 0.02 sec.)

a P 23 Statham pressure transducer. Having confirmed that the tip was in the ventricle, the catheter was further advanced posteriorly, through the mitral valve and into the left atrium. If the catheter tip was properly oriented when it was first passed into the artery it often pointed in the proper direction at this stage of the catheterization. Passage through the mitral valve usually proved more difficult than the aortic, and in four of the 19 animals who survived, it was not possible. The location of the catheter in the left atrium was confirmed by pressure tracings and by "spot" x-ray films developed later (Figs. 1 and 2). In some cases attempts were made to intubate a pulmonary vein. This was successful in five of

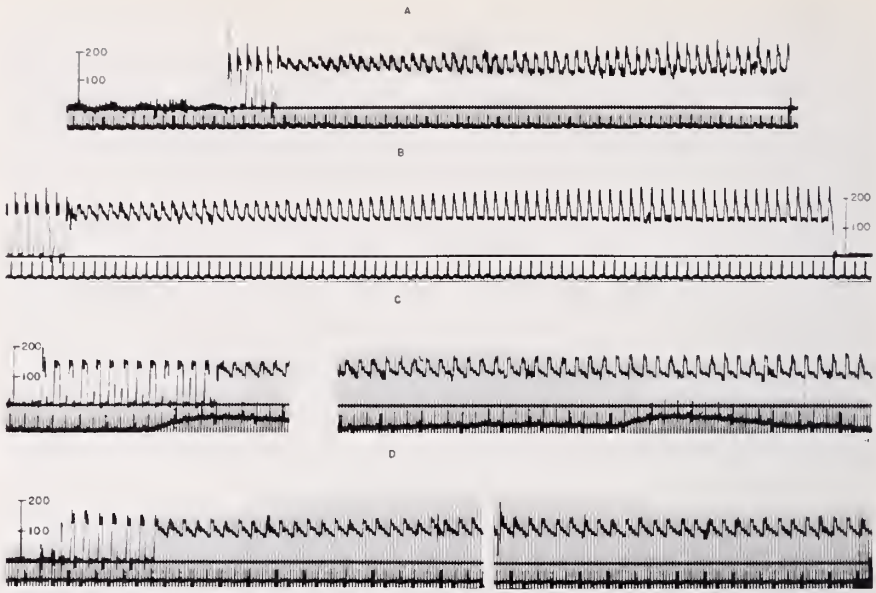

FIG. 5. Continuous tracings during withdrawal of catheter in four dogs, to show variations in transformation of the arterial pressure pulses. In C and D small segments have been excised. (Paper speed—25 mm. per sec.; time lines—0.1 sec.)

the eight animals in which it was tried (Figs. 3 and 4). Continuous pressure pulses were then recorded as the catheter was slowly and steadily withdrawn from the heart and out of the femoral artery (Figs. 3 and 5). The artery was tied proximal to the incision in the vessel and the skin sutured. Penicillin was given routinely by injection.

The animals were kept under observation, sacrificed and autopsied from the sixth to the twenty-third day after catheterization.

RESULTS

The left ventricle was entered in all 19 animals who survived; the left atrium in 15 and a pulmonary vein in five. A summary of the pressure measurements obtained is seen in Table I. The pulses appeared to be faithfully recorded with the exception of those in the ventricle, many of which exhibited a systolic overshoot (Fig. 5) which made determination of the systolic pressure difficult or impossible. In those cases the ventricular systolic pressure was arbitrarily taken to be the same as that in the aorta just distal to the aortic valve. In at least one instance ventricular curves were not obtained during slow withdrawal of the catheter from the atrium, indicating that the tip did not remain in the ventricle for a single heart beat (Fig. 3). There are two possible explanations for such an occurrence. One is that the catheter took the shortest possible route between the aorta and left atrium, a distance of two to three centimeters. The other is that the catheter was rapidly ejected during systole by the contracting ventricle. Pulmonary venous, left atrial, left ventricular and arterial curves are illustrated in Figs. 3, 4 and 5. The transformation of the arterial pulse waves down the aorta

SUMMARY OF LEFT HEART CATHETERIZATION DATA IN 20 DOGS

Exp No.	Fluor Time (min.)	Pulm Vein (m.p.)	Left Atrium (m.p.)	Left Vent (s/d)	Asc Aorta (s/d)	Asc Aorta (m.p.)	Fem Art (s/d)	Fem Art (m.p.)
1	11			189/1	166/120			
2	3.5		4	172/0	176/126	146	204/126	154
3	12			183/0	183/131	156	235/122	149
4	1.5		*	*	*		*	
5	2		9	167/9	167/131	139	194/126	139
6	2		13	171/8	171/115	146	210/112	155
7	2.5	8	8	142/5	142/110	127	180/110	126
8	4			208/0	200/126			
9	(Died on Table)							
10	6		8	181/3	172/129	146	210/116	149
11	2		10	194/10	194/144	178	220/144	186
12	2.5	3	4	198/7	192/140	171	228/133	164
13	.75	4	5	-	195/110	156	229/100	150
14	3			170/6	170/121	166	223/116	174
15	2	10	8	154/6				
16	1.5		7	184/7	176/129	149	193/131	149
17	1	8	7	135/7	129/96	106	159/98	108
18	2		4	144/3	134/93	114	164/91	120
19	2		7	179/3	175/120	154	205/114	148
20	3		3	143/2	130/83	107	145/85	112

All Pressures in MM.HG.
*Observed on Oscilloscope but not Recorded.

to the femoral artery is well shown. The average peak systolic pressure in the femoral artery (206 mm. Hg) was 23 per cent higher than thas in the ascending aorta (167 mm. Hg). The average diastolic pressure in the femoral artery amounted to 115 mm. Hg, that in the ascending aorta 118 mm. Hg. The average mean pressure in the femoral artery was 146 mm. Hg compared to 144 mm. Hg in the ascending aorta.

In 19 animals who survived the procedure, the average fluoroscopy time was 3.3 minutes. In one animal the pulmonary vein was entered after only 45 seconds of fluoroscopy.

COMPLICATIONS

Ventricular premature contractions often occurred as the catheter passed the region of the aortic valve, or when it was pushed against the apex of the ventricle. Once in the atrium or pulmonary vein, arrhythmias ceased so long as buckling of the catheter did not occur. The frequency and character of the arrhythmias were about the same as those noted in catheterization of the right side of the human heart.

The most serious complication was a fatal episode of ventricular fibrillation in the ninth dog. This will be described in some detail. As the catheter entered the region of the aortic valve a run of ventricular tachycardia of about six beats occurred. The operator was immediately informed of this and withdrew the catheter to the ascending aorta, whereupon the heart rhythm reverted to normal.

He readvanced the catheter and quickly passed to what was thought to be the apex of the left ventricle, whereupon a similar burst of ventricular tachycardia occurred, followed immediately by ventricular fibrillation. The catheter was again quickly withdrawn but the arrhythmia persisted. The lights were turned on and it was then noted that the artificial respiration device was not functioning. It was therefore impossible to attempt resuscitation.

The exact reason for the ventricular fibrillation was not clear. It was considered possible that the artificial respiration may have failed some time before, with consequent anoxia predisposing to an arrhythmia. An alternate explanation was that a coronary artery had inadvertently been entered. Since the catheter was immediately withdrawn from the irritable focus, no pressure records were made, which might have confirmed such a hypothesis. Post-mortem examination of the animal disclosed no abnormalities.

In two of the dogs a knot developed near the tip of the catheter. It was possible in both instances to pull the knotted catheter tip down the artery into the wound, and to deliver it by means of a small incision in the vessel, without further incident.

No complications occurred from ligating the femoral artery.

POST-MORTEM OBSERVATIONS

Tiny linear hemorrhages were observed in the substance of the aortic valves in about half the cases. In only one instance was a hematoma present which was large enough to cause a slight thickening of the cusp at one point. This occurred in the experiment in which a catheter was used without a J-shaped tip. No endocardial or mitral valve lesions were present. In a few cases, tiny hemorrhages were found in the pulmonary or tricuspid valves similar to those encountered in the aortic valve, despite the fact that no manipulation had occurred on the right side of the heart. These were therefore considered to be spontaneous.

The femoral artery characteristically contained an adherent organizing thrombus for a distance of 1 to 2 centimeters proximal to the ligatures. Distally the vessel was partially collapsed, although in at least one instance, when the artery was dissected before the death of the animal, this portion of the vessel bled profusely when cut.

SUMMARY

The left side of the heart was catheterized in retrograde fashion through a femoral artery in 20 dogs. There was one death from ventricular fibrillation. In two cases, a knot developed in the catheter. The left ventricle was entered in all 19 surviving animals; the left atrium in 15, and a pulmonary vein in six. The average fluoroscopy time was 3.3 minutes.

The only significant lesions found at autopsy were small hemorrhages in the aortic valve cusps.

Left heart catheterization in dogs is a simple and relatively safe procedure.

ACKNOWLEDGEMENT

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AN ANALYSIS OF 5357 ROUTINE BLOOD CULTURES (1953–1955)

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The analysis of a number of series of blood cultures obtained under a variety of physiological and pathological conditions has been the subject of numerous reports in the literature. These include the findings in normal healthy people (1), during physiological alterations (2, 3), after manipulation or trauma (4–10), following radiation (11–13), as well as in patients with different disease states (14–17).

It was believed of interest to examine and record the recent experience at The Mount Sinai Hospital with routine blood cultures performed on patients with a wide assortment of clinical conditions in whom the existence of bacteremia was suspected. The period under study (1953–1955) coincides with that in which a number of new antimicrobial agents covering a broad spectrum of activity were used extensively and with the development of resistance to their action by a number of originally sensitive bacterial species. These factors have undoubtedly exerted an influence upon the type and proportion of different microorganisms isolated during this interval. Although comparison with earlier reports is extremely difficult because of the lack of uniformity in laboratory techniques and culture media employed, clinical diseases investigated and geographical locations considered, it was nevertheless hoped that significant alterations in pattern could be revealed in this manner.

Interpretation of the significance of the presence of some microorganisms in the blood stream often poses considerable difficulty. They may be transient invaders or the result of existing physiological conditions or the consequence of contamination at the time the specimen is being collected or while being handled in the laboratory itself. However, bacterial clinical correlation can be established with some degree of certainty if the relation of the bacterium in question to the presenting clinical picture is carefully evaluated and if its persistence in repeated culture as well as its pathogenic potential is taken into consideration.

The basis for this report is the 5357 blood cultures performed during the three year period. Obvious contaminations and questionable isolates unable to meet the criteria noted above have been excluded from the tabulation. Confirmatory repeat positive examinations have not been counted either in the total number of blood cultures performed or in the total of positives.

MATERIAL AND METHODS

The routine method employed for performing blood cultures at The Mount Sinai Hospital consists of drawing approximately 25 ml of blood by venipuncture

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after careful preparation of the skin with iodine and alcohol. Using careful sterile precautions, the blood is distributed at the bedside as follows: 5 ml each into three flasks containing approximately 100 ml each of (a) 1 per cent yeast extract broth, (b) 2 per cent glucose broth and (c) .005 per cent paraminobenzoic acid broth. Three petri plates are also poured from melted agar sticks, two glucose and one plain, to each of which is added 2 ml of blood. Finally, the remaining blood is inoculated into an anaerobic culture tube containing liver extract broth to which a piece of cooked liver had been added and then sealed with melted petroleum jelly. Penicillinase is added to the cultures in order to neutralize the growth inhibitory effect of the antibiotic whenever the patient is receiving penicillin. All tubes and flasks are incubated at 37° C. and, when indicated, all flasks, plates and tubes are placed in a lighted candle jar in order to produce an atmosphere of increased carbon dioxide concentration. Smears are made daily from each medium and examined for growth. In addition, for the first four days, each flask is subcultured daily into a fresh glucose broth and an anaerobic liver tube and on a blood, Endo and mannite agar plate. When positive growth occurs, the organisms are isolated and identified. Colony counts are made from the pour plates. All cultures are incubated and observed for a two week period before being discarded as negative.

RESULTS

The results of this survey are summarized in Table I.

TABLE I

Summary of blood cultures performed at the Mount Sinai Hospital during 1953 1955

Total blood cultures	5357
Number positive cultures	346
Per cent positive cultures	6.5%
Multiple positive cultures	13
Two organisms	10
Three organisms	3
Total number organisms isolated	362
Per cent organisms isolated	6.8%

As may be noted from Table I, of 5357 blood cultures performed, 346, or 6.5 per cent were found to be positive. Thirteen of these were found to contain more than one organism, ten had two organisms and three had three for a total of 362 organisms recovered from the blood stream.

A tabulation of the different microorganisms and the number of times each was isolated in this and in previously reported surveys is contained in Table II.

Although comparison between the findings reported herein and those previously reported is extremely difficult for the reasons mentioned above, a number of observations derived from examination of this table are especially noteworthy:

A. Six and a half per cent of blood cultures were positive. This is considerably lower than the 20.6 per cent reported for one series (2) that encompassed a period prior to 1940, before antibiotics became available. That figure however

TABLE II

Tabulation and frequency of microorganisms isolated in patients on routine blood culture in various reported series

Series	A Present Report		B Waisbren (16)		C Kotin (5)*		D King (3)		E Fox and Forrester (2)†
Period	Jan. 1, 1953 to Dec. 31, 1955		July 1, 1950 to April 1, 1951		Jan. 1, 1949 to Jan. 13, 1950		1942 to 1946		Prior to 1940
Total Number Blood Cultures	5357		1396		5000		2233		5310
Organisms Isolated.	362		44		325		121		1098
Per cent of Total Cultures.	6.8		3.1		6.5		5.4		20.6
Organism	No.	% of Orgs. Isol.	No.	% of Orgs. Isol.	No.	% of Orgs. Isol.	No.	% of Orgs. Isol.	—†
Streptococcus viridans	55	15.2	—	0.0	27	8.3	38	31.4	+
Aerobacter aerogenes	53	14.6	5	11.0	13	4.0	4	3.3	+
Escherichia coli	47	12.9	9	21.0	42	12.9	10	8.2	+
Micrococcus pyogenes var. aureus	40	11.0	2	4.5	45	13.8	35	29.0	+
B. proteus	25	6.9	2	4.5	8	2.5	1	0.8	+
Pseudomonas aeruginosa	21	5.8	2	4.5	7	2.2	1	0.8	−
Diplococcus pneumoniae	17	4.7	12	27.5	110	34.0	4	3.3	+
Micrococcus pyogenes var. albus	16	4.4	2	4.5	9	2.8	13	10.8	+
Enterococcus	15	4.1	3	6.8	—	0.0	—	0.0	+
Paracolon or Atypical E. coli	11	3.0	—	0.0	—	0.0	—	1.0	+
Salmonellae	10	2.7	1	2.2	6	1.8	1	0.8	+
Hemophilus influenzae	9	2.5	—	0.0	6	1.8	1	0.8	+
Neisseria meningitidis	8	2.2	2	4.5	7	2.2	3	2.4	+
Streptococcus pyogenes	6	1.7	—	0.0	17	5.2	4	3.3	+
Alcaligenes fecalis	6	1.7	2	4.5	6	1.8	—	0.0	+
Gamma Streptococcus	5	1.4	—	0.0	14	4.3	—	0.0	+
Diphtheroid Bacillus	3	0.8	—	0.0	3	0.9	—	0.0	−
Klebsiella pneumoniae	3	0.8	—	0.0	—	0.0	—	0.0	+
Brucellae	2	0.6	—	0.0	—	0.0	—	0.0	+
Candida albicans	2	0.6	—	0.0	—	0.0	—	0.0	−
Anaerobic Gram Negative Bacillus	2	0.6	—	0.0	—	0.0	—	0.0	−
Clostridium perfringens	2	0.6	—	0.0	—	0.0	1	0.8	+
Diphtheroid streptococcus	1	0.3	—	0.0	—	0.0	—	0.0	−
Spirillum	1	0.3	—	0.0	—	0.0	—	0.0	−
Serratia marcescens	1	0.3	—	0.0	—	0.0	—	0.0	−
Cryptococcus neoformans	1	0.3	—	0.0	—	0.0	—	0.0	−
Neisseria gonorrhoeae	—	0.0	—	0.0	—	0.0	1	0.8	+
Miscellaneous	—	0.0	2	4.4	5	1.5	2	1.6	+

* 665 positive blood isolates were obtained which were divided into those with and those without positive bacterial clinical correlation. Only the former are tabulated.

† This report is limited to a list of microorganisms isolated from blood cultures without quantitative data. Those listed are marked +.

appears to be unusually high even for that time. Since then, the incidence of positive blood cultures for the remaining reportees has been fairly constant and ranges from 3.1 to 6.5 per cent.

B. The relative incidence of Streptococcus viridans bacteremia which undoubtedly reflects the number of clinical cases of subacute bacterial endocarditis admitted to each institution was found to be 15.2 per cent and varied from 0.0 per cent in Series B to 31.4 per cent in Series D.

C. Approximately 50 per cent of all organisms isolated from the blood stream in our experience belong to the group broadly classified as Gram negative enteric bacilli. A similar percentage was observed by Waisbren (16). Only about 25 per cent and 13 per cent of the total of positives can be so categorized in the series of Kotin (5) and King (3), respectively.

D. Bacteremia involving Micrococcus pyogenes var. aureus and albus accounts for a significant proportion of positive isolates in each of the studies, 15.4 per cent in our series, 9 per cent in Series B, 16.6 per cent in C and 39.8 per cent in Series D.

E. Twenty-one of the 362 blood stream invaders were Pseudomonas aeruginosa and 25 B. proteus. It is of interest that the former was not mentioned at all in the list of organisms isolated before 1940 in Series E but since then it has been found in every report with increasing frequency. Together with B. proteus, both species constitute a total of 12.7 per cent of our positive blood cultures, 9 per cent of Series B, 4.7 per cent of Series C and 1.6 per cent of Series D (Table II).

F. The proportion of strains of Diplococcus pneumoniae (4.7 per cent) is considerably less than that formerly experienced in this laboratory in the preantibiotic era when pneumonococcal infections represented a major clinical and epidemiological problem. This finding is at considerable variance with those reported in Series B and C where 27.5 per cent and 34.0 per cent respectively, of all organisms isolated belonged to this bacterial species. These may be due however to a special concentration of clinical cases of this nature at these institutions during the period reported upon.

G. Bacteremia due to Streptococcus pyogenes, which once accounted for so high a proportion of positive blood cultures, is now a relatively infrequent occurrence—1.7 per cent in our experience and 0.0 per cent, 5.2 per cent and 3.3 per cent in Series B, C, and D respectively.

H. In spite of its intense susceptibility to the action of almost all the currently available chemotherapeutic agents, Neisseria meningitis continues to be recovered from the blood at all the reporting hospitals with a frequency ranging from 2.2–4.5 per cent of the total positive blood cultures.

I. Not a single strain of Neisseria gonorrhoeae has been isolated in this series, or in any of the others covering the period after January 1st, 1949.

SUMMARY

An analysis was made of 5357 routine blood cultures performed in patients suspected of having a bacteremia at The Mount Sinai Hospital, New York, dur-

ing the years 1953–1955. There were 346 or 6.5 per cent positives. Thirteen were found to contain more than one organism, ten had two organisms and three had three for a total of 362 organisms isolated.

The specific microorganisms isolated during this period and the number of each have been tabulated and compared with those previously reported in earlier series.

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THE ROLE OF STRESS SITUATIONS AND PSYCHOLOGICAL FACTORS IN FUNCTIONAL UTERINE BLEEDING*

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I am grateful for the opportunity to speak before this combined group. May I say it augurs well that this meeting, the first of its kind, should take place on the 100th Anniversary of Freud's birth.

A few remarks to lead you into the subject matter. Scientific process in medicine is similar to all fields of science. More often than not the first step is an observation. Then if the mind is receptive what usually follows is a speculation, on which a hypothesis is constructed. For the hypothesis here presented, psychoanalytic concepts are used as the framework for weaving a fabric, the texture of which is composed of somatic symptoms interwoven with the strands of psychological reactions (affects) and environmental circumstances.

An audience of gynecologists and psychiatrists might not find it too far afield to approach this problem in such a way that no aspect is favored or given prominence over another—neither the somatic symptom nor the psychological state nor the environmental constellation. This impartial treatment of the subject of functional uterine bleeding would seem particularly desirable in view of the fact that so little is known about it.

Functional uterine bleeding is defined by Richardson (1) as a pathological event which appears at unexpected times, or in abnormal amounts, in the absence of gross lesions. My particular interest in this condition was aroused by the observation of a woman in her middle forties who gave me an astonishing history. It seems that for more than twenty years she had not left her apartment. Yet, far from being the typical recluse—withdrawn and out of touch with the world—she was lively and well informed, displaying no evidence of psychotic behavior.

The patient had come to The Mount Sinai Hospital from a private mental hospital where she had been for a year, recurrent and increasing uterine bleeding having necessitated the transfer. Up to the time she entered the private hospital, the patient had always refused to act on her family's advice that she see a psychiatrist. Still, it had been on her own initiative that she was eventually hospitalized.

What had motivated this woman, after twenty years of self-imposed imprisonment, to voluntarily leave her apartment? The patient said it was the onset of vaginal bleeding that made her seek psychiatric treatment. When she first entered her voluntary confinement, she was exactly the same age as her mother had been when she (the mother) had had an abortion. The patient's vaginal bleeding began after her own daughter married and left home.

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From what this woman told me I was able to understand a great deal about the unconscious meaning of her having spent half her adult life in her rooms, and the connection with her mother's abortion and her daughter's marriage. These findings permitted me to speculate about the role played by certain happenings in the lives of women with functional uterine bleeding, their psychological reaction to such altered circumstances, and the possible relationship between external events, psychological reactions and functional uterine bleeding.

Subsequently I studied 81 cases of functional uterine bleeding (54 from the literature, 2 in psychoanalysis, and 27 at The Mount Sinai Hospital.) The experiences of these patients found to be associated with the bleeding were either sexual or non-sexual in nature, or a combination of both. More specifically, experiences of a sexual nature were found where the bleeding was either a reaction to sexual stimulation—following intercourse, sexual propositions or sexual fantasies—or a reaction representing avoidance of sexual intercourse and/or pregnancy.

The earliest cases in the literature supporting the hypothesis that functional uterine bleeding is precipitated by or associated with psychological factors refer mostly to sexual experiences. Historically, this circumstance is in line with psychoanalytic writings of the time, uterine bleeding being then considered hysterical in nature.

More recently it has been observed that stress situations generally, and intense emotional reactions such as shock, fright and anger are also associated with functional uterine bleeding. The particular kind of stress situation involved is apparently of little import.

Regarding the group of women whose bleeding seems to be associated with experiences of a non-sexual nature, I noticed on surveying the literature and examining my patients that in a number of cases the bleeding was a reaction to events that had one important thing in common; namely, an experience of loss, prior to the onset of bleeding.

The loss could be that of a person—desertion by husband or lover, or of a son or daughter through marriage. Or it could relate to a subtraction or change in the person of the woman herself, such as having an abortion, a miscarriage, a reduction in weight, or the ceasing of an important function, as in hemiplegia. Of outstanding importance are situations where the bleeding is preceded by the loss through death of someone close to the patient—parent, spouse, child or fiancé. For such a person we use the term "love object."

To reiterate, a variety of both sexual and non-sexual experiences are found to be associated with functional uterine bleeding. Experiencing a loss of some kind assumes a prominent place in these cases. Further, it should be noted that a combination of sexual and non-sexual stress situations may be found in the same case, either concurrently or at different times in the patient's life.

In a statistically valid number of cases, there was some experience of loss preceding the onset of functional uterine bleeding. Yet, an understanding of this phenomenon is far from being simple. What is the connection between the environmental event—the loss of a love object—and the subsequent somatic event of functional uterine bleeding? The link between the two is provided by a typical

psychological reaction associated with the loss of a love object: namely, depression.

In this connection, it would be appropriate to present the first case reported in the literature in which psychological factors were acknowledged, and psychotherapy used successfully. The case was reported by Eisler in 1923 (2). Since the onset of the 40 year old patient's illness dated back to her teens, the incident of bleeding evidently took place around the turn of the century. As will be seen, at first the bleeding followed sexual stimulation, and later on in the woman's life it was apparently connected with the loss of a love object.

The case reads as follows: "Between her sixteenth and seventeenth years a young man whom she liked courted her. While dancing at a ball, he propositioned her and then pursued the shocked girl to the powder room. Here she suddenly and unexpectedly started to bleed. From this moment on her menstruation lasted for about five years. The best and most skillful gynecologists were called and after various attempts at treatment, a curettement was suggested. Following artificial defloration of the patient the curettement was performed, which, however, did not change the matter at all. There was another curettement of the uterus until finally one gynecologist sent the patient to a neurologist. This particular gynecologist, a well known specialist, had at that time—20 years ago—read the first papers by Freud, and influenced by this reading, made the diagnosis of hysteria.

"After a short therapy of suggestion, the condition of the patient ended. Only the suicide of her first fiancé, about three years later, brought about a short episode of bleeding. After another three years her much beloved brother died. In consequence there was a severe depression; however, the uterine bleeding did not take place."

What is perhaps most telling in this case is that the patient suffered a recurrence of the uterine bleeding several years later, when her fiancé committed suicide, and three years after that, when her "much beloved" brother died, she had a severe depression. It would almost seem that her depression took place as a substitute for the bleeding.

At this point a hypothesis may be suggested, formulated within the concepts of psychoanalytic thinking. Assuming that the woman responds to the loss of a love object with a depression—a common reaction, though varying in intensity with the individual—what is uncommon and requires explanation is that in certain women uterine bleeding might take place instead of or concomittant with this depression. Time does not permit a discussion here of the psychology of depression, other than to mention briefly what has been learned from psychoanalytic studies. Depression has been found to be preceded by fantasies of aggression towards the love object. This results in feelings of guilt, leading to what is called a turning of the aggression towards oneself.

The self-directed aggression may express itself in self-destructive thoughts or acts. Not uncommonly, the physician is used as an instrument for carrying out these self-destructive tendencies, as for instance when the patient requests surgery that is not indicated.

There is also not sufficient time here to discuss the affect of depression in

regard to its transmission into the somatic event of uterine bleeding. However, the matter of choice of the organ is worthy of mention. The uterus is the organ from which bleeding ordinarily occurs regularly, in the physiological event of menstruation. It would seem that the psychological reactions to menstruation may be correlated with those psychological reactions found in women with functional uterine bleeding.

Without distinguishing, for the moment, between conscious and unconscious responses to menstruation, a variety of such reactions have been observed. Among the most common, perhaps universal, is a reactivation of castration anxiety. It is understandable that bleeding such as in menstruation, appearing as it does without apparent cause, would give credence to the notion of injury being inflicted on the body. Another reaction to menstruation, not uncommonly seen, is the feeling of disappointment in women who wish to become pregnant. Menstrual bleeding at such a time has been called "the weeping of the disappointed womb."

In addition to other reactions not mentioned here, there are some women for whom menstruation takes on an added meaning. This meaning provides a clue to the suggestion that *functional uterine bleeding may be a possible equivalent of the state of depression following the loss of a love object.* If additional confirmation could be secured, it would seem that functional uterine bleeding, like depression, performs an important function by helping to maintain the psychological balance (homeostasis) of the woman.

Since depression is the expected psychological response to an actual loss of a love object, we are led to believe that women who are depressed in response to their menstruation are behaving as if they were experiencing a loss of a love object. In such women, depression may vary in degree from fleeting thoughts of suicide to preoccupation with the subject, attempts to commit suicide, or actual suicide. Why certain women react with such intensity to their menstrual period is not yet altogether clear, but seems to relate to experiences with parental figures in early childhood. The two patients with functional uterine bleeding whom I had the opportunity of studying psychoanalytically, despite differences in their lives and genetic history, had in common early separation from the mother.

In my opinion such reactions to menstruation—as if it represented an actual loss of a love object—cut the pathway along which responses are directed later on in life, following the loss of a love object. For those women menstruation revived the memory of an earlier experience of separation from or loss of a love object. Hence menstruation signified to them the loss of the love object. This then is the psychological structure which is later utilized when they again experience separation from or loss of a love object.

A similar mechanism is operative in regard to functional uterine bleeding which follows the loss of a love object. Instead of grief and mourning over the loss, we may find in women who are so disposed a somatic equivalent in the form of functional uterine bleeding. For this reason, I have called the uterine bleeding which follows the loss of a love object the "weeping of the mourner."

It would seem to be neither possible nor desirable to describe the characteristic features in the psychological makeup of women with functional uterine bleeding,

so that they fit a certain type. One can find such bleeding in neurotic as well as in psychotic individuals. If I were to single out some of the traits I observed most frequently, they would be oral fixation and a masochistic character structure. As previously pointed out, my psychoanalytic patients both experienced early separation from the mother.

The psychological mechanism operative in functional uterine bleeding might be outlined as follows:

1. A separation from or loss of a love object in early childhood or infancy, leading to fantasies of oral incorporation. In this way the love object becomes tied in with a bodily function, i.e. that of the intestinal tract.

2. In puberty, menstruation—regardless of how well it is understood mentally—is experienced as a loss of a love object because of the earlier fantasies of oral incorporation.

3. Following establishment of menstruation, the actual loss of a love object may precipitate functional uterine bleeding. This bleeding has in common with menstrual bleeding an unconscious connection with the idea of the loss of a love object. As in early childhood, a reunion with the love object is therapeutically effective.

The case histories that follow represent a cross section of the material one finds in instances of functional uterine bleeding. These patients had a careful medical and gynecological work-up, and more than one dilatation and curettement. In cases where the curettement did not reveal a pathology responsible for the bleeding, or where the bleeding continued or recommenced after the procedure, it was logical to assume that the bleeding was a symptom not of local pathology but rather of either hormonal or emotional imbalance. In passing it may be mentioned that hormonal and emotional imbalance are often mutually interactive.

Case #1

C. V., a 26-year-old Puerto Rican woman, mother of a 4-year-old girl, and separated from her husband, was hospitalized for bleeding, three times between September 1953 and April 1954. Each time a dilatation and curettement was performed. On her first admission the pathological report showed hyperplastic endometrium and endometrial polyp. The findings of the subsequent curettements were non-contributory.

The difficulties of this patient began in March 1953 when she and her husband and his mother were all living together. The patient could not get along with her mother-in-law whom she considered quite fussy and selfish. Eventually, she asked her husband to choose between her and his mother. Whereupon the husband left the apartment, taking his mother with him. Two months later the mother-in-law was admitted to Bellevue Hospital in an acute psychotic state. There she had an attack of asthma and died suddenly. One month later the patient's vaginal bleeding started.

Of the patient's past history, the following data are significant: She was born in Puerto Rico, the ninth of 12 children. At the age of 21 she married, becoming pregnant soon thereafter. All through her pregnancy she vomited, a condition which grew worse towards the sixth month when she became depressed, cried constantly, and refused to eat. The patient described her feelings: "I didn't want to eat, I didn't want to talk to anyone, I wanted to be dead and I wanted to die." She wondered if perhaps she had wanted to kill herself by not eating. Apparently because of this suicidal mood, she was closely watched by her mother with whom she was then living.

The patient left her daughter, who was then about two years old, with her mother in Puerto Rico, also leaving behind her husband, and came to the United States. A year later

she was reunited with her husband and child. Following their separation, she gave her child to her mother once more and moved into the dormitory of a hospital where she was employed.

A rather attractive young woman, she appeared resentful and reticent. From her description of her mother and her mother-in-law it seemed that the disagreeable character of her mother-in-law played into the patient's hands since it served her ambivalence towards her own mother. It permitted a division of her feelings, so that all her positive feelings were attached to her mother and all her negative ones to her mother-in-law. While there was no apparent depressive mood, preoccupation with death could be found on closer examination. The vomiting and depression during her pregnancy are particularly significant. In this case, the bleeding followed the death of the mother-in-law which was preceded by the patient's separation from her husband.

Case # 2

C. C., 45-year-old Puerto Rican woman, separated from her husband for the past 15 years, was admitted to The Mount Sinai Hospital for the second time for vaginal bleeding. Both times a dilatation and curettement were performed. The second time, during which I saw her, she had been bleeding for the past 7 weeks. The pathological report read, "Endometrial Hyperplasia."

Married at the age of 20, she separated from her husband nine years later. With no close relative in town, and being rather withdrawn and suspicious, her life centered around her only child, a son. Two years ago, when he was 19, he informed her that he was going to be married. She became quite distressed at the news and expressed her objections. It was following her son's marriage that her bleeding started. Even on superficial examination it was evident that the patient was depressed and fearful. She said she found it more agreeable to live without men, and thought her home was so much more peaceful without them.

There was constant preoccupation with death. She felt she was an old woman, constantly thought of death, and expected to die any day. She wondered whether I too did not think of death all the time and was greatly surprised to learn that everyone is not perpetually brooding about death. Her bleeding considerably accentuated her fear of dying. In this case, the depression was so obvious that it was recorded by the interne who took the history. The significant factor here is that it was the marriage of her son—the only person in her life who meant anything to her—that had precipitated the bleeding.

Case # 3

A. N. is a 29-year-old, married Puerto Rican woman. She had an excellent work-up from the gynecologic, endocrinologic and hematologic points of view. It is noteworthy that this patient demonstrates a severity of symptomatology that is in sharp contrast to what appear to be the contributing causes.

The medical history is as follows: At the age of 19 the patient had her appendix removed, and a year later she married. The wedding took place on March 30th and a baby girl was born on the 18th of December. The patient believes she became pregnant on her wedding night. Several months after the birth of her baby she started having pain in her right side and vomited. Actually, the vomiting began prior to the appendectomy, continued during the first three months of her pregnancy and set in again several months after delivery. At the age of 22 she was operated on and a resection of an ovarian cyst performed. When she was 25, the family moved to New York.

In May 1952, when she was 27 years of age, the first episode of bleeding started. She bled constantly until July when the first dilatation and curettement was performed. Two years later, again in May, she had another episode of bleeding which continued until September when the second dilatation and curettement was performed. When the time for her next period came around, she started to bleed once more, continuing until the third dilatation and curettement in December of 1954. Again, four weeks later when she expected her period, she started to bleed and this continued until the fourth dilatation and curettement was done. The pathology report shows blood with minimal endometrial tissue fragments,

and endometrium in the pre-menstrual phase. The basal metabolic rate as well as iodine studies revealed normal metabolism. A hysterogram was normal. Urinary 17-ketosteroids were normal. A bleeding work-up was done and this was also normal.

The patient has a very pleasant appearance and a charming smile. There is a Madonna-like quality in her facial expression. She seemed curiously indifferent towards her own difficulties. In contrast to most of the patients I observed, this woman had apparently led a happy family life with her husband and daughter. At home in Puerto Rico, she remained with her family even after her marriage. She assured me that after her first child was born she wanted another one very much. But although they tried to have one, she could not conceive again. She thought the doctor might have removed her tubes when he operated on her for the removal of the ovarian cyst.

With all her friendliness, I could not escape the impression that she was not revealing significant material. All I had to go by in this puzzling case was the fact that her first episode of bleeding started in May 1952 and the second, also in May of 1954. This timing was reminiscent of a case by Blaikley where a woman had an episode of bleeding on the anniversaries of the death of her three sons who had all been killed in action during the war.

I saw the patient again when she was admitted for her fourth curettement. At that time she was depressed and said, "I am rather dead than go suffering on like this." Having had a chance to speak to the doctor who had removed her cyst, she had made the important discovery that her tubes had actually been removed. By now she realized that the doctors could find no cause for her bleeding, and she thought perhaps God was punishing her. She recalled a passage in the Scriptures in which there was a woman who bled for 12 years.

At this point the patient revealed that while living at home with her parents, she had treated her next younger sister, a girl eight years her junior, as if she were her own child. When the patient and her husband came to New York, they took this sister along. In May 1952, the sister, intending to marry, left them to return to Puerto Rico. It was at this time that the patient's first episode of bleeding started. With perplexed amazement the patient realized that there might be a connection between her sister's having left and her own bleeding. However, there was contentment in the tone she used to announce the fact that "My mother and father are going to come to live with me." In other words, this would make everything all right again.

The preoccupation of the patient with religion was rather intense, and she attached guilt to the bleeding, fearing punishment from God. The self-destructive attitude was there, but it was not manifested in a state of depression. Instead, there were the two abdominal operations which were associated with vomiting. Since her functional bleeding followed the loss of her younger sister, who represented the love object, we may speculate that in her fantasy this sister represented the patient's own child, thus making the patient's guilt understandable.

I shall close with the biblical quotation referred to by the patient, which I found in the Book of Mark, Verses 25 to 29, Chapter V.,

> "And a certain woman, which had an issue of blood twelve years,
> "And had suffered many things of many physicians, and had spent all that she had, and was nothing bettered, but rather grew worse,
> "When she had heard of Jesus, came in the press behind, and touched his garment:
> "For she said, If I may touch but his clothes, I shall be whole.
> "And straightway the fountain of her blood was dried up; and she felt in her body that she was healed of that plague."

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THE EMOTIONAL IMPACT OF WARD ROUNDS

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"*An honest business never blush to tell.*"
Alexander Pope's translation of Homer's *Odyssey*.

The purpose of this study was to examine the emotional reactions of ward patients to ward rounds conducted by the attending staff.

The psychiatrists who carried out the study are assigned as liaison psychiatrists on the services observed; one one the female medical ward (D.K.) and one on the female surgical ward (A.N.F.). The latter also made rounds frequently on the male surgical ward and occasionally on the gynecological ward from which several of the cases reported are drawn.

This study was carried out with the approval and cooperation of the chiefs of the Department of Medicine and the Department of Surgery. It was agreed, however, that it would be best if the rest of the staff were not informed of the fact that such a study was in process in order that ward rounds might be observed as they are normally conducted.

METHODS OF CONDUCTING WARD ROUNDS

The Medical Service

Attendings' rounds on the female medical ward are conducted at the bedside daily in the afternoon. Generally there are two attendings who are accompanied on rounds by from two to six members of the house staff, including interns, assistant residents, and residents along with occasional visitors. New cases are usually presented first after which old cases are seen. The intern presents the history and findings on each new case before the group approaches the patient's bedside. One or both of the attendings then examines the patient and may ask her further questions. Others in the group also may examine the patient. Most often the group then moves away from the bed to discuss the case, but not infrequently discussion is started as the attending is going over the patient.

The Surgical Service

The procedure on the female surgical ward is for Grand Rounds to be held once a week for the entire staff on Saturday mornings when no operations are scheduled, and then for additional rounds to be held at other times during the week, usually in the afternoons, at times in the morning, by the chief of service, the attendings, and the residents respectively. There may be as many as twenty

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or thirty in the group at the bedside, including physicians and nurses, as in Grand Rounds, or as few as two to four when the chief of surgery makes personal rounds with the chief resident and an intern or two.

The group enters the ward *en masse* and goes straight to the first bed where it pauses for the case presentation. In general, the procedure is for the intern to whom the case is assigned to give a resumé of the case history and findings, including x-ray and laboratory data, and to answer questions from the group. The attending then begins the discussion by commenting on the case and inviting comments from colleagues and visiting physicians who may be present. He then questions the interns and residents, answers their questions, recalls other cases and introduces pertinent experiences of his own or other members of the group. Each bedside visit may last from a few moments, if the case is well known to the group, to as long as fifteen to thirty minutes if it is a new, especially interesting or puzzling case. The group then moves on to the next patient where the same procedure is repeated. Usually the discussion of the case is begun and completed at the bedside, though on rare occasions when information or a prognosis which the patient should not hear is involved the discussion may be completed in the outside corridor after leaving the ward. In general, rounds last from one hour to an hour and a half in all.

PROCEDURE OF THIS STUDY

An effort was made by the psychiatrists to attend enough rounds during the period of this study to afford a good sampling of their character and procedure on the respective wards. It was deemed desirable in this study to explore the immediate reactions of the patients to ward rounds without allowing too much time for the impact to wear off. Hence, in order to see the reactions while they were fresh, patients were interviewed by the psychiatrist immediately after the staff had passed on from the bed of the patient being studied, the time interval being anywhere from a minute or two to a maximum of half hour. The interviewer was usually a part of the bedside group while the patient was being examined and discussed and was thus in a position to observe the patient's reactions to the comments and procedures of the staff.

The psychiatrists' interviews generally began with a question such as "How are you today?", followed by "How do you feel having all these doctors around you discussing your case?". Beyond this, the interviews did not aim to follow any pattern, questions and comments being framed to suit the need of the situation based upon the observations made during the rounds and designed to elicit the patient's reactions fully both to the general situation and to any special circumstances noted.

It was decided in advance to limit the findings to the patient's verbal expressions plus whatever emotional phenomena could be directly observed by the interviewer as he talked with the patient. Brief notes of the findings on each patient interviewed were made before leaving the ward and were amplified within a day or two. The effort was made insofar as possible to record the patient's exact words.

FINDINGS OF THE STUDY: MEDICAL ROUNDS

General Atmosphere: Female Medical Ward

A word is in order first of all about the behavior of attendings and house staff on the medical ward toward each other. The general impression obtained was that interns seem to feel quite free to ask questions and express opinions, even opinions that differ from those of the attending. Discussions were animated with free give and take. No instance could be recalled where an intern or resident was criticized in the presence of a patient. The dominant atmosphere of rounds was that of a friendly discussion between junior and senior colleagues. At times in a case of grave illness, when the discussion approached data that could disturb the patient, and this was signalled to the attending by the intern or resident, this action was not objected to in any way by the attending in the instances observed. On the contrary, the attending's expression often indicated appreciation for being reminded that he was talking too freely in the patient's presence. It should be said that this maneuver did not always succeed, the timbre of the voices of some attendings being such that remarks were audible throughout the ward no matter where the group stood.

Specific Findings: Female Medical Ward

Fifteen patients on the female medical ward were interviewed over a period of two months; during this interval with rotation of services, two different groups of attendings were on service on the ward.

The most frequently heard reaction from patients was that they understood that rounds were beneficial to them, as it gave them the benefit of the opinions of a number of doctors. Many patients also were aware that the "outside doctors" were older and more experienced men, and they welcomed their participation. The quality of this reaction to rounds varied from a welcoming attitude to a resigned acceptance of the procedure as a discomfort which must be borne, because it was beneficial.

Patients who remained on the ward for any length of time came to accept rounds as part of the day's routine. Many of the same patients who showed this degree of understanding, at the same time showed considerable resentment of the multiple examinations during rounds. As one patient graphically put it, "All hands, nothing but hands coming at me." Three other patients used the conventional metaphor of being "used as a guinea pig", with such added comments as "They all have to have a look!"

In the present series of fifteen cases, no instance was observed in which a patient was perceptibly upset to any significant degree after rounds. However, cases had previously been observed in which patients were acutely distressed or in a state of panic after rounds. These were, for example, patients with a malignancy who first learned of their diagnosis through careless talk at rounds, or cardiacs who were frightened by hearing words like "failure" or "attack". Gross indiscretions of this sort did not occur in this series.

It is equally true, however, that one saw few indications that rounds had had any positive meaning to the patients. While, as mentioned above, some

patients were gratified, in a general way, to know their treatment was under competent supervision, one did not hear any specific reactions that would suggest a feeling of relief, reassurance or gratification arising from anything said by an attending. This point will be discussed further later.

Discussion of what patients overheard during rounds elicited some interesting facts. More than half of the patients interviewed said either that they could not understand a word of what the doctors were saying or that they had paid no attention. One patient went further, saying "*I don't want to know what they're saying.*" A minority said they listened very hard but learned little that they didn't already know.

While it may be true that modern medical talk grows ever more incomprehensible to laymen, these responses suggest that something more is involved than the mere fact that doctors use a jargon of their own. What seems to be operating is the psychological mechanism of "denial", a device by which one avoids knowing or thinking about anxiety-producing facts.

A classic example of this was furnished by an intelligent young woman admitted for a second bout of acute disseminated lupus. The discussion at rounds had been discreet, and she was in good spirits both during and after rounds. When she was asked what she knew of the nature of her illness, she disclosed an accurate knowledge of its name and nature. After her first admission, she had looked it up in a medical dictionary, where it was defined as "a chronic, fatal disease".

"You know," she said brightly, "a thing like that could scare you." For herself, she managed not to believe that this definition could apply to her, and succeeded in being sure she would get well. The talk at rounds, which she said she hadn't listened to very carefully, had done nothing to shake her unfounded optimism.

CASE REPORTS: FEMALE MEDICAL WARD

There were a number of individual reactions that are worth describing in detail.

Case #1. A 39 year old woman with rheumatic heart disease, admitted for evaluation as to the use of cardiac surgery and very eager to be accepted for surgery, was upset because she thought the "head doctor" was opposed to operation. Although the discussion was carried on at a distance from her bed, the chief's voice was audible, and she had caught snatches of his remarks. As it happened, the chief was actually in favor of surgery, but discussed all the pros and cons with his staff. The patient heard some of the cons and was deeply distressed at the prospect of being denied the chance of a surgical cure.

Case #2. A 52 year old patient, a woman of some sophistication, was suffering from severe angina pectoris, whose control was proving a difficult problem for the staff. On more than one occasion, there was considerable discussion of possible therapeutic procedures, although no immediate conclusion was reached. The patient's reaction to this was directed at the "head doctor", to whom she looked for some answer to the problem that the younger men could not solve. "What are they going to do for my pain?" she asked. "I'd like to take that head doctor and shake him and make him tell me what they're going to do."

In less emphatic ways, other patients also conveyed the feeling that they missed some comment from the attending that would explain, reassure, or indicate a prognosis. While they had heard answers to their questions from the house staff, this was not, for them, the same thing as hearing something from the attending physician.

Case #3. Two patients who had just been admitted, had a specific reaction to their first

experience with rounds. Unfamiliar with ward routine, the sight of a crowd of doctors bearing down on the bed, struck terror to their hearts. The immediate thought, as one put it, was "I must be doomed for sure, or else why would all these doctors be coming to see me?"

Case #4. A young Negro girl with a pneumonic consolidation of uncertain nature was in one of the bedrooms. Her x-rays were looked at and discussed at the other side of her room but within easy view and earshot. There was considerable talk about the nature of the shadow visible in one lung field. When she was spoken to, the word "shadow" was uppermost in her mind. "I wanted to tell the doctors that maybe that shadow on the x-ray was because I had this gown on when they took the picture." Further discussion brought out the fact that several members of her family had had serious lung ailments (possibly TB, though she professed not to know) and she had heard talk about x-ray shadows in this connection. Her naive comment about the gown was probably an expression of her fear that she, too, might have what the others had had, and she preferred to believe that the shadow came from her clothing rather than her lung.

Case #5. A 26 year old girl, admitted for the seventh time with a possible recurrence of rheumatic fever and with old rheumatic heart disease, was a diagnostic problem and therefore the subject of lengthy debate. As in other cases, although the group had moved away from her bed, the patient could clearly hear the various diagnoses being argued back and forth. Although she probably could not understand the terms she heard, it was unmistakable even to a layman that the staff were unsure and were turning over various possibilities. On speaking to her, it was obvious that she was upset. But she steadfastly denied this. She knew her diagnosis was unclear, but said, with all the effort at bravado of one whistling past a graveyard, "I'm sure they'll find it." One was convinced that she was frightened at the realization that her doctors were in the dark, and she was trying hard to reassure herself.

COMMENTS: FEMALE MEDICAL WARD

Rounds as they are currently carried out on the medical wards are, on the whole, not traumatic to the patients. This is, apparently, due to two chief factors. The *first* is the fact that the medical staff are generally discreet in what they say in front of patients, and that the atmosphere at rounds is a comfortable one, not likely to create tensions in the patients. The house staff seem to be a little more alive to the importance of discretion than the attending staff. The *second* is that many patients are able to control their anxiety by denying the facts of their illness so that, unless doctors are grossly careless in their remarks, patients are often able to insulate themselves from what they overhear.

There are occasional lapses which do create unnecessary anxiety or concern in the patient. Probably the most common lapse is not in the use of frightening words, but rather in permitting patients to become aware of differences of opinion or perplexity among the staff. It should be recognized that prolonged doubt can be more frightening than the grimmest certainty. Most disturbing of all is the feeling that one's doctors are at sea, are fumbling for an answer, or cannot agree among themselves. Also, such instances as that of the girl with the "shadow" point up the fact that one can never know which chance remark will provoke anxiety. The safest course is to carry on *all* discussion of a case well out of the patient's hearing.

FINDINGS OF THE STUDY: SURGICAL ROUNDS

General Atmosphere: Female Surgical Ward

On the female surgical ward the general tone was one of a seemingly more structured pattern than that reported on the medical ward. The discussion all

took place at the bedside rather than before and after in a more isolated location. This is perhaps due to a considerable degree to the mechanical aspects of surgery and the frequency with which there are things to see and feel. Discussion of wounds, colostomies, etc. is probably best done while these are in view. The attending physician set the tone of the conference on a didactic plane. The interns and residents appeared to be somewhat in the position of pupils striving to make a good showing in the presence of exacting teachers, and fearing to have their shortcomings and inadequacies revealed publicly if they should chance to slip up. There were a few instances actually observed when the attendings "chewed out" a subordinate when a diagnosis had been missed, a proper therapeutic procedure not instituted or a questionable one used.

The observer got the feeling that a "hierarchy" existed, the higher echelons of rank and status having rights and prerogatives not accessible to those immediately below them. Interns and residents seemed often hesitant to ask questions or expound divergent points of view if they felt they were of a rather elementary nature, lest they embarrass or humiliate themselves publicly. The tendency seemed to exist for interns to put off questions until the residents' rounds when greater freedom of inquiry seemed to prevail. This attitude may stem from the fact that there were instances (as detailed below) where interns and residents were actually reprimanded or chided at a patient's bedside and in the hearing of the entire ward for seeming lack of knowledge or judgment or or for using therapeutic procedures which the attending questioned.

Observation of the protocol in the operating rooms which was undertaken for a corollary study appeared to lend some confirmation to this finding. The assistants were on occasions seemingly over-severely spoken to by the operating surgeons. During the period of this study, both on the ward and in the operating room, the feeling that older and younger colleagues equal in respect and professional dignity, despite differences in age and rank, were working together for the benefit of the patient was not always apparent.

Specific Findings: Female Surgical Ward

Forty-nine patients on the various wards mentioned were observed over a period of over two months. The chief and most of the attendings on surgery conducted the ward rounds observed, affording what was probably as good a cross section of the character of the procedure as was obtainable under the circumstances. The findings reported and the specific observations on which they are based follow. The case reports are included with the findings in this part of the report.

The presence of a large group of doctors around the bedside of the patient has in and of itself, as might be expected, an impact. If it is for a brief period of time and nothing is said which can be interpreted unfavorably by the patient, the effect may be reassuring. This is seen in cases 9, 30, 31, 35, 21 (Table I).

As noted in cases 9 and 21 (Table I), even when the patient's condition is not satisfactory, she is eager to accept reassurance from all the doctors, together. In some cases the patient seems to ignore or "deny" her emotional reaction, putting on a garb of seeming calm, as shown in cases 33, 48, and 29, Table II.

TABLE I

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
9 n.f. (55)	Carcinoma with colostomy.	"An adeno lesion. Doing fine."	"Feel good. The doctors have saved my life."
30 w.f. (40)	Radical mastectomy, post operative.	Examination of incision and discussion of progress.	Patient does not mind doctors discussing case. "Hope it will have been in time."
31 w.f. (40)	Gall bladder, post-operative.	Examination and discussion.	Patient does not mind having all the doctors around talking about her. "I feel better; they helped me."
35 w.m. (40)	Intestinal obstruction. Treated non-operatively.	Discussion of condition and treatment.	"I feel good about having all the doctors around. They have helped me without an operation."
21 w.f. (30)	Thyroidectomy, which on operation showed extensive mediastinal metastases.	Intern said: "Thyroidectomy 3 days ago. Doing fine." (No further discussion of case until after rounds, when it was discussed fully in the corridor.)	Patient felt good about the doctors' thinking she was doing well. (Had no suspicion whatsoever about her prognosis.)

In cases 4, 23, 41, 11, 39, and 6 (Table III) the patient's emotional reaction is glowingly positive but reveals by its very effusiveness an underlying anxiety. Sometimes the anxiety can actually be verbalized in the midst of masking protestations about "feeling good at having all the doctors" around the bedside. In case 4 (Table III), even though the doctor says the patient "has been a headache to us", the patient hastens to justify the doctors, but queries "Will I get better?", revealing her anxiety. Patient 11 also justifies doctors, despite a frightening discussion of ulcer deaths in dogs.

Many patients say "I don't mind, but . . . . ", and go on to reveal that the rounds were really disturbing to them for one reason or another. Sometimes it is the patients' anxieties about their condition (cases 26 and 36, Table IV). Sometimes they resent not being told more about their condition or the procedures contemplated (cases 3 and 34 of Table IV; also 32, Table V). Others resent the manner in which they are treated, or the fact that they have to be ward patients (case 7, Table V). In case 13 (Table IV), there was a paranoid reaction, the patient feeling the doctors were laughing at her colostomy.

The bedside consultation is sometimes disturbing to patients even though nothing untoward is said or done (case 16, Table V). The patients may express open resentment or nervousness, or fear that the presence of all the doctors bodes ill for them (cases 12, 7, 17, 27, and 28, Table V). Case 16, Table V, lay quietly while the consultation was in progress, then could scarcely hold her diarrhea, seemingly due to her fear and distress. This patient has a previous

TABLE II

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
33 w.f. (70)	Possible obstruction.	Discussion of condition and desirable procedures.	"I don't pay much heed to the discussion of the doctors. They will do what they think best."
48 w.f. (40)	Coronary after colostomy.	Full presentation of the cardiac episode.	Patient smiled and seemed unconcerned. Later recognized that she had prepared so long for colostomy that she was unwilling to accept another "insult". She had excluded it from her thinking about why she was confined to bed for 2 extra weeks.
29 w.f. (82)	Jaundice.	Long discussion of whether to operate or wait.	Patient, very intelligent old lady, reading fine literature, listens with interest to discussion but "leaves it to the doctors." (Patient was discharged to rest home and rushed back as emergency within 24 hours and operated on. Did not resent handling and took procedures philosophically. Was glad to know at last she would be better.)

psychiatric history and was transferred within a day or two to the psychiatric ward.

Patients sometimes react disproportionately to something they either hear or think they hear, or to some act of omission which becomes the focus of their anxiety or resentment. Thus, in case 38 of Table VI, mention of the diagnosis "gynecomastia" made the patient anxious because he thought it meant "carcinomatous degeneration". Patients 8 and 19 (Table VI) were furious because they could not hear the discussion of their case. Patient 18 (Table VI) misunderstood the surgeon's remark to mean another operation was necessary, and was ridiculed by him for it, which made her very angry, and patient 44 (Table VI) was upset because her question was ignored.

Sometimes the patient is upset by carelessly used terms which have an ominous significance like "five year survival", "C.A.", "carcinomatous", or "malignancy". Generally, the surgeons were very careful to substitute masking terms, but it is perhaps inevitable that a slip should occasionally occur. The patient may be visibly upset but may not be willing consciously to "believe her own ears", and may use the mechanism of denial.

TABLE III

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
4 w.f. (55)	Repeated episodes of intestinal bleeding of unknown origin.	"This patient has been a headache to us."	"The 'headache' is from thinking what to do to help me. I don't mind all the doctors talking about me. Just so they help me. Will I get better?"
23 w.f. (60)	Accidentally severed common duct on gall bladder operation.	Extensive discussion of why it occurs and what to do about it.	"I feel wonderful about having all the doctors talk about me. They will help me. The Bible says every doctor has an angel to help him. The Talmud says 'Don't live in a place where there are no doctors'."
41 w.m. (55)	Probable gastrectomy.	Long discussion.	Patient thinks having a lot of doctors around helps. (Is a very intelligent Swiss.) Had been treated with palliatives for a long time and now is prepared for what is to come. "I know I will be uncomfortable for a few days, but I was no good when I came in, and what's the use of that?" Is anxious about the possibility of cancer, but "now I will know, and something will be done about it, if it is." Happy to have opportunity to discuss his case.
11 w.f. (c.30)	Ulcers	Discussion of dog experiments where animals hemorrhaged and died; also term "C.A." was used.	"Don't mind. Dog experiments save humans. Interesting. Hope they can help me."
39 w.m. (40)	Leg abscess of unknown origin; deep; spontaneous improvement.	Long discussion of possible causes and course.	Patient raised head 5 inches off pillow and listened anxiously to every word. "I was interested and didn't want to miss a word." Feels good about having all the doctors around. "Two heads are better than one, and they will be better able to help me."
6 w.f. (40)	Cholecystic disease, plus angina.	Long discussion of which is which and what to do.	"I don't mind because they are good doctors and are trying to help me. The tests were long and disagreeable, but how else are they going to find out? I resented being in the hospital weeks with nothing done. Am glad to be going now to rest home."

TABLE IV

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
26 w.f. (70)	Post-operative abdomen, with abscesses and fever.	Long discussion of her "mitotic lesion", procedures at her age, etc.	"Don't mind all the doctors around, but I feel terrible and no one helps me."
13 w.f. (c.40)	Closure of colostomy (pre-operative).	Discussion of proposed operation and demonstration of colostomy.	"Don't mind discussion by all the doctors except when they make me show my colostomy. It embarrasses me. Especially when two of the doctors laughed and another had to call them aside and tell them to stop."
3 w.f. (32)	Multi-glandular, post-operative, with more surgery in the offing.	Full discussion of her condition, lasting 10 to 15 minutes. Probable thyroid and parathyroid requiring surgery.	"No, I'm not bothered by the discussion, only confused by all the different conditions mentioned that I have. What about my parathyroid? I hope it won't be a bad operation."
34 n.f. (30)	Possible ulcer (Pre-operative).	Discussion of condition and possible procedures.	"I don't mind all the doctors, but I don't understand what they said and am bothered by it. I have 4 children and need to know whether I will have an operation so I can make arrangements. Why don't they tell me?" (Patient is unwed mother but devoted to her brood.)
35 n.m. (45)	Mass in the lung.	Discussion of x-rays, held up in view of patient.	Patient was very anxious throughout the discussion and peered at x-rays. Is unwilling to express opinion about having doctors around, at first saying "Oh, it's all right." Later, gives vent to intense fears of cancer.

With reference to patient 15 (Table VII), these terms were used frequently, but she was quite willing to accept the intern's statement that she has a stone which must be removed. However, her doubt crops up in her repeated use of the phrase "a stone—*or whatever it is.*"

In several instances where ominous terms were used, the patient was deaf as in case 40, not very bright as in Table VIII, case 37, or did not understand English very well as in case 5 (Table VIII).

The cases in Table IX show that sometimes, in their zeal in discussing a case,

TABLE V

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
16 w.f. (19)	Appendectomy, post-operative.	Very brief discussion of post-operative condition. "Doing fine." As soon as rounds moved on to next bed, patient clambered over other side of her bed and dashed out, carrying bathrobe.	"I was upset and scared by having all the doctors around and had to rush to the bathroom. Almost didn't make it. Why did I get a spinal anyway? I wanted to be put to sleep. Can't stand all these doctors."
12 n.f. (e.40)	Question of stone left in common duct.	Long discussion. Should one take it out?	"I don't want another operation."
7 w.f. (35)	Splenectomy.	Long discussion of condition and all its ramifications.	"I resented all the doctors and the long consultation. Felt like a bug on a pin. I am accustomed to private care, but have fallen on hard times. No one thinks of you here as a human being."
17 w.f. (12)	Chronic Appendix?	Very brief pause at the patient's bedside, with only the statement by the intern, "Suspected appendix. Her third admission for it."	Patient had been up and about, talking and playing cheerfully with the other patients when the staff entered. She got into bed and lay rigid, with a malar flush (which resident says she often gets). Later says "I'm scared of the doctors and don't want any operation." Her friend adds that she is so scared that she will not tell the doctor when it "really hurts bad."
32 w.f. (55)	Epigastric hernia, post-operative.	Examination and discussion of possibility of further surgery.	Patient does not look very intelligent but is. Alert and distressed over entire discussion of need for further surgery. Is anxious. "Nobody told me the full facts."
27 w.f. (82)	Radical breast, post-operative.	Long bedside discussion of alternative procedures, age of patient, etc.	Terribly nervous about having all the doctors around discussing her case. Accustomed to the German doctors who "don't do this way". Also resentful because accustomed to private treatment. Angry at her German doctor because he said it was nothing and it turned out to be cancer. Is worried that the operation was too late (at 82!). Also had a cataract operation and needs another. Is allergic and asthmatic she says, also fearful and anxious.

TABLE V—Continued

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
28 w.f. (40)	Constrictive lesion of oesophagus.	Long discussion of condition and what to do.	Patient bird-like in agitation and anxiety refuses all procedures. "I want to die. They keep feeding me with needles when I know I can swallow. I swallow water." (Patient responded to discussion and consented to I.V.s but kept darting out of bed and coming to ask further questions and reassurance until I.V. was in.

the surgeons may forget that the patient is listening, too. Then a traumatic piece of information may slip out, or a prognosis which is not intended for the patient's ears may be pronounced (case 1). At other times, an unusual condition may be examined by too many doctors for the comfort of the patient (case 20). When a discussion goes off into theoretical territory and research is brought in, the patient may not follow the doctor but keep thinking that the discussion is about her and become very upset (case 2).

Through carelessness in drawing the curtains around a patient who is to be undraped, or through leaving her undraped while the discussion continues after examination, the patient may be caused embarrassment and distress (case 24, Table X).

Sometimes a long discussion evoked differences of opinion which divided the group as to a diagnosis or a procedure. Before the operation, patient usually regards this favorably, as a sign that much thought and concern are being given to her case. In some cases the patient is disturbed at the possibility that the wrong procedure will be the one chosen. However, after the operation, intimations that another procedure might have been used or criticisms of what was done are disturbing to the patient.

In case 8 (Table XI), the patient knew the difference of opinion as to whether a midmetatarsal or a mid-thigh operation should be done and vented her hostility upon the staff for a whole year, because the operation chosen was the conservative one, despite the fact that it was motivated by the desire to save her limb. Every ward round was an occasion for further recharging of the batteries of her anger.

In a number of cases the patient was left disturbed because discussion centered around whether the attending would have chosen the procedure that the resident or intern performed. In case 10 (Table XI), the patient was very ill but listened while an attending scolded the intern and said the tube was not passed right and had not reached the place where it could do the patient any good. The patient finally concluded that he was going to die, in spite of all his suffering. This patient had tubes from both ends and also intravenous apparatus attached to him.

TABLE VI

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
38 w.m. (22)	Gynecomastia.	Discussion of whether or not operation is desirable for cosmetic reasons.	Patient was scared by use of the term "gynecomastia" and feared it meant "carcinomatous degeneration". Was relieved on learning it was merely the name of his condition. A rather immature young man who readily discussed his condition and is not troubled too much by it. Somewhat effeminate.
8 w.f. (26)	Mid-metatarsal amputation and tenotomy (all in one year).	Chief and staff moved off, out of range, to discuss.	Angry, because "when they finally get to look at me, they go off where I can't hear what they are saying."
19 w.f. (50)	Diabetic with gangrenous spot on toe.	Statement was made: "The prognosis in this case . . .", then doctor turned away to finish discussion.	Patient was anxious and very upset at his turning away. Has read everything she could lay hands on about diabetes and is in mortal dread of having to lose foot. "I am alone in the world and if I have to lose my foot, I can't work and there is no point in going on living." Said she would never consent to operation. (This patient reacted well to full and frank discussion of her condition and consented to amputation of hallus. Had lost husband suddenly after a late marriage and 4 idyllic years.)
18 n.f. (35)	Hernia, third day post-operative.	Patient became visibly upset at remark "If I were operating on this one . . ."; when she broke in with "when are you going to operate?" was told "you silly girl. You've had your operation." to staff: "Doesn't that beat all? Doesn't know she's been operated!"	Patient says "I was frightened stiff and in pain at every touch. I thought he meant he was going to do it over again. I left my children with no one really to take care of them and just couldn't go through it again. I got panicky. They didn't have to laugh at me. How do they expect me to understand their 'doctor talk'?"

TABLE VI—*Continued*

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
14 w.f. (30)	Abdominal tumor, probably ovarian, requiring oophorectomy. Patient is pregnant.	Patient asks questions, apprehensive lest ovary be removed, and lest pregnancy be interrupted. Questions ignored.	Patient was angry at ignoral of her questions. Was not told full facts, including probable necessity for removal of ovary or that pregnancy need not be interrupted, and one ovary sufficient for future pregnancies. After discussion of all aspects she accepted loss of ovary as possibility and calmed her anxiety. Operation resulted in loss of ovary without interruption of pregnancy, but when she asked whether she had lost ovary was still not told. She was anxious and angry. Told the truth, she accepted it and was able to relax.
14 n.f. (25)	Pilonidal cyst post-operative.	Chief tells of procedure during war—excision and packing with gauze.	"I don't like to see so many doctors standing around me. Makes me nervous and frightened. Don't understand what they said about packing me with gauze. Am worried. I don't understand why I need another operation."

TABLE VII

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
15 w.f. (55)	Carcinoma Pancreas, preoperative.	Long discussion, using terms "ca" and "malignancy" frequently, in deciding whether to excise or do partial pancreatectomy, bypass, etc. Resident finished by saying "Well, you've got a stone, and we're going to take it out." ("Mitotic lesion" was also used a number of times.)	"I am worried about the operation, but if I've got a stone —or whatever it is— I'd better have it out." (Patient upset by "C.A." discussion, but the nearest she could come to verbalizing her worry, was "or whatever it is". Resident's positive statement gave her something to latch onto and assured her emotional consent to the operation. She repeated "or whatever it is" several times.)

TABLE VIII

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
40 w.m. (50)	Gastrectomy after massive hemorrhage (post-operative).	One of staff asks about the "carcinomatous possibilities" in hearing of the patient.	Patient proves to be rather deaf and "did not hear anything" that was said.
37 w.m. (50)	Hernia with persistent constipation, treated non-operatively.	Lengthy discussion. "I originally thought there was a carcinomatosis."	Patient is talkative and anxious but did not react to the discussion or to the mention of carcinoma, which apparently went completely over his head. Is of moderate intelligence and had language difficulty.
5 w.f. (65)	Radical mastectomy.	Discussion of "five year survival", "metastases". Question by chief: "Was this the right procedure?"	"I didn't mind all the doctors talking. I didn't understand them's language so much. So don't know what the doctors were saying." (Norwegian with little English.)

In all instances observed it was upsetting to patients to have their doctor scolded, disciplined or humiliated in their presence by his superiors. Invariably, the patients defended their doctor and expressed sympathy for him. Since the patient must rely on the intern or resident for her care, she evidently dare not lose confidence in him. In case 46 (Table XII), the patient blocked the episode completely out of mind and did not remember it a few minutes after it had happened. But it was clear from the discussion which followed how much it had upset her. It released for the first time the flow of her long-suppressed grievances.

Occasionally there seems to be evidence that the well-known process of "denial" can be a two-way street, the doctors "denying" in some cases, too. A patient with an unsympathetic personality or with too many complaints may be shrugged off because of the effect she creates, although a serious condition may exist (case 49, Table XIII). In other instances, even the most thorough attention to such patients, despite their personality, fails to reveal what is actually there (case 47, Table XIII).

In one instance, on the contrary, in a patient with a very negative personality but in mortal danger, great efforts were made to persuade her to undergo life-saving surgery, without avail, and patient died (case 43, Table XIV).

This is also in contrast to the attitude expressed by one of the attending staff in the hearing of the patients during ward rounds: "I don't waste time pitying the patient. This is it. Take it or leave it." One patient who overheard this remark (case 8, Table VI) said, "If he had been my doctor, I would have been

TABLE IX

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
1 w.f. (65)	Mid-metatarsal amputation, diabetic (on ward 8 months).	"Most of these come to a higher level."	Very disturbed by rounds. "After all the trouble healing this wound, don't tell I am going to be cut higher."
20* n.f. (45)	Large ligneous mass in neck at left sternocleidomastoid.	Six or seven of staff examined the mass thoroughly.	"I think it's fine for all the big doctors to take an interest, but my neck hurts now. It didn't before. I wasn't afraid—just nervous."
2 n.f. (40)	Ulcerative colitis (on ward 2 months).	Question (by chief, of visiting doctor "Have you had experience with this kind of case, Doctor?" Answer: "I've lost one." (In discussing another procedure used on another series of cases.)	Patient's mouth fell open and eyes popped. "When he said 'I've lost one' I thought I'd die. I was scared to death. I know it wasn't about me and something else was under discussion, but I've suffered long and hard from this sickness for years, and I'm just plain discouraged. I was panicked."

* Note on case 20, above: Seen two weeks later, stony hard neck mass had proved to be an abscess, had shrunk and was now small and soft, also painless. "I didn't mind the doctors today, because my neck doesn't hurt, but last time it hurt terribly and I got very nervous. All the doctors poking and poking made my neck terribly painful. I'm glad, though, that I'm getting better."

TABLE X

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
24 n.f. (40)	Liver abscess	Statement made "Pus has no odor" disturbed patient. Also, in draping patient after examining, breasts were left exposed while discussion went on 5 minutes.	Patient felt very upset and nervous and terribly embarrassed that her body was exposed before all the doctors all the time they were talking about her. Couldn't understand why her pus had no odor and thought that was a bad sign. "But thank God, I'm getting better."

out of the hospital long ago." (This is the patient with mid-metatarsal instead of mid-thigh amputation.) Another (case 7, Table V) who had resented all the doctors around her said, "Some doctors are dolls; some are just brutal. '

Sometimes an overly optimistic attitude toward a very sick patient leaves

TABLE XI

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
10 w.m. (old)	Intestinal obstruction with tubes top and bottom.	"We have here an upper and a lower problem." Long discussion on whether tube is down to the obstruction and how to get it down. "Was it done right? If you don't get it down in 24 hours we may have to go in and operate. Otherwise we'll miss the boat." (Latter repeated.)	Patient very ill but listened carefully and on "miss the boat" his eyes popped. "Doctors are trying, but I'm going to die."
22 w.f. (50)	Possible cholecystectomy, common duct stone.	Description of conservative handling evokes angry retort from attending: "What's a hospital for?" Tearing down of intern continues in front of patient and in hearing of others.	Patient is glad her doctor (intern) is not rushing to operate. Sorry he was "bawled out by the professor."

her with the feeling that her real needs are not understood or met (case 45, Table XIV).

COMMENTS: SURGICAL WARD ROUNDS

Differences between the medical and surgical ward rounds findings are apparent in this study. They may be based on the variety of factors which operate in reality to differentiate the two situations. Some of the factors which suggest themselves as perhaps relevant follow.

Those Related to the Knife. All people fear illness. However, the knife may evoke a special reaction in patients, not only because of the fearful conscious implications (i.e., the seriousness of illnesses requiring surgery; the calculated risk of death; the certain pain and discomfort; the possibility of permanent disability, as in amputations, colostomies, etc.) but also because it evokes and mobilizes unconscious emotions (such as deep-seated castration fears and death-wishes). The knife may also become endowed in the mind of the patient with exaggerated positive significance and powers, creating an almost magical aura around this aspect of medical practice. This is highlighted in a simple but poignant statement by Schweitzer (4), " . . . . The native soon realizes that the white physician is superior to his fetish doctor, when he learns that the white doctor knows how to bring cures with a knife." This attitude is not limited to aborigines. The process of bringing "cures with a knife" evidently has psychological implications, both before surgery, during the operation, and during the period of recovery.

Those Related to Anesthesia. The use of anesthesia in surgical procedures is

TABLE XII

Case. Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
46 w.f. (65)	Mid-metatarsal amputation.	Attending had ordered tubes for surface irrigation. This had not yet been done. Attending asked intern why not. He replied that he had not had time. Was blasted "sky-high" in front of patient and in hearing of entire ward.	Patient asked "What did you think of the incident with your doctor?", replied "What incident?" "I mean about the tubes." "I don't remember anything special happening." Patient continued to deny the episode until it was specifically mentioned. "Oh, that. It was terrible. But that's the way things always are on this ward. The nurses are always screaming at patients or nurses or doctors." Then followed a long pent-up list of grievances and instances of alleged neglect. "Why haven't you spoken up before this?" "I was afraid, and what's the use?" (This patient had been listed for a consultation with the psychiatrist by Social Service because she was too quiet and uncomplaining.)
42 w.f. (42)	Gall bladder. Question of operation or conservative treatment.	Intern and resident were talking during presentation. Attending asked a question but reply was "I didn't hear the question." "Of course you didn't. That's why I called on you. You were talking away all the time. I don't think that's right." (Talk was actually about whether I.V. Cholangiograms were ready and could be gotten for presentation at rounds.)	Patient was upset about her doctor being "bawled out" like a school-boy in presence of all the doctors. "All the other patients could hear, and I was ashamed for him."

also a factor with a psychological implication. The surgical patient must not only accept the knife, but under the most commonly used forms of anesthesia must also yield consciousness and bodily control. To some, this is undoubtedly a traumatic experience, while others probably crave the oblivion which it affords and seem to object to such procedures as spinal anesthesia. Sometimes pain fails

TABLE XIII

Case, Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
49 w.f. (49)	Colostomy with extensive anal and rectal surgery.	Quickly passed by with the aside—"a chronic belly-acher."	Patient claims it is impossible to get anyone to believe her that her legs are weak and caused her to collapse, and that thighs and knees are numb. Patient complained excessively of pain and generalized misery. (Neurological consultation with positive findings confirmed patient's complaints about legs and numbness.)
47 w.f. (65)	"Cardiac Neurosis".	Patient was passed by quickly with remark that she has endless complaints not substantiated by any physical findings on numerous examinations, including ECG. "Grabs hold of anyone who will listen, goes on hysterically, and won't let go."	Patient behaved exactly as described but chart showed more evidence than seemed to be recognized. Patient's attitude repelled, and doctors seemed to "deny", to escape being with her. Further study, including ECG repeat, revealed nothing. But the following day the patient died of a coronary.

to be deadened completely by the anesthetic, causing a great emotional upheaval in the half-conscious patient. Case 49 (Table XIII), the "chronic complainer" fell into this category and claimed that she suffered excruciating pain throughout the operation. Another patient under general anesthesia for a leg amputation (not reported in this series because her case did not come in the ward rounds study) had a cardiac arrest on the operating table which required life-saving surgical intervention. She stated afterwards, "I made up my mind not to come out of the anesthetic. I didn't want to live with my foot cut off."

All the factors which have led to the establishment of "Recovery Rooms" may also apply here, since surgical ward patients do not have the benefit of this facility at this hospital. Also, the "Case Study" procedure being used at this hospital in the training of nurses, wherein the trainee stays with a patient throughout the preparation, anesthetization, operation and recovery, has potential value for us, probably as a source of information, and merits further exploration.

Those Related to the Physician. There are a number of questions raised by this study in relation to vocational choice and certainly the apparent differences between some of the findings on the Medical and Surgical Services may have something to do with the type of person who selects one or the other as a specialty.

In this limited series of observations (over a period of several months), no intern or resident was observed to receive open commendation or approval from

TABLE XIV

Case Description and Age	Diagnosis	Procedure or Comment of Surgeons	Patient's reaction (as elicited by psychiatrist)
43 w.f. (72)	Intestinal obstruction. Patient refused permission to operate.	Staff pleaded with patient to grant permission for operation.	Question was whether to tell her of the mortal danger, if not operated. It was done. She still refused. She said, "Doctors told me that before, and I lived. If I can't live without an operation, I want to die." Patient finally said she would think it over and make a decision in the evening when her children came. Her decision was still negative, and she died the following morning.
45 w.f. (26)	Colostomy, post-operative, with severe complications, multi-abscesses, etc., due to opening left into abdominal cavity.	Brief observation of patient with cheerful statement, "You're doing O.K."	Patient knows she is very sick and really doesn't care whether she lives or dies, but thinks all the doctors are trying and doing their best for her. "Too many doctors do too many things for me at too many different times. I find myself dreading the dressing or irrigation all day and am worn out by the time it is done. Couldn't it be done the same time every day so I can prepare myself to take it? The uncertainty is wearing me down."

an attending on surgical ward rounds, while, on the contrary, open rebuke or criticism in the presence of patients did occur. It is, of course, possible that the residents and interns, knowing their chiefs and working with them daily, may have received implicit signs of commendation or approval to which the observer lacked the necessary clues. It may also be a question for future exploration whether the observed fact that patients are frequently upset by ward rounds on surgery, but rarely on medicine, stems from this same factor or is due to other causes, such as the fact that on medicine only part of the presentation takes place at the bedside, whereas on surgery, the long conferences take place wholly at the bedside.

DISCUSSION

Ward rounds may be regarded as having a dual function: didactic and therapeutic. This has been well expressed by the Council on Medical Education and

Hospitals of the American Medical Association. "The most important phase of intern instruction consists in daily, regularly organized ward rounds with well-conducted teaching at the bedside. By this is meant systematic instruction of the intern by the attending physician with an ample discussion of the history, the physical examination, the clinical and laboratory findings, the diagnosis, and the treatment of each patient. The social and psychologic aspects of the case should receive proper emphasis. It is the duty of the attending physician in direct charge of the patients assigned to the intern to conduct such teaching . . . "

It would seem a worthy subject for staff discussion whether it is possible to increase the therapeutic value of ward rounds without impairing their teaching value. On the basis of what we learned in this study, we would offer the following for discussion:

1. Can the bedside conference on surgical wards be limited in greater degree than at present to the examination and observation of the patient, conducting more of the discussion of history, findings, and diagnostic possibilities out of the patient's earshot?

2. Keeping in mind the rather exalted position the attending occupies in the eyes of the average patient, could this position be exploited for positive therapeutic purposes? The attending who is conscious of the therapeutic as well as the didactic functions of ward rounds might, perhaps as a routine, initiate the bedside conference with a friendly greeting and give the patient a chance to voice some of his comments and complaints directly. Afterward, the attending might offer the patient whatever summary and reassurances he deems appropriate. The patient would of course, as far as possible, be talked "to" rather than "about" in any discussion which goes on in his presence.

3. Since we all know that uncertainty can be more distressing than the most unpleasant facts when they are clearly known, care will naturally be taken at rounds by the aware surgeon that the patient is not left in a state of agitated uncertainty as to her condition and outlook.

4. This study calls attention again to the need for respect for the patient's person and privacy and also to some of the special problems inherent in open examination of ileostomies, colostomies, incisions, etc. It was also emphasized again that painful examinations on rounds will be kept at a minimum by the sensitive physician.

5. When ward rounds serve to increase the dignity and authority of the interns and residents in the eyes of the patient who must rely on them for daily care, their effectiveness seems to be enhanced. The older colleague making rounds thus lends the aura of his position to his younger colleagues for the ultimate benefit of the patient.

6. This study emphasizes how important it is that the greatest possible care be exercised to avoid diagnostic terminology which can be disturbing in the presence of the patient. This seems to apply also to the discussion of animal experimentation, morbidity, and mortality statistics and the like.

ACKNOWLEDGMENT

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CURRENT CONCEPT OF COSMETIC SURGERY

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"He that has a great nose thinks everybody is speaking of him."
Thomas Fuller (Gnomologia).

The term, cosmetic surgery, denotes that branch of plastic surgery in which the aim is restoration or improvement of personal appearance. It is, in a sense, reconstructive surgery of the human form and restoration of function based on esthetic principles. The primitive art of plastic surgery which had its roots in ancient India made a remarkable advance after World War I. The pioneers then were Harold Gillies of England, and Vilray Blair of the United States. After World War II, there were increasing demands for reconstructive surgery. As in all fields, the demand is usually met by supply. Several surgeons soon became interested and engaged in the practice of cosmetic surgery to the expressed and un-expressed disdain of their confreres.

As early as 1935, Dr. Joseph C. Beck (1), one of the pioneer otorhinologic plastic surgeons of this country, quoted Gillies in a discussion of the erroneous view of some concerning the indications for cosmetic surgery. Beck had previously refused requests for borderline cosmetic operations. He was thus among those referred to by Gillies in the Transactions of the American Laryngological, Rhinological and Otological Society (1908):

"This subject has been and is yet, to a great extent, treated by the general surgeon, notwithstanding the fact that detailed intranasal surgery is often necessary to obtain the best results. Again, a large majority of external nasal deformities are treated by charlatans because general surgeons, as well as rhinologists, often refuse and discourage treatment of the above-named conditions for cosmetic purposes. This fact, I believe, is responsible for many bad results, accidents and malformations, rather than improvements. These patients should be prevented from falling into the hands of an unskilled, so-called specialist and beauty doctor. Those of you who have seen some of these cases after they were corrected by the so-called specialists wonder if you have not acted unwisely by refusing to listen to those unfortunate individuals."

Beck continued to stress the need for plastic surgery clinics in medical colleges where patients who desired reconstructive, as well as cosmetic operations, could receive the benefits of advice, and where courses in those specialties could be given. Here was a surgeon with vision, open to conviction, and who was aware of the sugical cosmetic problems discussed in our own day.

The nascent art of cosmetic surgery was frowned upon by surgeons (echoing Dryden, the poet), church, state and the lay public in that it attempted to alter God's handiwork. Then, too, the early attempts made by peripatetic quacks

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cast discredit upon the art. The trend was and still is to depreciate cosmetic surgery and its indications. It is indeed, time for a fair, un-prejudiced evaluation of cosmetic surgery, because of the many great economic, social, and psychologic benefits which accrue to the patient. There is frequently a change in personality for the better when the patient undergoes this type of surgery. Everyone is aware that satisfaction with personal appearance is of profound importance to the ego. It is sometimes maintained that those who desire cosmetic surgery are neurotics. This is far from the truth. They are, generally, normal people who lack self-respect and confidence because of dissatisfaction with their facial features. A successful cosmetic surgical operation does not *per se* enhance the patient's appearance. It merely removes irregularities or deformities which are objectionable and which give an abnormal expression of one's personality. This belief is reflected in the person's face, behavior and thoughts. Then, too, the surgeon's esthetic sense is satisfied.

As concerns treatment of facial deformities, pronounced advances took place during the two World Wars when man used the most powerful weapons to destroy his fellowman. Maxillofacial injuries, perhaps the most poignant of war mutilations, required a new approach in treatment—methods which called for the services of plastic and oral surgeons and prosthetists. Closer cooperation of these groups marked an important advance in therapy. As a consequence of experience gained with acquired deformities, much was learned that could be applied for cosmetic correction of congenital malformations. Since cessation of hostilities, there has been a natural decrease in the number of patients with acquired deformities. One is still confronted with those whose deformity has been brought about by injury or disease; however, the number of patients with congenital malformations remains fairly constant. This should advance opportunity for research in the latter field if it receives encouragement.

After the successive World Wars, the recent Korean War and the increasing demand for plastic surgery, many interested surgeons continued in the specialty of plastic surgery when they returned to civilian life or were recalled to fill army medical quotas. There was, of course, a pronounced decrease in acquired deformities. Interest in the cosmetic aspects of otolaryngology is a normal development indicating progress in the surgical field.

Specifically, Millard, in his article, "*Oriental Peregrinations*" described the art of "saving faces" in Korea when he was recalled there for military duty (2). The Army headquarters, after fighting ceased, approved a so-called "new look" program designed for psychologic and other reasons to "pin" protuberant ears, correct deviated noses, improve prognathic chins and "Andy Gump" chins, and even to perform "face lifts" for army personnel and civilians. Millard found that there was a persistent demand by many Orientals to be facially transformed into Occidentals. Since the advent of American forces in the East, there was a "yen" for facial change. Chinese, Japanese and Korean women especially wanted to be deorientalized.

Surgical opinion today, as previously stated, is still influenced to a degree by the belief that the patient who requests cosmetic surgery is a neurotic or has a

foolish purpose. "The practice of the art lacked professional dignity," it was said. There were few qualified surgeons who were, and are still willing, to devote their skill to the surgical branch in question. The real advances have been made by those surgeons who, for a time, worked in obscurity. They devoted time, thought and energy to development of refinements in the technique, often perforce, under the guise of restoration of function.

For cosmetic surgery to achieve and maintain its deserved status among physicians, surgeons and the lay public, it is of importance, that the doctor should cease to undervalue or disapprove of the art of reconstructive surgery, unfortunately termed "cosmetic surgery." In addition, more physicians should receive adequate training in this field and so achieve more gratifying results, esthetically and functionally. Cosmetic surgery, like all other arts, is an exacting one. It requires, as was anciently said of the qualifications of a good surgeon, "an eagle's eye, a woman's hand, and sometimes a lion's heart." There is obviously great need for extreme accuracy and finish in surgical craftsmanship to produce the best possible esthetic results. In addition to study of techniques and of other problems relating to his art, the surgeon should have some knowledge of anthropology, psychiatry, and above all, of physiognomy. He will thus be able to correct views concerning diagnosis in contemplated operations for cosmetic and other purposes.

The large number of persons who require help to remove their specific frustrations and sense of inadequacy should be informed that they can be helped. The medical profession is rightfully concerned with alleviation of pain, diagnosis, progress in physiology, pathology and research, but it owes an obligation to the person who suffers from physical handicaps which can be easily corrected. Not infrequently, a patient with a deep sense of inferiority because of a facial handicap is discouraged from seeking surgical correction because of the attitude of the family physician or other prejudiced persons.

De Kleine (3), in an excellent editorial wrote that "esthetic surgery can no longer be treated as a hushed-up stepchild, quietly relegated to the background of scientific discussions." At clinical meetings devoted to plastic surgery, he found the subject of the cosmetic variety largely ignored. The papers read were concerned with questions of functional improvement. The problems of the esthetic art, although in disrepute, in some professional quarters, must be discussed. Only thus can exchange of ideas and progress be made. As in other fields, there is, of course, need for research in esthetic surgery because many problems remain unsolved. Some plastic surgeons have been reluctant to report their experiences in the art, and consequently there has been little pooling of direct and related problems.

Fortunately, the attitude towards esthetic surgery is changing. In many hospitals today, there are beds and clinics exclusively set aside for patients requiring cosmetic surgery. The pioneer in this trend is the Mount Sinai Hospital in New York City. Recently, the Manhattan Eye, Ear and Throat Hospital, also in New York, endowed a clinic specifically for poor persons who require cosmetic facial plastic surgery. In view of this trend, other hospitals no doubt

will eventually follow suit. Cosmetic surgery should be made available to all persons who, for adequate reasons, require it. The psychologic outlook of persons financially insecure is little different from those who can afford corrective surgical intervention to overcome their frustrations.

According to Berndorfer (4), cosmetic surgery should be regarded as a healing science and art, because it comprises, like all other healing means, diagnosis, prognosis and therapy. It, therefore, deserves elevation to a truly scientific level. Today, the recognition of corrective procedures for modification of facial contour is the justifiable concern of all physicians and surgeons. The welfare of the patient with a cosmetic defect must take priority over professional bias.

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THE LUMBAR PUNCTURE IN THE PRESENCE OF PAPILLEDEMA

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There has been much discussion during recent years as to the desirability of performing a lumbar puncture in patients who have papilledema. The purpose of this paper is to attempt a clarification of the factors which are considered whenever this situation arises.

In 1909 Cushing (1) categorically stated that a lumbar puncture can be dangerous: "One recognized characteristic of the brain under pressure is its tendency to herniate through a cranial defect, and as there is normally an opening at the foramen magnum, a certain degree of protrusion is usually present there. In the presence of such conditions the withdrawal of the cerebrospinal fluid from the spinal meninges by a lumbar puncture is often hazardous, as it may tend to a sudden wedging of the bulb in the opening, with anemia and paralysis of the vital centers." In contradiction to this statement Masson (2) studied 200 consecutive patients with increased intracranial pressure in all of whom a lumbar puncture was performed. In 62 verified supratentorial tumors the removal of a small amount of fluid by lumbar puncture did not give rise to any serious symptoms. In none of the patients with 61 infratentorial neoplasms did any untoward symptoms develop following spinal tap. One case in the entire series died 22 hours after the lumbar puncture, but the time interval is of sufficient duration as to question a causal relation. Masson concluded that in patients with brain tumor and increased intracranial pressure there is no danger from a diagnostic lumbar puncture.

MATERIAL

The material consists of all 87 cases with papilledema admitted to the Neurologic Service of The Mount Sinai Hospital since July 1952. Papilledema is an ophthalmoscopic observation and indicates swelling of the optic nerve. However, it is not a completely objective finding and what may be papilledema to one observer may be a slightly blurred disc to another more skeptical, more conservative or more experienced physician. All such controversial cases have been omitted and only those were included in which papilledema was definitely considered to be present. The causes of papilledema varied but in all cases intracranial hypertension was suspected. Cases of optic neuritis and vascular retinopathy were excluded. The material has been divided into two groups according to the presence or absence of retinal hemorrhages because of the implied difference in severity of the pathological processes and the clinical fact that pseudopapilledema is characterized by the absence of such hemorrhages. Of the 87 patients 56 had lumbar punctures, and 9 had pneumoencephalograms. Thirty-one patients had no lumbar punctures. A total of 75 spinal taps were performed.

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TABLE I

Papilledema without retinal hemorrhages

I. Space Occupying Lesions		20
Above the tentorium	13	
Glioblastoma	4	
Meningioma	3	
Craniopharyngioma	2	
Oligodendroglioma	1	
Metastatic carcinoma	1	
Subarachnoid hemorrhage from a neoplasm	1	
Unverified neoplasm	1	
Below the tentorium	7	
Eighth nerve tumor	2	
Hemangioblastoma	2	
Meningioma	1	
Metastatic carcinoma	1	
Unverified Neoplasm	1	
II. Other Conditions		7
Pseudopapilledema	3	
Subarachnoid hemorrhage due to vascular anomaly	2	
Brain tumor suspect	2	

RESULTS

In the first group (Table I) there were 27 patients who had a total of 41 lumbar punctures including five pneumoencephalograms. The patients were from eight to 61 years of age. The abnormal initial pressure readings varied from 200 to 560 millimeters of water. Seven patients had normal initial pressures. There was no correlation between the manometric pressure and the clinical condition of the patient. The duration of symptoms before hospitalization was as long as three years in a patient with a meningioma in the posterior fossa and as brief as two days in a youth who had a subarachnoid hemorrhage from a tumor. Most of the cases had symptoms from one to three months. The clinical picture on admission varied with the pathological process. All patients with space occupying lesions (Table II) had unquestionable findings, many of which were of localizing value. A review of the clinical records of this group revealed that none had been made worse by the spinal tap. Of the 18 patients who were operated upon, nine showed no progression of symptoms before surgery. The other nine did show progression but this could as well have been due to the underlying disease (glioblastoma multiforma, meningioma, craniopharyngioma, vascular anomaly, metastatic carcinoma, and an unverified posterior fossa tumor). No case became an emergency after the lumbar puncture although one seriously ill patient with metastatic disease was scheduled in the operating room before the spinal tap and was operated upon three hours later. The remaining patients did not undergo surgery until from one to 24 days after spinal tap, 12 of them being scheduled the second week after the lumbar puncture. Three patients with tumors had pneumoencephalograms. One was operated upon two days after the procedure and was found to have a glioblastoma of the cerebrum. Another had an angio-

TABLE II

Space occupying lesions with papilledema without retinal hemorrhages

Pathology	Age	Duration of symptoms P.T.A.	Initial pressure (mm H_2O)	Time bet. L.P. and surgery
Cerebral Glioblastoma	44	5 wks.	340	2 days
Cerebral Glioblastoma	37	3 mos.	280	18 days
Cerebral Glioblastoma	49	3 mos.	—	12 days
Cerebral Glioblastoma	60	1 wk.	260	4 days
Meningioma above tentorium	41	8 days	310	7 days
Meningioma above tentorium	34	2 wks.	110	3 days
Meningioma above tentorium	42	1 year	300	7 days
Craniopharyngioma	45	1 year	500+	13 days
Craniopharyngioma	29	6 mos.	360	4 weeks
Oligodendroglioma	16	9 years	500	24 days
Cerebral Metastases	46	3 mos.	—	3 hrs.
Hemorrhage from neoplasm	17	2 days	560	disch. impr.
Unverified tumor—Cerebral	51	5 wks.	200	1 day
Eighth Nerve Tumor	52	5 mos.	240	7 days
Eighth Nerve Tumor	45	3 mos.	160	10 days
Hemangioblastoma Cerebelli	40	5 mos.	140	7 days
Hemangioblastoma Cerebelli	17	6 mos.	180	2 days
Meningioma of tentorium	39	3 years	280	7 days
Cerebellar Metastases	61	2 mos.	150	(died in 9 days)
Unverified Tumor– Post. Fossa	18	12 years	210	23 days

gram the same day as a pneumoencephalogram which revealed metastatic cerebral disease. He went gradually down hill without surgery. The third case is most interesting since we have been recently doing pneumoencephalograms in the presence of papilledema. He had his pneumoencephalogram in 1931. Moreover, whereas today we feel it is safer not to remove any cerebrospinal fluid, at that time 100 cubic centimeters of fluid in 10 cubic centimeter quantities were removed and replaced by air. This patient had his pneumoencephalogram two weeks after a lumbar puncture had revealed increased intracranial pressure. He signed out against advice, but he returned two weeks later because of poor vision. At that time a decompression operation was done. He became a part of this report when he was readmitted 23 years later for recurrence of symptoms. This patient is the only one in which blurring of vision was reported following lumbar puncture, but his lesion (craniopharyngioma), most likely involved the optic chiasm.

Of the two brain tumor suspects, one had headaches and a transient homonymous field defect which disappeared. She was discharged without a procedure. The other was a very complicated case and is now considered to have had pseudopapilledema. Last but not least are the three cases of pseudopapilledema. The clinical picture is important in that two only had headaches, although one of them had generalized convulsions eight years before admission. The third patient's difficulties began after a routine eye examination. None had neurologic findings other than the blurred discs. Actually these three cases stimulated the

TABLE III

Papilledema with retinal hemorrhages

I. Space Occupying Lesions		18
Above the tentorium	15	
Metastatic carcinoma	5	
Glioblastoma	2	
Tumor unverified	2	
Astrocytoma	1	
Ependymoma	1	
Pinealoma	1	
Retrochiasmal tumor	1	
Porencephalic cyst	1	
Subdural Hematoma	1	
Below the tentorium	3	
Meningioma	1	
Brain tumor unverified	2	
II. Other Conditions		11
Serous Meningitis	2	
Lead Poisoning	1	
Torulosis	1	
Ethmoiditis	1	
Subarachnoid Hemorrhage	2	
Brain tumor suspect	4	

present report for there were dissenting opinions voicing the need for ventriculography. Two of these patients had pneumoencephalograms which were normal. (The procedure was done in one case because of the history of seizures and in the other case to relieve the overwhelming anxiety of the parents who were told the child most likely had a brain tumor.) The third whose problem began with a routine eye examination had a normal spinal tap and it was felt no procedure was indicated.

In the second group (Table III) consisting of patients who had retinal hemorrhages there were 29 patients who had 44 spinal taps including four pneumoencephalograms. In reviewing these cases one can make no statement other than the two groups apparently overlap (Table IV). Again reviewing the clinical records it became evident that the lumbar puncture did not influence the patient's course. Two patients doing very poorly continued to do so following a spinal tap. One was operated upon four hours later and was found to have a subdural hematoma; he did well following surgery. The other died three hours after the spinal tap of a massive intraventricular hemorrhage.

The non-tumor cases are most interesting. Over a six-week period, one patient with serous meningitis had initial pressures on three occasions of 340, 460, 560 millimeters of water. Decompression was done but the patient still maintained high initial pressures for another six weeks during which time four spinal taps were done. She had blurred vision as an initial complaint and this symptom did not worsen during the prolonged period of increased intracranial pressure. A patient with torula meningitis had a pneumoencephalogram before the diag-

TABLE IV

Space occupying lesions with papilledema and retinal hemorrhages

Pathology	Age	Duration of symptoms P.T.A.	Initial pressure (mm H_2O)	Time bet. L.P. and surgery
Cerebral metastases	46	5 mos.	140	No surgery
Cerebral metastases	38	2 weeks	230	10 days
Cerebral metastases	53	3 mos.	210	No surgery
Cerebral metastases	60	4 weeks	190	No surgery
Cerebral metastases	46	5 weeks	278	10 days
Glioblastoma	50	3 weeks	240	27 days
Glioblastoms	42	3 weeks	275	7 days
Tumor Unverified	41	1½ years	240	12 days
Tumor Unverified	51	5 weeks	180	6 days
Astroeytoma	20	6 weeks	500+	1 day
Ependymoma	45	4 years	160	5 days
Pinealoma	29	3 mos.	90	14 days
Retrochiasmal Tumor	48	3 weeks	290	8 days
Poreneephalic Cyst	13	2 mos.	240	3 days
Subdural Hematoma	10	5 days	600+	4 hours
Posterior Fossa Meningioma	8	10 days	180	14 days
Posterior Fossa Tumor Unverified	57	6 days	220	19 days
Posterior Fossa Tumor Unverified	20	3 weeks	240	2 days

nosis was made and there was no immediate untoward effect of the procedure. A patient with lead poisoning had three spinal taps, the first two showed an initial pressure of 500 millimeters of water and the third, after a course of calcium versenate, revealed an initial pressure of 170 millimeters of water at which time the patient, whose clinical condition was improving, still had severe retinal pathology. A patient with ethmoiditis was feared to have a brain abscess. Cerebral spinal fluid on two occasions revealed high protein but no cells, and he improved with antibiotics. Bloody cerebrospinal fluid with xanthochromia confirmed the diagnosis of subarachnoid hemorrhage in two cases. Of the four patients who were brain tumor suspects one was admitted in coma, had two lumbar punctures two days apart, went progressively down hill and died five days later. There was no autopsy. The second case was admitted with ataxia and an organic mental syndrome. He had normal cerebrospinal spinal fluid, a normal pneumoencephalogram and was discharged. The third case had no symptoms other than headache and blurred vision in the right eye. He had a normal lumbar puncture, the blurring cleared up and he was discharged. The fourth case was admitted with an organic mental syndrome and aphasia. The lumbar puncture was normal. Nine days later a pneumoencephalogram revealed an incompletely and inadequately filled ventricular system. Ten days later an angiogram was not diagnostic. A repeat lumbar puncture was again normal. Seventeen days thereafter ventriculography revealed no definitive pathology. She had a decompression, went progressively down hill and died. Unfortunately no autopsy was obtained.

DISCUSSION

In 1933 Schaller (3) took issue with Cushing's statement that lumbar puncture is contraindicated in the presence of intracranial pressure. He studied 103 unselected cases of lumbar puncture in the presence of intracranial pressure. There were four deaths, within 13½ hours, six hours, 17½ hours and 40 hours after the procedure. However, the first patient had a rupture of a vascular sarcoma, the second and third had no evidence of posterior fossa herniation. The fourth case, suffering from a cystic cerebellar glioma had been considered one of cerebral spinal syphilis and had what the author felt to be "improper lumbar decompression and drainage". Schaller concluded that the lumbar puncture procedure is reasonably safe . . . and justifiably indicated because of the valuable diagnostic information it affords. However, Ayer and Schwab (4) in the 1955 edition of Baker's *Clinical Neurology* restate Cushing's warning: "Lumbar puncture should not be performed in the presence of a brain tumor since it may cause medullary compression from herniation of the brain into the foramen magnum leading to respiratory embarrassment and even to death due to release of fluid below." Nevertheless, they go on to agree with Masson and Schaller: "In the presence of choked discs, lumbar puncture should not be performed unless the indications are definite, and then only with extra care as to technique, using a small-bore needle and taking a small amount of fluid. There are two sets of conditions in which lumbar puncture is indicated, despite the possibility of brain tumor. These are (a) diseases which cause papilledema or retinal changes simulating choked discs, such as retrobulbar optic neuritis occlusion of retinal veins, diabetic retinopathy, syphilitic papillitis, toxic conditions, uremia, and meningitis; (b) diseases and disorders closely simulating brain tumor but not causing papilledema. These comprise headache of many types, character, changes, psychoneurosis, encephalitis, and cranial nerve disturbances, as well as many pathologic conditions of the brain of questionable etiology." The question which has not been clearly resolved is whether the complication which occurs following the lumbar puncture is due to the procedure itself or due to the pathologic process existing in the cranial cavity. Lubic and Marotte (5) have recently reviewed 401 cases of verified brain tumors in which a lumbar puncture was performed. Forty-five of these cases had definite evidence of papilledema. One-hundred-and-twenty cases (including probably most of the patients with papilledema) had abnormally high initial pressures. They reported only one case (cerebral glioblastoma) in which there was an untoward affect and the protocol does indicate a temporal relation but not necessarily a causal relation to the spinal tap. They felt that lumbar punctures aided in establishing a diagnosis but that it should not be performed when a diagnosis of brain tumor is evident. However, it has not been the experience at The Mount Sinai Hospital that a diagnosis of brain tumor is absolutely evident and many times we have found non-space occupying lesions in patients who seem to have "classical" histories and findings of brain tumors. On the basis of the data in this report it seems clear that a lumbar puncture can be performed in a patient

TABLE V

Patients with "non-operative" conditions

Brain Tumor Suspect	6
Subarachnoid Hemorrhage	4
Serous Meningitis	2
Lead Poisoning	1
Torulosis	1
Ethmoiditis	1
Pseudopapilledema	3
Total	18

with papilledema without fear. The value of this diagnostic test can be seen in Table V, which lists the cases in which the spinal fluid findings assisted in the diagnosis and management of the patient.

It should be emphasized that although Table V indicates non-operative conditions two patients, one with serous meningitis and one a brain tumor suspect were operated upon. The data do not reflect the diagnostic difficulties involved in these cases especially those with serous meningitis and pseudopapilledema. However, the current neurosurgical opinion may be understood if one considers the 31 cases in which no lumbar punctures were performed. Twenty-one patients were admitted directly to neurosurgical service where lumbar punctures are not done in patients with papilledema and all but one had brain tumors. The exception had a stenosis of the aqueduct.

On the other hand there were ten cases admitted to neurology who did not have a lumbar puncture. Six were in very critical condition on admission and there was enough clinical information so that a lumbar puncture was deemed unnecessary. Of the remaining four cases, three were not tapped because the attending neurologists were reluctant. The fourth cases is most instructive and illustrates the problem. A 12-year-old girl entered the hospital with headaches of three months duration and occasional double vision. Examination was normal except for nystagmus. Although serous meningitis was considered she was transferred to neurosurgery without lumbar puncture. Although nothing was found by ventriculography a subtemporal decompression was performed. Today her nystagmus is considered to be of congenital origin. Thus two of the three cases of serous meningitis were operated upon.

The one clinical fact to be emphasized is that in the six patients with serous meningitis or pseudopapilledema none was acutely ill, and objective neurological findings were minimal.

CONCLUSION

In conclusion it is felt that the data presented demonstrate:

1) The lumbar puncture is not a dangerous procedure in patients who have ophthalmoscopic findings which might indicate increased intracranial pressure.

2) The lumbar puncture is of diagnostic value in such patients and the spinal fluid findings assist in managing such problems.

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CARCINOMA OF THE ENDOMETRIUM

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Although it is generally agreed that carcinoma of the fundus has a less rapid progression and less lethal growth potentiality than carcinoma of the cervix, it should nevertheless be regarded with greater caution and respect than usually accorded. For example, in the year 1942 the Bureau of Census reports that 16,393 women in the United States died from cancer of the uterus, and of that number slightly more than 20 per cent had primary carcinoma of the endometrium. Randall states that 40 per cent of women who have uterine bleeding after one year or more of amenorrhea suffer from carcinoma of the fundus (1). Excluding such conditions as fibroids, cervical polyps and erosion, he finds that 9.1 per cent of those who bleed irregularly from a normal sized uterus during their menstrual lives develop a corpus malignancy. While it is true that the condition is most frequently post-menopausal, approximately 25 per cent of the cases of corpus carcinoma are encountered in the pre-menopausal women. In our own series of 156 cases of carcinoma of the fundus treated at the Mount Sinai Hospital from 1934 to 1949, 20.5 per cent occurred in women below the age of 50 years (Table I).

The age of the menopause appears to be related to the occurrence or nonoccurrence of corpus carcinoma. Moss found that patients who developed intrauterine cancer had a more prolonged menstrual life than those who did not (2), and Crossen demonstrated the relationship of a late menopause to the increased frequency of carcinoma of the corpus (3).

It is well at this time to consider some of the factors which might predispose to the development of a corpus carcinoma. Although chronic irritation has always been a popular etiologic theory for cancer in general, and has achieved additional prominence lately through the co-relationship of cigarettes and lung cancer, there is little to support this theory as it applies to the uterus. Meigs believes with many others that true chronic inflammatory changes are actually rare in the uterine fundus, since during the menstrual years the uterus has the unique property of periodically shedding its lining (4).

Much has been written about hyperestrinism with associated hyperplasia as a carcinogenic factor. In support of this one may note the frequent incidence of fibroids and endometrial polyps with corpus carcinoma. Mussey believes that the association of functioning ovarian tumors (granulosa and theca cell tumors) with fundal cancer is approximately ten times greater than one would expect if the two were unassociated (5). Novak believes that during the reproductive period hyperplasia of the endometrium is not a precursor to cancer, and he claimed that only 1.3 per cent of the cases of hyperplasia present difficulty in differentiation from adenocarcinoma. However in post-menopausal women he feels there is a

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TABLE I

Age incidence of carcinoma of fundus

30–39 yrs.	9 cases
40–49 yrs.	23 cases
50–59 yrs.	61 cases
60–69 yrs.	44 cases
70–79 yrs.	17 cases
80–89 yrs.	2 cases
Total	156 cases

connection, for in them he finds the incidence of hyperplasia and carcinoma to be 21 per cent (6).

Among predisposing factors, the significance of the delay of the menopause was mentioned earlier. Obesity, too, seems important, and Smith found that 28 per cent of patients in his series weighed more than 160 pounds (7). Scheffey stated that 11 per cent of his patients had diabetes mellitus (8). There is also an increased incidence of nulliparity. Corscaden reported that 38 per cent of his patients with endometrial carcinoma were nulliparas opposed to 16 per cent in those who were afflicted with cancer of the cervix (9).

Finally one should mention the possible relationship between irradiation of the uterus for benign lesions and the subsequent development of carcinoma. Of 1,100 women who had had their menopause induced by radium, Corscaden discovered that 15 had developed fundal cancer (9). In our own series of 156 cases, 14 had x-ray castration performed from 2 to 15 years prior to development of the malignancy.

The symptomatology of carcinoma of the endometrium is chiefly uterine bleeding. It is regarded as the most important single symptom. Bleeding is the first symptom in nearly 80 per cent of patients. Its character depends on the age of the patient. In the pre-menopausal group there may be menorrhagia, polymenorrhea, or metrorrhagia. Since many of these cases co-exist with fibroids and polyps, the bleeding is frequently considered functional, due to endocrine imbalance, which results in a diagnostic delay averaging 11 months (10). In the post-menopausal group the bleeding is usually first manifested as continuous or intermittent vaginal spotting, often following a transient increase in intra-abdominal pressure, such as occurs with defecation. While it is true that senile vaginitis, polyps and even hypertension may be responsible for such bleeding, it should be axiomatic that a woman has carcinoma who bleeds after the menopause unless it is proven due to another cause.

Unfortunately the problem is complicated by the widespread use of estrogens for menopausal symptoms. Even if one rejects the thesis that estrogens may be carcinogenic, they can still mask an early cancer because the uterine bleeding that so often follows hormone administration may be mistakenly considered to be estrorhagia. For that reason many physicians administer male and female hormones together to eliminate or minimize the subsequent bleeding. Certainly it is

wise to regard with suspicion any uterine bleeding that persists after hormone therapy has been discontinued.

Next to bleeding, vaginal discharge is the most frequent symptom. It may precede the bleeding. At first it is usually watery or serous, but if the condition goes untreated the discharge turns seropurulent and even malodorous due to necrosis of the superficial portions of the tumor.

Pain is an inconstant finding and when present usually indicates an advanced lesion, particularly if associated with pyometria, hematometra, or local extension. Anemia, weight loss, urinary symptoms, are generally of little importance as early symptoms.

The physical findings may be meager indeed, especially in an early case, and unless there are associated pathological conditions such as fibroids or pyometra due to cervical stenosis, the uterus is often unenlarged. Fricke and Bowing have suggested a clinical classification into four stages of advancement similar to that used in carcinoma of the cervix (11), but it has not found general acceptance.

Curettage is the method par excellence for the definitive diagnosis of fundal malignancy, and no case of post-menopausal bleeding should be regarded as one of benign bleeding unless the curette has explored the entire cavity of the uterus. Inasmuch as carcinoma of the cervix occurs approximately five times more frequently than fundal carcinoma, the endocervix should be separately curetted (fractional curettage) and a biopsy of the cervical canal done at the same time.

The Papanicolaou smear technique has become increasingly accurate in recent years because of the new method of endometrial aspiration with a fine cannula, but aspiration cytology should not be relied upon for ruling out corpus carcinoma.

Hysterography has also been employed as an additional diagnostic aid but many feel that unless extreme caution not to over-distend the uterus is used, there is real danger of causing extrusion of carcinoma fragments into the Fallopian tubes. In our own series of 156 cases the hysterogram was employed 18 times and in 16 showed an irregular filling defect suspicious of malignancy.

Despite the several diagnostic measures available a small percentage of cases of carcinoma of the fundus will be first discovered as an unsuspected incidental finding when the pathologist cuts open the extirpated uterus; therefore it is important, unless a complete operation is done (total hysterectomy and bilateral removal of the adnexae), that the uterus be opened in the operating room.

The great majority of adenocarcinomata of the corpus begin as a circumscribed proliferation in the fundus with a tendency to form papillary or polypoid projections which may be sharply demarcated from the rest of the mucosa. In a tumor so localized it is conceivable that thorough curettage may remove all gross evidence of the disease, even so completely that multiple sections from the site in the extirpated organ will fail to reveal any residual neoplasm. Novak has collected from the literature 85 cases of this occurrence (12). As the tumor grows it may extend into the endometrial cavity, invading the muscularis, eventually producing fistulae into the bladder or rectum, or it may remain superficial extending along the surface of the endometrium. Extension of the disease beyond the uterus other than by direct invasion takes place late in the disease and generally occurs through five mechanisms: the lymphatics, fallopian tubes, blood stream,

direct invasion through the uterine wall, and the implantation of cells broken off to other peritoneal areas.

Compared to cervical carcinoma the lymphatic spread of fundal carcinoma is much slower, and the parametria are less often involved unless the tumor originates in the lower part of the corpus. Similarly, regional nodes may show no disease. Ewing states that in 66 per cent of his fatal cases the regional nodes showed no tumor deposits at post mortem (13). The spread to the cervix and vagina may be either by local or retrograde lymphatic extension.

There is some difference of opinion as to the importance of the endosalpingeal route as an avenue of extension. Offutt in a study of 53 cases found that 15 showed evidence of direct extension through the lumen of the tube (14). Randall claims that tubal spread is relatively rare and that early metastases may be found deep in the ovary without involvement of the tubes (15). Novak finds that most tubal metastases are submucosal and interstitial (12), and agrees with Randall that surface endosalpingeal implants rarely account for tubal involvement (15).

Inasmuch as there is rich vascular anastomosis between the uterine and ovarian circulations one would expect a high incidence of ovarian metastasis. This is not the case. Novak found only 7 among 147 cases, and he feels that the hematogenous route is not important in the dissemination of this type of carcinoma (12). Peritoneal implants of course indicate advanced spread and are found in over one half of the terminal cases.

The microscopic recognition of adenocarcinoma is usually simple, but in some cases of endometrial hyperplasia there may be difficulty in differentiating the two conditions. Novak states "There is a small group in which I do not believe that any pathologist can be absolutely sure". This is especially troublesome in post-menopausal cases in which the endometrium instead of being thin and atrophic has become hyperplastic. Whether or not this indicates a prolonged state of hyperestrinism Novak is unwilling to state, but he is convinced that post-menopausal endometrial hyperplasia and carcinoma co-exist in almost 25 per cent of these patients (12).

The microscopic grading of these tumors is made for the purpose of prognostication. The least malignant type is called adenoma malignum, the intermediately malignant group is the papillary adenocarcinoma, and the most malignant, the solid adenocarcinoma. In the least malignant group one may find evidence of squamous cell metaplasia, and when present in sufficient degree the tumor is designated an adenoacanthoma. About 60 to 70 per cent of these cases have the low or medium grades of malignancy, the remainder, the more undifferentiated class, are the most malignant.

The three types of treatment for carcinoma of the corpus include irradiation alone, irradiation and surgery and surgery alone. In an attempt to determine the optimum therapeutic approach an appraisal is made of the results of treatment in 156 consecutive cases of fundal cancer admitted to the Mount Sinai Hospital from 1934 to 1949.

With the exception of a few clinics, irradiation as the sole method of treatment is reserved for two classes of patients, those who are poor operative risks because of medical complications, and those in whom the lesion is too extensive for sur-

TABLE II

Type of Treatment	Clinical Cure (5 yrs.)	Percentage Cured	Died within 5 years	Total
Surgery only	26	76.5%	8	34
Radiation followed by Surgery	15	62.5%	9	24
Surgery followed by Radiation	30	66.6%	15	45
Radiation only	10	30.3%	23	33
Terminal and Inoperable	0	0	20	20
Total	81	51.9%*	75	156

*Excluding the 20 terminal cases for which no therapy was given, the corrected over-all five year cure rate is 60.9 per cent.

gery, and radium is given in hope of palliation. In any large series between 20 and 30 per cent of patients will fall into this group; of our 156 cases, 33 or 21.2 per cent had radiation alone. On the other hand, Heyman at Radiumhemmet in Stockholm believes radiation to be the treatment of choice, considering surgery only after radiation fails (16). He reports a 66.7 per cent cure with primary radiation. It is not our intention to discuss in detail various techniques, such as single or divided dose treatments, or radium versus x-ray, feeling that this is more the province of the radiotherapist. Suffice it to say that therapeutic radiation for fundal carcinoma is not without danger, and unless properly administered one may encounter severe radiation necrosis of the bladder, vagina, or rectum, with subsequent fistulae. Furthermore, there may be difficulty in obtaining homogeneous radiation of the entire uterine cavity despite the ingenious contrivances presently in use.

In general, the extent of post-radiation morbidity varies in relation to the stage of the disease when radiation is applied, and the degree of tumor differentiation; such complications as pyometritis, phlebitis, pelvic cellulitis, and peritonitis are not infrequent. Fricke and Bowing report an over-all incidence of 9 per cent morbidity in their radiation series, but this figure jumps to 60 per cent in patients with very advanced lesions (11).

We were especially interested in determining whether pre-operative radiation would increase our salvage rate. In 24 cases the patients received intra-cavitary radium in doses somewhat in excess of 5,000 mg. hours and usually external radiation in doses ranging from 1,000 to 3,375 r. The rationale of the pre-operative radium is to destroy or at least devitalize the more sensitive elements of the tumor and minimize as far as possible the dissemination of the disease at the time of surgery. In addition any associated infection would be reduced, and the regional lymphatics sealed off. Within six to eight weeks the inflammatory reaction incident to the use of the radium subsides sufficiently to permit a complete hysterectomy without undue technical difficulty. The use of external radiation is considered a supplementary measure and most observers who advocate this preoperative regime, use both intra-cavitary and external radiation.

The following are pertinent features of the 24 cases:

1. 4000 mg. hrs. radium plus x-ray (1000 r through 4 fields). Operated upon

after 6 weeks. Remnants of carcinoma cells found. Clinically well 6 years later.

2. 6050 mg. hrs. radium. Operated upon 6 weeks later. Remnants of carcinoma cells found. Clinically well after 6 years.
3. 5000 mg. hrs. (tandem) plus 4300 mg. hrs. (colpostat). Laparotomy 6 weeks later. Inoperable. Died 7 months later.
4. 7500 mg. hrs. plus 2200 r (4 fields). Operated 8 weeks later. Remnants of carcinoma with necrosis. Died 2 years later.
5. 6650 mg. hrs. Operation 6 weeks later. Remnants of carcinoma with necrotic foci. Well after $5\frac{1}{2}$ years.
6. 6000 mg. hrs. (tandem) plus 3000 mg. hrs. (colpostat) Plus 1000 r (through 4 fields). Operation 6 weeks later. Remnants of carcinoma with necrosis. Well after $6\frac{1}{2}$ years.
7. 8960 mg. hrs. plus x-ray (dosage not stated). Laparotomy 6 weeks later. Remnants of carcinoma. Died 2 years later.
8. 5285 mg. hrs. plus 1200 r (through 3 fields). Operated upon 8 weeks later and carcinoma found. Well after 6 years.
9. 7920 mg. hrs. plus 3375 r. Laparotomy 6 months later. Carcinoma of the uterus and ovaries. Died $1\frac{1}{2}$ years later.
10. 3152 mg. hrs. Laparotomy 8 weeks later. Necrosis of endometrium; no carcinoma seen. Clinically well after $5\frac{1}{2}$ years.
11. 3500 mg. hrs. followed by 4846 mg. hrs. three years later for recurrent bleeding. Operated 6 months following 2nd radiation treatment. Died 6 months post-operatively.
12. 2300 mg. hrs. plus 2475 r (4 fields). Three months later received 3600 mg. hrs. for recurrence of bleeding. Laparotomy revealed metastasis to the Fallopian tube and appendix; fecal fistula. Died 3 years later.
13. 4000 r (another hospital). No radium. Operated upon 6 weeks later. Carcinoma present. Well after $5\frac{1}{2}$ years.
14. Radiation at another hospital (dosage?). Laparotomy 6 weeks later. Questionable carcinoma remnants found. Well after 7 years.
15. No details as to dosage. No carcinoma found at laparotomy. Well after $6\frac{1}{2}$ years.
16. 7575 mg. hrs. plus x-ray treatment (dosage?). Laparotomy 2 months later. Extensive necrosis of endometrium, but no carcinoma seen in uterus; metastatic nodule in right ovary. Died 2 years later.
17. 9000 mg. hrs. plus 2000 r. Laparotomy 8 weeks later. Nests of carcinoma cells in myometrium. Well after 7 years.
18. 6032 mg. hrs. No x-ray. Laparotomy 6 weeks later. Residual carcinoma. Well after 5 years.
19. Radiation menopause in 1936. Carcinoma discovered in 1947. 6650 mg. hrs. Laparotomy 6 weeks later. Residual carcinoma found. Well after 6 years.
20. 5490 mg. hrs. plus 1200 r. Laparotomy 8 weeks later. Residual carcinoma with metastases to left ovary. Well after $6\frac{1}{2}$ years.

21. 10,125 mg. hrs. Laparotomy 4 months later. Residual carcinoma. Died after 3 years.
22. 5650 mg. hrs. Laparotomy 8 weeks later. Residual carcinoma. Died $2^1/_2$ years later.
23. 5000 mg. hrs. Laparotomy 8 weeks later. Necrosis of endometrium but no carcinoma. Well after 5 years.
24. 5000 mg. hrs. Laparotomy 8 weeks later. Residual carcinoma. Well after $5^1/_2$ years.

It is at once apparent that in only 4 of these 24 cases was there complete disappearance of intra-uterine carcinoma, and that in 3 cases where carcinoma cells were still present there was considerable necrosis of the endometrium as well as the carcinoma cells. It is interesting to note that in case # 16 the uterus showed no residual carcinoma, but a metastatic nodule was present in the ovary, and the patient died after two years. The reports in the literature (Parsons) on persistence of residual carcinoma vary from 33 to 89 per cent, the discrepancies due in large measure to the dosage of radiotherapy and the diligence of the pathologist. For example, among 53 cases in which no remnants of carcinoma cells were discovered in the endometrium, Stowe found 19 instances of carcinoma nests deep in the muscle after having done serial sections (17).

The surgical treatment of carcinoma of the fundus is best carried out by the abdominal approach. The operative procedure should include:

(a) preliminary suture closure of the cervical os to prevent vaginal spill; (b) ligation of the tubes to prevent seeding of carcinoma fragments into the abdominal cavity; (c) gentle handling of the uterus. Tenacula must not be used and the uterus should be grasped at its junction with the round ligaments; (d) complete removal of both adnexae, no matter how young the patient or how early the lesion; (e) there should be wide dissection of the parametria and removal of at least a 2 cm. vaginal cuff; and (f) where there is a downward extension to the endocervix, a radical Wertheim should be done with bilateral pelvic lymphadenectomy.

Of the 156 patients in our series, 103 were operated upon. Three died during the post-operative period; one each of peritonitis, pulmonary embolism, and cardiac failure. The post-operative morbidity was essentially the same as for benign conditions.

Post-operative x-ray therapy was used whenever the lesion was of moderate or high grade malignancy as determined by microscopic characteristics, or when there was evidence of extension beyond the uterus.

Vaginal metastases occur in about 5 to 6 per cent of the cases (7). These are treated with radium, but the results are not encouraging.

The prognosis depends upon four factors: the duration of symptoms, the grade of malignancy, the extent of the disease, and the type of treatment. A fifth factor may be added, namely, the general condition of the patient, since with this type of lesion one is frequently dealing with patients of advanced years. However it is manifestly unfair to include a mortality as a cancer death if the patient dies of an intercurrent illness before five years have elapsed from the time of therapy.

As mentioned before, bleeding is the cardinal symptom and is therefore accepted as the criterion for determining the time of onset of the disease. However, if during the menstrual life there is an associated lesion such as fibroids, it becomes difficult to determine at what point the bleeding becomes a symptom of carcinoma. Norris and Dunne found that in this group the duration of symptoms was approximately four times as long as for the whole group of patients (18). Likewise when estrogen has been administered to the early menopausal group, both physician and patient may pay little attention to the bleeding for some months. Pain as an index of disease extension beyond the uterus is not reliable for prognostic purposes, since Murphy found that among 56 patients who had pain as a major symptom, in only 16 had the lesion extended outside the uterus (19). Conversely there were 43 patients who had proven extension beyond the uterus and none had any pain.

Just as in carcinoma of other organs, a highly undifferentiated lesion offers a more grave prognosis, but one should not grade the malignancy solely on the curettings. Randall has noted that sections from curettings frequently show evidence of greater maturity than sections obtained from the deeper invasive portions of the tumor, and that specimens from different parts of the same tumor may show different degrees of differentiation (15).

The clinical classification of the extent of malignancy is not as readily determined with fundal carcinoma as it is with a cervical malignancy. In general, if there are no associated fibroids, the smaller the size of the uterus, the better the prognosis. Naturally with evidence of vaginal down-growth or broad ligament fixation the outlook changes accordingly.

The last prognostic factor is the type of treatment. Parsons estimates that surgery should offer a 90 per cent cure in lesions of low grade malignancy, about 65 per cent in medium grades, and about 50 per cent in anaplastic growths (20). Fricke and Bowing obtained a much lower cure rate when radiation was employed as the sole treatment; 39 per cent for low grade malignancy, 25 per cent for medium grade, and 12 per cent for anaplastic tumors.

To present the over-all picture, Parsons compiled the following statistics from reports in the literature through 1948 (20):

	Surgery alone	Radiation plus surgery	Radiation alone
Total cases	1384	1230	2387
5 year cures	63.7%	60.3%	38%

Is it possible, then, from a review of the literature and from our own results, to formulate a policy for the treatment of carcinoma of the fundus? With very few exceptions, most clinics now utilize surgery as the chief weapon of attack, and greater emphasis is placed on the so-called "adequate operation". While it is true that corporeal carcinoma is usually slow growing and is contained within the confines of a thick muscular wall, to increase the number of cures it is necessary that a more extensive operation be done than a simple panhysterectomy. A great deal has been written about pre-operative radiation, and although cogent, logical arguments are advanced in its favor, the end results appear no better than sur-

gery alone. Certainly in our series this is true. It is our feeling that the six to eight weeks postponement of surgery to allow pre-operative radiation is precious time lost. It may be true that the carcinoma cells are destroyed or devitalized, but positive evidence of this was found in only 7 of our 24 cases. In case #16 the the metastatic nodule in the ovary completely escaped the effect of the radiation. Post-operative x-ray, however, should be utilized wherever there is any question of extra-uterine extension or when the tumor cells have a highly anaplastic appearance.

The ten per cent higher five year cure rate in our series of patients who had surgery alone (76.5 %) over those who had surgery followed by post-operative x-ray (66.6 %) is more than likely due to the more serious disease of the latter group.

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HYPOTENSIVE THERAPY IN ACUTE INTRACRANIAL BLEEDING

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INTRODUCTION

The purpose of this report is to describe the technique and preliminary results of a therapeutic method which is currently being applied to cases of acute intracranial bleeding in place of the more usual, time honored (but still present day) practice of "conservative" management (i.e. "do-nothing"). The clinico-pathologic data upon which this method is based includes the results of the author's dissection of the vasculature of 130 brains with especial regard to the circle of Willis, its remarkably frequent variations and its clinical importance in impairing the cerebral circulation (1). Thus in the case of aneurysm it was felt that the hoped-for (but doubtfully achieved) advantages of carotid ligation would be achieved by the far more flexible hypotensive medication method while the hazards associated with carotid ligation, some of which are very likely related to the presence of a deficient circle of Willis, would be reduced to a minimum. Poor surgical results, in part due to carotid ligation's suddenness and irreversibility (some surgeons have already given up the use of clamps which were supposed to mollify the precipitous nature of ligation) as well as its further impracticality in the case of many of the 20–25 per cent of aneurysmal cases in which multiple aneurysms occur, have led to the discarding of carotid ligation in some very large clinics. (2). The case histories of four patients in whom hypotensive therapy was used are herein presented. Two (Cases #1 and #2) are cases of acute subarachnoid hemorrhage (with probable co-existent intracerebral hemorrhage in one), and one (Case #3) is a case of subarachnoid hemorrhage in a patient in whom angiography subsequently revealed the presence of an aneurysm. One (Case #4) is a patient with a subarachnoid hemorrhage in whom angiography subsequently revealed the presence of two aneurysms. Patients #2, #3, and #4 have been discharged and are being followed in the clinic. Case #1 has recovered from the acute phase of his illness and is now receiving physiotherapy preparatory to discharge.

CASE REPORTS

Case #1. A 44 year old man with known hypertension of 12 years duration noted numbness of the left side of his face, his left arm and left leg occurring after an afternoon nap on April 25, 1956. An hour later, headache, mainly occipital but also frontal and right retro-orbital, began. Vomiting occurred and then anorexia. Two to three hours after the onset of symptoms, weakness of his left extremities and left side of his face was noticed along with the lack of feeling on the left side of the body. On April 26, severe headache, restlessness, insomnia, neck pain and stiffness occurred. There was also some pain radiating through the

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chest and shoulders. His private physician administered codeine. The left hemiplegia was almost complete but he was alert and anxious. On April 27, he became alternately restless and then drowsy and the headache became more severe. He was admitted to The Mount Sinai Hospital on that day. Past history disclosed an episode three years ago of epigastric distress and black stools which was diagnosed as a bleeding ulcer. No ulcer symptoms had recurred. For the past several years he had complained of easy fatigability, exertional dyspnea, poor concentration, short temper and had generally been increasingly difficult to get along with. On admission, general physical examination disclosed a slightly enlarged heart with an apical systolic murmur and increased force of the PMI. Blood pressure was 210/120 and the pulse was 88 per minute. There were occasional Cheyne-Stokes respirations. The positive neurologic findings included lethargy and very marked nuchal rigidity with positive Kernig and Brudzinski signs. The margin of the right optic disc was indistinct, with a probable left homonymous visual field defect. In addition there were small pupils with the left greater than the right (each was less than 2 mm. in diameter) but both pupils reacted to light. There was depression of the left corneal reflex and hypalgesia to pinprick on the left side of the face. A severe left facial paresis including eye closure was present; the uvula elevated only slightly and deviated to the right and the tongue deviated to the left. A complete left flaccid hemiplegia was present along with a left hemisensory defect for pinprick, vibration sense and position sense. The left knee jerk was slightly more active than the right and there was left ankle clonus. It was felt that the patient probably had suffered a vascular lesion of the right cerebral hemisphere within the distribution of the right middle cerebral artery with meningeal irritation. On the night of admission lumbar puncture revealed grossly bloody cerebrospinal fluid with supernatant xanthochromia. The initial pressure was 250 mm, there were 55,000 RBC, 550 polys and 3 lymphocytes. The protein content was 148 mg%. Thereafter, the blood pressure rose to 220/124 and the pulse was 92/min.

Hypotensive therapy was begun with 2.5 mg reserpine intramuscularly followed by oral reserpine with gradual lowering of the blood pressure to 170/94. There was constant observation by a physician with repeated neurologic examinations. The decrease in blood pressure was maintained until the next day when, after being taken to and from the X-Ray Department for films of the skull and chest, his blood pressure rose to 208/116, and he had become much more lethargic. Pentolinium was begun (10 mg orally). Less than one hour later his blood pressure was still elevated (210/110), the pulse was 100 and he was disoriented. Pentolinium was given in increasing doses and, less than three hours after the onset of disorientation he was again oriented, more alert, his blood pressure was 180/100 (with subsequent further decrease) and the pulse was 104. On the next day (April 29) his blood pressure was 146/96, the pulse was 100 and lumbar puncture revealed amber colored fluid with a reddish tinge. The initial pressure had decreased markedly to 40 mm. There were 50,750 RBC and 1,460 WBC/cubic ml., 90% of which were polys and 10% lymphocytes. The protein content was 210 mg%. The blood pressure decrease was then maintained, sometimes reaching levels as low as 138/80 with a pulse of 86 and with gradual but steady clinical improvement. On May 4, lumbar puncture revealed clear yellow fluid with an initial pressure of 105 mm. There were only 41 RBC, 2 polys and 1 lymphocyte. The protein had decreased to 22 mg%. Subsequently, bilateral carotid angiography revealed no abnormality except for poor filling of the right anterior cerebral artery. The hypotensive dosage requirement has since decreased but the blood pressure has remained at the same desired levels. The nuchal rigidity which was so marked on admission is now completely gone. There is minimal if any lethargy and there has been no recurrence of disorientation. The severe left facial paresis has almost completely cleared and there is steadily increasing return of voluntary movement in both left extremities. The patient now sits up in a chair and is able to stand with assistance.

Case #2. A 38 year old right handed woman entered Mt. Sinai Hospital on March 14, 1956 for removal of a uterine polyp. She had had meno-metrorrhagia for 15 years. She had had hypertension for 16 years with severe generalized headache often accompanied by

nausea, occasional dizziness and veering to the left and also occasional spots in front of her eyes. On the day of admission, as she got off the table after pelvic examination she felt the sudden onset of bursting pain behind the left eye. Blurred vision was noted and then neck stiffness. Physical examination revealed nuchal rigidity, eyeball tenderness, photophobia and a positive Kernig sign. Her blood pressure was 180/120 and her pulse was 78. Lumbar puncture revealed grossly bloody fluid with supernatant xanthochromia. The initial pressure was 400 mm, there were 26,000 RBC, 3 polys, 1 lymphocyte/cubic ml. and 66 mg% protein. The Wassermann reaction was negative. On March 19, the headache was worse and was primarily occipital. Hyperacusis and marked photophobia were present. There was a slight defect in sensation to pinprick and touch on the right side of the body and face. On March 20, lumbar puncture revealed grossly bloody fluid with an initial pressure of 460 mm and the supernatant was deeply xanthochromic. There were 65,000 RBC and 11,200 WBC/cubic ml. of which 80% were polys. Her blood pressure was 185/100. On March 21, her blood pressure was 170/96 and oral reserpine was begun. On March 22, her blood pressure was 152/98. Reserpine was increased to 0.25 mg t.i.d. and then pentolinium was begun at levels of 10 mg b.i.d. Lumbar puncture revealed pink fluid with supernatant xanthochromia and an initial pressure of 280 mm. There were 18,950 RBC/cubic ml. and 85 mg% protein. On March 23, headache and photophobia were greatly diminished. At 1:10 P.M. her blood pressure was 130/82 with a pulse of 84. Four hours later she became mildly aphasic and had right sided motor and sensory defects including the face and a right Babinski. There was no papilledema nor change in nuchal rigidity. It was felt that cerebro-vascular insufficiency secondary to over-medication rather than recurrent bleeding was responsible and an immediate lumbar puncture revealed clear fluid with xanthochromic supernatant (less xanthochromia than previously) and an initial pressure of 300 mm. There were 14,900 RBC. The pentolinium dosage was decreased and eventually cut entirely. At 9:00 P.M. of the same day her blood pressure was 148/94 and her pulse was 84. The aphasia and motor deficit had completely cleared, with the only residua consisting of the minimal right hemisensory defect which had been present before this episode. The patient subsequently had two additional transient (and less marked) episodes of aphasia without motor deficit nor Babinski sign. She recovered completely from these episodes and was well except for transient left sided headache which responded to mild analgesics. The photophobia decreased and then disappeared as did transient nightmares also. Her dosage of hypotensive medication was gradually reduced so that her blood pressure levels ranged from 124–162 systolic to 82–100 diastolic without recurrence of hypotensive symptoms or signs. She was gradually ambulated. On the day of discharge her reclining blood pressure was 130/98 and her pulse was 64/min. After standing and walking for four to five minutes her standing blood pressure was 130/88 with a pulse rate of 84. Because of her good recovery a left sided carotid arteriogram was not done. Her reserpine dose on discharge was 0.1 mg per day. She is being followed in the clinic where her reclining blood pressure has been 144/100 and her pulse 70. After standing and walking for nine to ten minutes her standing blood pressure has been 144/90 and her pulse 96. Physical examination discloses only the same minimal right hemisensory defects which she had had prior to treatment. At home she is active in her housework. Her reserpine dosage is still only 0.1 mg per day.

Case #3. A 60 year old right handed woman was found unconscious early in the morning on January 22, 1956 having retired late after an active evening during which she had felt perfectly well. She was subsequently drowsy and complained of severe pain in the back of the neck. Her private physician noted that she was hypertensive. The patient became increasingly somnolent until admission to Mt. Sinai Hospital on January 26, at which time the following positive findings were noted: blood pressure was 212/100. The optic disc margins were indistinct. There was a left facial asymmetry and weakness of the left hand grip and wrist extension. There was marked nuchal rigidity. Lumbar puncture on the day of admission revealed frankly bloody fluid with xanthochromic supernatant after centrifuging. The initial pressure was 220 mm and there were 118,800 RBC. There were 150 WBC, mostly polys, 82 mg% protein and a negative Wassermann reaction. On January 27, the patient was re-

portedly restless and confused. On January 30, she was alert, had no headache nor eyeball tenderness. She was disoriented, her memory was not good and her neck was stiff. Her blood pressure was 162/80. On February 2, lumbar puncture revealed slightly xanthochromic fluid with an initial pressure of 220 mm. There were 130 RBC, 2 WBC and 39 mg% protein. On February 10, lumbar puncture revealed clear, slightly xanthochromic fluid with an initial pressure of 100 mm. There were 39 RBC, 54 lymphocytes and 25 mg% protein. On February 16, her blood pressure varied from 200/112 to 170/100. On February 20 her mental status was reported normal. A right percutaneous carotid angiogram using Hypaque revealed the presence of an aneurysm of the right internal carotid artery in the region of the anterior clinoids. On February 24, L-P revealed slightly yellow fluid with an initial pressure of 155 mm. There were 76 RBC, 2 lymphocytes and 24 mg% protein. On February 26, she seemed fully recovered and had been ambulatory for a few days. On February 28, reclining blood pressure was 204/104 and her pulse was 96; standing blood pressure was 180/116 with a pulse of 120. At this point oral reserpine in a dose of 0.1 mg per day was begun. Four hours later, reclining blood pressure was 158/94 and her pulse was 76; standing blood pressure was 148/94 and the pulse was 100. On hypotensive medication her blood pressure then progressively decreased to a reclining systolic pressure ranging from 134 to 144 with a diastolic pressure ranging from 72 to 84. The pulse ranged from 68 to 80. Her standing blood pressures (standing up to five minutes) ranged from a systolic of 134 to 154 and a diastolic ranging from 84 to 94. The standing pulse ranged from 92 to 100. The patient was discharged to the clinic on reserpine 0.75 mg per day without any side effects. Pentolinium was then added in gradually increasing doses till the patient was taking a total of 60 mg per day. On this regimen the reclining blood pressure was 138/80 with a pulse of 56. The blood pressure on standing (after five minutes) was 120/70 with a pulse of 72. There were no complaints except that one day while waiting for a bus she had noted a transient feeling of unsteadiness. She had continued to have occasional slight headache which had begun before reserpine therapy. Reserpine has been decreased to one sustained-release capsule (0.25 mg total) per day. The pentolinium dose has been continued at 60 mg per day. She is active in her housework and has no complaints.

Case #4. A 51 year old hypertensive woman entered Mt. Sinai Hospital on February 9, 1956 because of progressive stupor of approximately 4 days' duration. On January 26, 1956 she was found unconscious. (For one week previously she was said to have been irritable and had occasionally spoken irrationally.) She was hospitalized elsewhere, lumbar puncture was done, skull x-rays were taken and she was diagnosed as having suffered a "stroke" and discharged home on February 4th. At this time she was alert although she had indistinct, monosyllabic nonsensical speech along with headache and neck pain. Four years prior to admission she was said to have had a "stroke" consisting of transient blindness or blurred vision which lasted for a few hours. The onset had been during intercourse. Concomitant with the visual disturbance there occurred a severe headache which lasted four days. Her hypertension was of many years' duration. On admission to Mt. Sinai Hospital she was unresponsive to verbal stimuli. She occasionally shouted "no, no" if disturbed by noxious stimuli. She occasionally opened her eyes. There was bilateral papilledema with hemorrhage including the peripapillary area. The eyes moved conjugately. There was a left facial weakness and the left palpebral fissure was larger than the right. There was a flaccid left hemiparesis with greater involvement of the upper extremity. There was moderate nuchal rigidity and eyeball tenderness. She withdrew from pinprick less readily on the left side, including the face, than on the right side. Her blood pressure was 180/100 and the pulse was 72. The general physical examination was negative except for a distended bladder. On the day of admission lumbar puncture revealed clear faintly yellow fluid with an initial pressure of 200 mm. There was 45 RBC, 2 polys, 13 lymphocytes and 84 mg% protein. Calorie responses were normal. On February 10, the papilledema became more marked. A right percutaneous carotid angiogram using diodrast revealed the presence of an aneurysm of the right anterior cerebral artery in the region of the anterior communicating artery but no definite displacement of vessels was seen. On February 11, coarse, jerky nystagmus on left

lateral gaze was noted. She seemed more alert and made a few sounds. On February 14, lumbar puncture revealed clear colorless fluid with an initial pressure of 160 mm. There were 78 RBC, 2 polys, 9 lymphocytes and 56 mg% protein. On February 16, she had continued to become more alert, was found to be aphasic and had a droop of the right side of her face. There was no nystagmus, her tongue deviated to the right and there was left hemiparesis. On February 19, her blood pressure was 180/100; at this point her clinical status remained the same. On February 28, lumbar puncture revealed clear colorless fluid with an initial pressure of 140 mm. There were 10 RBC, no WBC and 48 mg% protein. Over a one week period her blood pressure had been ranging from 170 to 200 systolic and 100 to 120 diastolic. On February 29, repeat caloric responses were again normal. On March 1, since the results of the right sided carotid angiogram did not explain the present picture, a left carotid angiogram using Hypaque 50% and also a right-sided retrograde technique described by this author elsewhere (3), revealed the presence of an aneurysm of the left anterior cerebral artery at the bifurcation of the pericallosal and callosomarginal branches. The ipsilateral vertebral, the basilar and posterior cerebral arteries showed no evidence of aneurysm. On March 2, because her reclining blood pressure was 170/102 and her pulse was 96/min., oral reserpine (0.1 mg) was begun and gradually increased to 0.25 mg. t.i.d. On March 5, the patient began dangling. It was noted that her aphasia had continued to improve. On March 9, pentolinium was added. Her blood pressure in the next few weeks usually ranged from 130 to 166 systolic and 70 to 92 diastolic with a pulse of 50 to 60. On March 14, she was out of bed in a chair and on March 16, physiotherapy was begun. On March 18, standing was begun and the time in the erect position was gradually, subsequently increased. On March 19, a lumbar puncture revealed clear colorless fluid with an initial pressure of 90. There were no cells and 26 mg% protein. On April 25, she was discharged with residual aphasia, left hemiparesis, and right facial paresis. On the day of discharge her blood pressure was 144/94 and her pulse was 68. She was able to stand and walk for five minutes at one time. She is being followed in the clinic where her blood pressure levels and dosage of hypotensive medication have remained the same. At home she walks about unassisted and continues to feel well.

COMMENT

A combination of two anti-hypertensive agents, reserpine and pentolinium, has been used without any other form of treatment than bedrest in four consecutive cases of intracranial bleeding in both the acute phase (Cases ✻1 and ✻2) and the 'convalescent' phase (Cases ✻3 and ✻4). The cases herein reported included subarachnoid hemorrhage with aneurysm along with one case with a probable co-existent intracerebral hemorrhage. These drugs were used both therapeutically and prophylactically. They are to be used *whether or not* hypertension as ordinarily conceived is present on the premise that a lower blood pressure level represents a safer level in a patient who harbors an aneurysm or who has bled intracranially as a result of other causes. Lowering of normotensive blood pressure via hypotensive agents has been previously demonstrated by others (4). Worthy of note is the consideration that phlebotomy may result in a transient hypotension. Unfortunately this method can not be accurately quantitated and controlled.

Reserpine has thus far been administered initially because of (a) its gradual hypotensive effect even if given parenterally, (b) its calming effect in the restless patient, (c) its cathartic rather than constipating tendency (a factor of importance in reducing straining in these patients), and (d) the low incidence of nausea and vomiting associated with it. However, in the lethargic patient pentolinium

may have to be used from the very beginning. (Another drawback to the use of reserpine is the reported occurrence of miosis associated with its use. This may possibly have occurred in Case # 1 cited above. However, pentolinium has been reported to cause mydriasis in some animals.)

As noted above, full consideration to the rationale of the above therapy is given in another report. Suffice it to say here that an attempt is made to decrease the likelihood of continued or new bleeding by decreasing the systolic, diastolic and pulse pressures. Eventual total evaluation of this method must of course reside in the long-term follow-up of many additional cases—(a) those with treatment by this method, (b) those with treatment by other methods such as vitamin K and (c) those cases without specific treatment. The problem of acute intracranial bleeding with *shock* may perhaps be resolved by other means such as hibernation techniques.

The statement that many patients with intracranial bleeding survive does not alter the fact that many patients with intracranial bleeding die and that many of those who do survive are severely disabled. At any rate, current "conservative" therapy leaves much to be desired. Intracranial bleeding continues to result in death and disability year after year. Cerebral hemorrhage manages to remain the third leading cause of death in this country. In 1954 in this country 108,443 persons died of cerebral hemorrhage and an additional 4,706 died of subarachnoid hemorrhage (5). It is glaringly apparent that there is definite room for improvement in the present status of our methods of treatment and prevention of these disorders. Surgery has unfortunately proved disappointing. It is hoped that the approach described in this paper will improve the prognosis in the cases with subarachnoid and/or cerebral bleeding. This mode of treatment is absolutely dependent on careful, *repeated neurologic* examination and judgement including the timing of whatever laboratory procedures may be necessary, such as lumbar punctures, x-rays, electroencephalography and cerebral angiography. Apropos of the traditional teleological dogma that hypertensive blood pressure levels are strictly a "compensatory mechanism" it is worthwhile to note that in Case # 1, the *only* episode of definite clinical *deterioration* occurred concomitant with blood pressure *elevation* whereas subsequent definite clinical *improvement* occurred concomitant with a *decrease* in blood pressure (under intensive anti-hypertensive therapy) and a marked *decrease* in cerebrospinal fluid pressure.

SUMMARY

A preliminary report of a new therapeutic and prophylactic approach to the problem of intracranial bleeding is described with encouraging results in all four cases in which it has been used thus far. It is obvious but nevertheless re-emphasized that these four cases are intended to represent a preliminary descriptive report of a method by which neurologists may attack an old clinical problem through the use of new drugs. Many additional cases with many controls must be collected before any definite conclusions can be drawn. This work is in progress.

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AN EVALUATION OF NICOTINYL SALICYLIC ACID IN ARTERIOSCLEROSIS OBLITERANS

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In 1941 Silbert enumerated eight methods for increasing circulation in the extremities in peripheral vascular disease (1). Of these the most important is sympathetic vaso-dilatation produced by medical or surgical means. The surgical method consists of lumbar sympathetic ganglionectomy. The medical effect is achieved by drugs acting as sympathetic blocking agents, smooth muscle relaxants or adrenolytic agents. Some of the better known drugs in this category are xanthines, papaverine, nicotinic acid, tetra-ethyl-ammonium bromide, tissue extracts, alcohol, ether and mecholyl. The effectiveness of these drugs in the treatment of arteriosclerosis obliterans is questionable, even though some of them have been used in peripheral vascular disease.

Vaso-dilatation of itself does not necessarily produce increased blood flow to the extremities. The stronger vaso-dilating agents, such as the hexamethoniums produce generalized vaso-dilatation which could result in a hypotensive effect. This action could reduce the blood flow to the peripheral parts and produce an ischemic effect.

Although surgical sympathectomy is the most dependable blocking method for overcoming vaso-constriction, all patients with peripheral vascular disease are not suitable candidates for such treatment. Thus the search continues for an effective peripheral vaso-dilating agent, one that presumably has little central and ganglionic effect but strong peripheral arteriolar effect. Adrenolytic agents and sympatholytic drugs, although of some benefit, do not completely answer the problem of reduced arterial blood flow in arteriosclerosis obliterans. An effective drug should overcome the effects of ischemia such as intermittent claudication, rest pain, night cramps, trophic disturbances and beginning gangrene.

It is difficult to evaluate the exact effects of vaso-dilating drugs. Results are usually measured by increased skin temperature of the extremities, decrease in intermittent claudication and increased walking ability. Changes in oscillometric readings are rarely noted with these drugs. Moreover, such readings are far from accurate and are not of definitive value in determining improvement in arterial circulation. Plethysmographic studies of arterial circulation are of value in digital circulation but are not significant in determining general peripheral blood volume.

A great many factors, such as external temperature, atmospheric conditions, emotional and psychogenic factors as well as eating, drinking and smoking habits have greater effects, beneficial or deleterious, on peripheral circulation than most drugs. In fact, many so-called improvements in vascular disease ascribed to drugs and measured and reported as increased walking ability, lessened intermittent claudication and increased skin temperature could well be due to psychogenic factors.

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In a search for a more effective vaso-dilating drug Martin and Byers suggested investigation of nicotinyl salicylic acid as a possible agent for increasing arterial blood flow in the extremities in arteriosclerosis obliterans (2). These investigators found that compared to other salicyl compounds there was an unusually prolonged duration of blood level with nicotinyl salicylate. When nicotinyl salicylic acid was ingested marked flushing of the body occurred. Because of its potential vaso-dilating properties the drug was clinically investigated.

METHODS

From the Peripheral Vascular Clinic of The Mount Sinai Hospital twenty-two patients were selected for study who were under treatment for occlusive arterial disease of the lower extremities. The group comprised nineteen males and three females. In addition to the vascular pathology, four of the patients had had previous coronary attacks, and three others had diabetes. They ranged in age from 44 to 81 years with an average of 65. The peripheral vascular disease existed from two years to fourteen years, the average being six years. All complained of inter-

TABLE I

Nicotinyl Salicylic Acid Administration: Duration and Reactions

Patient	Age	Sex	Duration of peripheral vascular disease	Duration of Nicotinyl therapy	Reactions	Blood pressure	
						Before therapy	After therapy
1. F.G.	58	M	9 yrs.	1 week	vertigo	170/88	168/84
2. C.S.	67	M	8 yrs.	1 month	none	156/80	160/82
3. L.U.	44	M	4 yrs.	1 month	none	180/92	180/90
4. M.B.	60	M	3 yrs.	9 months	occasional abdominal cramps	180/100	180/100
5. M.S.	68	M	2 yrs.	3 months	none	190/100	184/100
6. S.S.	66	M	10 yrs.	1 day	increased claudication	164/86	170/86
7. S.N.	57	M	7 yrs.	1 yr.	none	114/74	120/74
8. R.K.	74	F	8 yrs.	6 months	none	174/80	176/82
9. H.L.	71	M	4 yrs.	8 months	none	160/80	156/80
10. J.P.	64	M	6 yrs.	1 week	nausea	182/92	178/94
11. H.F.	54	M	2 yrs.	1 month	none	140/90	180/94
12. I.S.	65	M	4 yrs.	1 month	none	150/80	154/80
13. G.B.	56	M	4 yrs.	5 months	none	150/80	190/90
14. L.A.	57	M	14 yrs.	2 months	none	200/80	218/98
15. D.G.	62	F	8 yrs.	1 day	severe anginal attack	190/84	192/84
16. M.G.	78	M	9 yrs.	1 day	gastric upset	168/84	166/80
17. M.R.	81	M	15 yrs.	4 months	none	210/100	204/90
18. P.R.	59	M	4 yrs.	2 months	none	254/112	246/110
19. B.W.	69	F	7 yrs.	4 months	none	154/80	160/78
20. A.B.	68	M	6 yrs.	5 months	none	176/84	170/80
21. S.N.	63	M	9 yrs.	6 months	none	156/80	158/78
22. M.W.	70	M	12 yrs.	4 months	none	136/80	146/82

TABLE II

Results of Nicotinyl Salicylic Acid Therapy

Patient	Average skin temp. change, C.			Relief of pain (Intermittent claudication)	Walking ability		Oscillometric readings at ankle		Pedal pulses	
	Before therapy	After therapy			Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
1	76°	75°	−1°	none	2 blocks	2 blocks	0.5	0.5	absent	absent
2	78°	78°	0	none	1 block	1 block	1.0	1.0	diminish	diminish
3	78°	79°	+1°	none	3 blocks	3 blocks	1.5	1.5	diminish	diminish
4	75°	81°	+6°	none	1 block	1 block	0	0	absent	absent
5	74°	74°	0	none	4 blocks	4 blocks	1	1	absent	absent
6	72°	72°	0	increased	½ block	½ block	0	0	absent	absent
7	76°	81°	+5°	none	1 block	1 block	0.5	0.5	absent	absent
8	72°	72°	0	none	4 blocks	4 blocks	0	0	absent	absent
9	78°	78°	0	none	2 blocks	2 blocks	0	0	absent	absent
10	74°	74°	0	none	3 blocks	4 blocks	1	1	diminish	diminish
11	70°	70°	0	none	2 blocks	2 blocks	0	0	absent	absent
12	76°	75°	−1°	none	4 blocks	4 blocks	1	1	diminish	diminish
13	72°	72°	0	none	1 block	1 block	0	0	absent	absent
14	74°	74°	0	none	3 blocks	3 blocks	0	0	diminish	diminish
15	75°	78°	0	none	1 block	1 block	0	0	absent	absent
16	76°	76°	0	none	1 block	1 block	0	0	absent	absent
17	74°	74°	0	none	½ block	½ block	0	0	absent	absent
18	78°	78°	0	none	3 blocks	3 blocks	1.5	1.5	diminish	diminish
19	80°	80°	0	none	4 blocks	4 blocks	1	1	diminish	diminish
20	74°	75°	+1°	none	1 block	1 block	0	0	absent	absent
21	76°	76°	0	none	2 blocks	2 blocks	1	1	absent	absent
22	72°	72°	0	none	½ block	½ block	0	0	absent	absent

mittent claudication which usually occurred after walking one-half to three blocks. Previous therapy, including commonly used vasodilator drugs, had been of no value.

The patients were given nicotinyl salicylic acid* in 60 mg. capsules, one capsule to be taken after meals and the dose increased to two capsules after meals if no untoward effects developed. The patients were observed twice a month for systemic as well as vascular reactions. The patients were particularly observed for gastrointestinal, urinary, nerve and blood reactions in addition to the peripheral vascular effects related to walking ability, temperature changes in the feet, intermittent claudication, oscillometric readings, peripheral pulses and trophic changes in the lower extremities. The medication was taken by the patients from one day to one year, the average being three months (Tables I and II).

RESULTS

In three cases, within 24 hours after taking the medication, untoward reactions occurred which precluded continuation of this therapy. One developed marked

* Nicotinyl Salicylic Acid was provided through the courtesy of the National Drug Co.

vertigo, one complained of severe angina and one had an increase in intermittent claudication. A fourth patient develped mild abdominal cramps which did not necessitate interdiction of the drug.

There were no deleterious systemic effects. Blood pressures remained unchanged, usually hypertensive in most cases. Blood counts and urinalyses were normal and the diabetic condition of the three patients was not altered.

As for the peripheral vascular effects in the lower extremities, they were of no significant value. Only two patients showed a rise of foot skin temperature of approximately 5° C. However since skin temperature is dependent on many variable factors and is not a constant in the majority of the cases in this study, the temperature rise cannot be attributed to a vasodilating effect of nicotinyl salicylic acid. Two patients occasionally felt a generalized body warmth after several weeks of therapy.

There were no significant effects relating to increased walking ability. Only three patients found that their walking ability was increased by three blocks. The other nineteen patients experienced no benefit relative to walking. They still could walk only one-half to two blocks. There was no change relative to pedal pulses and oscillometric readings also remained unchanged.

No undesirable effects resulted from the use of the drug. Although no distinct vascular benefit was found with the use of nicotinyl salicylic acid, ulcerations, phlebitis, and trophic changes did not occur.

CONCLUSION

Nicotinyl salicylic acid was used as a possible vasodilator in 22 patients with arteriosclerosis obliterans. The results show that the drug is of no therapeutic value in occlusive vascular disease.

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Nathan E. Brill, M.D.

DR. NATHAN E. BRILL

A Profile

REUBEN OTTENBERG, M.D.

New York, N. Y.

When I first came to the Mount Sinai Hospital as a fellow in pathology in 1907, I at once became acquainted with two fairly common diseases, neither of which I had seen during my two and one half years of interneship at the German Hospital (now called the Lenox Hill Hospital). One of these was ulcerative endocarditis (subacute bacterial endocarditis) which I learned from Libman; the other was Brill's disease which was demonstrated to me by all the medical men in the hospital except Brill himself. He apparently paid little attention to it. He was then probably gathering the material for his famous paper of 1910, "An Acute Infectious Disease of Unknown Origin, a Clinical Study Based on 221 Cases". The name, "Brill's disease" was in common use throughout the hospital in spite of Brill, who never lowered his dignity to use it. The rumor would go through the halls: "There is a new case of Brill's Disease in Ward E. The patient has a spot in one of his palms." And the entire staff would go at once to see that spot.

When I first read Brill's paper of 1910 (1) I thought, "How wonderful and unusual to wait until he had 221 cases before publication!" And then I saw in a footnote that he had staked his claim as early as 1898 in a preliminary announcement under the title, "A Study of Seventeen Cases of a Disease Clinically Resembling Typhoid Fever but without the Widal Reaction"; (2) New York Medical Journal, January 1898.

The stress was on clinical differentiation from typhoid fever. There is no doubt that in all the years before Brill these cases were treated as typhoid. And it is interesting in reading Brill's 1910 paper to see that he devotes the first few pages to the fascinating history of the long struggle in the first half of the 19th Century to differentiate the various "pestilential fevers". He tells how the French first recognized typhoid by its intestinal lesions, how the great clinician, Louis, gave the name "typhoid" in 1829 and how the English failed at first to confirm the French findings because they were very likely dealing mainly with typhus fever.

Brill, in the beginning of his paper, excuses himself for making no reference to the pathological basis of the new disease because there were no fatalities. All the 221 cases recovered (despite the fact that it was not a mild disease and very often the patients were desperately ill). This is very different from the high mortality of both typhoid and typhus fever, as known in the army camps and epidemics of the old world.

I soon met Dr. Brill himself and fell into the habit of following him on rounds, as did many other younger men for the sake of what could be learned from him. He was tall, straight, handsome and serious. He certainly looked more like a military man than a physician. I have always carried in my mind a mental image

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of him in a peaked military cap such as had been worn by the officers in the Civil War, and in this connection, it may be worth quoting two paragraphs from a long letter which I recently received from Dr. Brill's son, John A. Brill, a chemist of Newark, Delaware. He says: "You might be interested in the story my father told me of how he happened to go into medicine. As a young boy, he had been interested in the army and in a military career and he had succeeded in obtaining an appointment to West Point. Shortly before he was to go to the Military Academy, his father told him that Army life was a poor peacetime occupation and that he had therefore changed his mind about permitting my father to go to West Point, but that he would back him in any other career of his choosing. My father chose medicine."

"My father always had a strong inclination toward the military and therefore it was a source of considerable gratification to him when shortly before our entry into the First World War, he was commissioned in the Reserve and given the job of organizing and heading up what was to become Base Hospital Unit No. 3. It was also probably the greatest disappointment of his life that the early stages of his illness, which ultimately proved fatal,* prevented his going overseas with the Unit." †

Dr. Brill was born in New York in 1860. His college days were spent at C. C. N. Y. and he studied medicine at Bellevue. Probably he learned his internal medicine directly from that great clinician, E. G. Janeway.

Medical rounds with Brill were serious and sober matters. No one whispered jokes. There was none of the dramatic showmanship which brought crowds of visitors to Libman's rounds. With Brill no one spoke except in strict order of seniority when called on by the chief. I remember one occasion when one of the newest internes volunteered that he could hear a faint cardiac murmur which no one else had noted or could hear at the time. The house physician led him out of the ward and quietly explained to him 'that this just was not done'.

Toward all his assistants Brill's attitude was kindly and paternal. When I was appointed an adjunct visiting physician he always addressed me as "Boy", although I was 35 years old at the time. He would meet me in the attendings' coat room or the main entrance and say, "Well, Boy, what is new on our ward today?". In spite of his kindliness I never got to know him very well. I would have regarded any attempt at intimacy on my part as presumptious.

Toward patients he was most considerate; to even the poorest ward patient his manner was almost courtly. He never exposed a patient unnecessarily during examination, and objected if anyone else did so. I remember one incident well. Brill was examining a new patient, a woman who had a freely movable abdominal mass. After palpating the mass and determining the extent of its mobility, he stood at the bedside with one hand on the mass and proceeded to deliver a splendid academic lecture on the diagnosis of abdominal tumors. In so doing he made involuntary gestures and thus moved his hand on the patient's abdomen. After

* Dr. Brill died in December, 1925 of carcinoma of the larynx.

† Dr. George Baehr became Commandant of Base Hospital No. 3.

about five minutes of this he suddenly noticed what he was doing, blushed deeply, stopped his discourse and apologised profoundly to the woman.

Dr. Brill was a man of great learning, but he never made a show of his learning. He always spoke as though he thought that everyone else present knew the literature as well as he did. I quote another paragraph from the recent letter from his son, John L. Brill: "My father was an avid reader with a great liking for the classics which he could quote at length. He was a student of both Latin and Greek and retained his familiarity with those classical languages until his death. He had a prodigious memory".

One or two additional paragraphs from the same letter may throw a little further light on his life and character: "In his early professional days he made his rounds with a horse and buggy. He was among the first private individuals in New York to own an automobile. In 1904 he purchases a Knox, which had its crank on the side, its door in the rear and folding steps which let down when the door was opened. In spite of making his daily rounds by automobile for the next twenty years, he never learned to drive. My father was an ardent and expert fly fisherman. He did a good bit of trout fishing in the Adirondacks, but his greatest passion was for salmon fishing. Fortunately, he had friends who owned a camp and fishing rights on the Restigouche River in New Brunswick and they invited him up there yearly to fish for Atlantic salmon. His accounts of the salmon he caught, the length of time it took to play them to gaff, their weight and so forth, are among my earliest recollections. He played a little tennis, rather poorly, but he enjoyed it thoroughly. When he reached fifty years of age he took up golf and pursued it ardently. I can remember his practicing putting in the living room and clipping the heads off dandelions on the front lawn with his driver."

In 1909, Howard Taylor Ricketts, then assistant Professor of Pathology at the University of Chicago, delivered the Wesley M. Carpenter lecture of the New York Academy of Medicine on the subject of "Rocky Mountain Spotted Fever". Dr. Brill was a fellow at the Academy of Medicine and must have heard the lecture, or he may have met Ricketts, who visited The Mount Sinai Hospital. At any rate, in his 1910 article Brill did not mention the striking resemblance of the disease which he described to the less fatal form of Rocky Mountain Spotted Fever as it occurred in Idaho. In the First World War which followed a few years after that, it became evident that fevers resembling greatly the traditional scourge, epidemic typhus fever, and known by a great variety of different names now obsolete, such as "war fever", "camp fever", "jail fever", etc., were occurring in various parts of the world—"Tsusumaguchi or Valley fever" in Japan, "Brush Typhus" in Malaya. "Q Fever" in Australia (Queensland), Rocky Mountain Spotted Fever in the United States, "Tarbadillo" in Mexico, "Trench Fever" in France, "Brill's Disease" in New York, Texas and other southern states. A vast amount of experimental work was done and it was established that each of these diseases was kept alive in its special locality by the infection of some ground-living small animal (rat, squirrel, rabbit, small marsupials in Australia) and each was transmitted from animal to animal and then to man by a different insect vector: the louse in Europe, the tick in the Rocky Mountains, the mite in

Japan, etc. Easy identification by animal inoculation and the identification of each disease by the high degree and specificity of the immunity in animals which recovered, were established.

Thus, when the Second World War broke out, the United States Army was ready with new insecticides such as DDT and new mechanisms for their rapid and widespread application. The rapid extinction of a serious epidemic of typhus in the crowded city of Naples was one of the wonders of modern science.

Meanwhile, the causative agent was recognized—Rickettsia. It was not a bacterium, although it looked and stained like one; but its biology was peculiar in that it could not be grown on artificial nutrient media but only in the interior of living cells of warm blooded animals. This was traced to its lack of an essential oxidative enzyme—cytochrome oxidase—needed by all cells and supplied in the case of Rickettsia by the host cell.

After the end of World War II, a great symposium on "The Rickettsial Diseases of Man" was held in Boston in December of 1946 and all the papers read there were published in one volume by the American Association for the Advancement of Science. What had become of Brill's Disease in the meantime? There is no special article on it. It is only mentioned along with Rocky Mountain spotted fever as one of the forms of typhus endemic in America. I can find nowhere a description of its mode of transmission, its immunology, or its cross relationship to other diseases. But Brill's writing remains as a monument, one of the best primary clinical descriptions of a disease in the entire literature of medicine.

Does Brill's Disease still occur? I suppose so, though I have not seen or heard of a case in the last 15 or 20 years.

It must not be thought that Brill's only contribution to medical knowledge was the disease named for him. There is one other condition which might fairly have borne his name—namely, Gaucher's disease. Apparently it was Brill who first used the name, "Gaucher's Disease", or "Primary Splenomegaly of the Gaucher Type". Indeed, it is interesting to see how little Gaucher himself contributed. His work was a graduation thesis of the University of Paris in 1882 and was based entirely on a single post mortem specimen. He even misinterpreted that, calling it "Epithelioma of the Spleen".

The 1913 article of Brill and Fred S. Mandelbaum was a masterly piece of work. Mandelbaum was responsible for the pathology, Brill for the clinical description. The previous articles in the literature had been based on a single case (even Bovaird's article of 1900). How many cases Brill and Mandelbaum had is not certain, but one can judge from the details which they give concerning the variations in symptomatology that they must have had ten to fifteen cases at least and it is evident that Brill followed up the cases in detail for many years—some of them as long as 30 years. In fact, Brill's is the first adequate description of the clinical disease. Had not Brill himself used the term, "Gaucher's Disease", it could just as well have become known as "Brill's Disease No. II", or "Brill's Splenomegaly".

Brill and Mandelbaum recognized the condition as a *storage disease*: that is, as a disturbance in which the body is compelled to store up large amounts of some

abnormal substance, or abnormally large amounts of some normal substance. As to the nature of the hyaline substance which fills the characteristic large cells they could offer only speculation. Mandelbaum tried a variety of stains and was unable to extract the substance with any of the lipoid solvents. The conclusion was drawn that if not a lipoid the substance must be, at least, a lipo-protein; that is, a lipoid so inextricably combined with a protein that it defied extraction. As to the origin of the large cells, in their first article they accepted them (as had previour workers) as endothelial cells; in their 1913 study they reversed this and offered conclusive evidence that the cells had originated from the reticulum; i.e., the "reticular phagocytes of the hematopoietic organs". Brill had his last comment about Gaucher's Disease in 1932 in Tice's Practice of Medicine. This is in essence a repetition of the Brill and Mandelbaum article of 1913. No explanation was offered for the iron-containing pigment found in the skin, spleen, liver and affected lymph nodes.

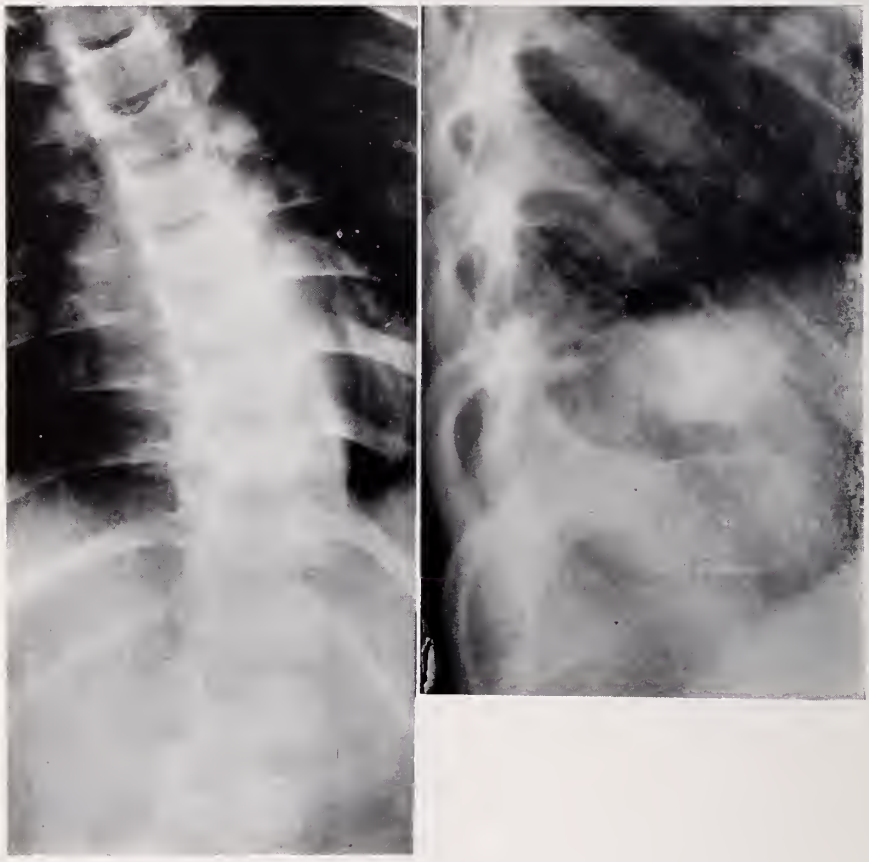
The second contribution of Brill was the use of splenectomy in the curative treatment of thrombocytopenic purpura hemorrhagica. This was in 1923 in an article with Dr. N. Rosenthal. The idea (for which the authors did not claim originality) was based on researches by Eppinger, E. Frank and Kaznelson. The last named had published the first successful use of splenectomy for the cure of thrombocytopenic purpura in 1916. Armed even with this justification it must have taken great courage to propose so formidable a procedure as splenectomy in a patient already bled white, in whom the slightest incision invariably bled profusely and persistently. Brill, however, did not lack courage; remember, he had originally intended to become a soldier. Brill and Rosenthal reported splenectomy on two patients, a boy and a girl. The results were brilliant and the cures lasted for at least eight months as reported in a final footnote added to the paper eight months later just as it was going to press. The operation has now become a standard procedure in severe cases of thrombocytopenic purpura.

Radiological Notes

Edited by Bernard S. Wolfe, M.D.

CASE OF OSTEOID OSTEOMA OF THE TENTH THORACIC VERTEBRA EXTENDING INTO SPINAL CANAL

M. L., a boy 6 years old with upper back pain and scoliosis.



A B

FIG. 1A. Antero-posterior projection of dorsolumbar spine showing marked scoliosis convexity toward left with minimal rotatory component. Body of D10 appears sclerotic and the pedicle of D10 on the right is indistinct.

FIG. 1B. In lateral projection, sclerotic changes appear mottled and the posterior aspect of the body is excavated in a symmetrical concave fashion. Question of central sclerotic nidus in center of body.

From the Department of Radiology, The Mount Siani Hospital, New York, N. Y.

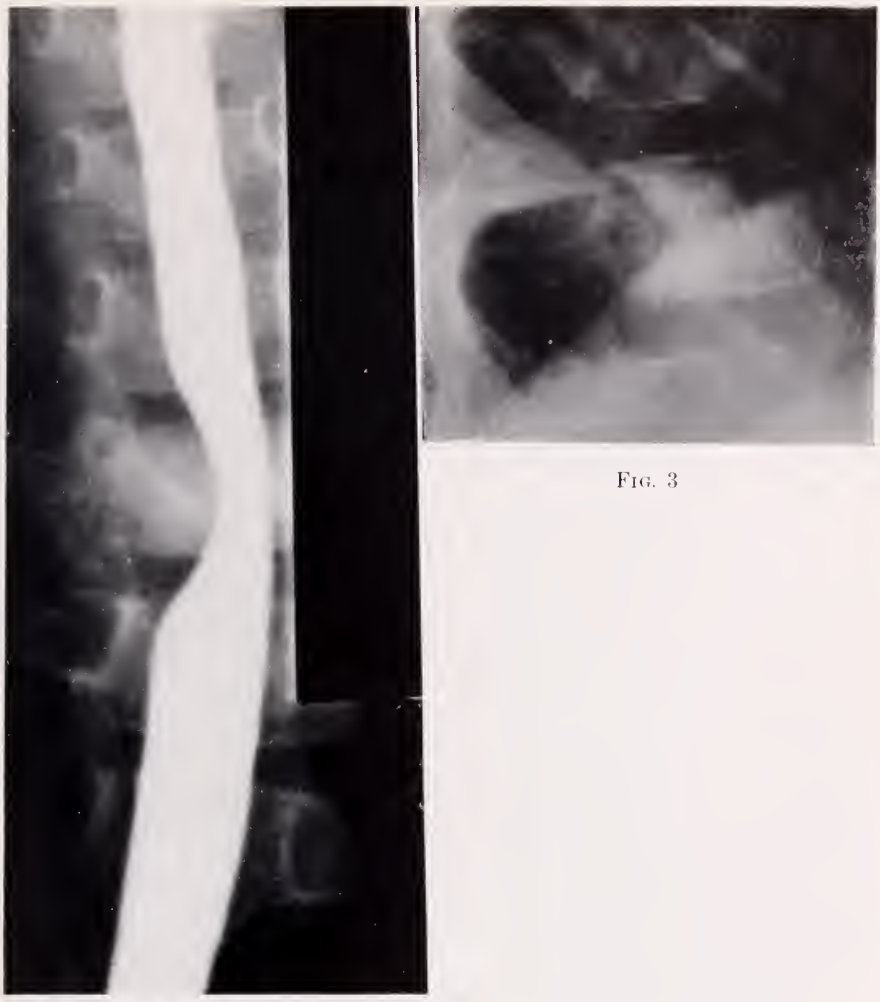


FIG. 3

FIG. 2

FIG. 2. Myelogram demonstrates extradural defect on right at the level of D10; no block. Indistinct sclerotic right pedicle is well seen. At operation, (Dr. Leo Davidoff), tissue was found deep to the posterior longitudinal ligament extending into the spinal canal and involving the body and the right pedicle. Pathological report was osteoid osteoma (Dr. Sadao Otani).

FIG. 3. Lateral view of D10 after operation. Excavation posteriorly is more prominent. Ovoid lucent area is present in the body at the site of previous sclerotic nodus.

CASE OF ILEOJEJUNITIS WITH JEJUNAL CARCINOMA

G. M., a female of 36 was admitted (Dr. David Adlersberg) with the chief complaints of vomiting, abdominal pain and loss of weight for four weeks. For six years, patient had had recurrent attacks of diarrhea diagnosed as colitis and ileitis.

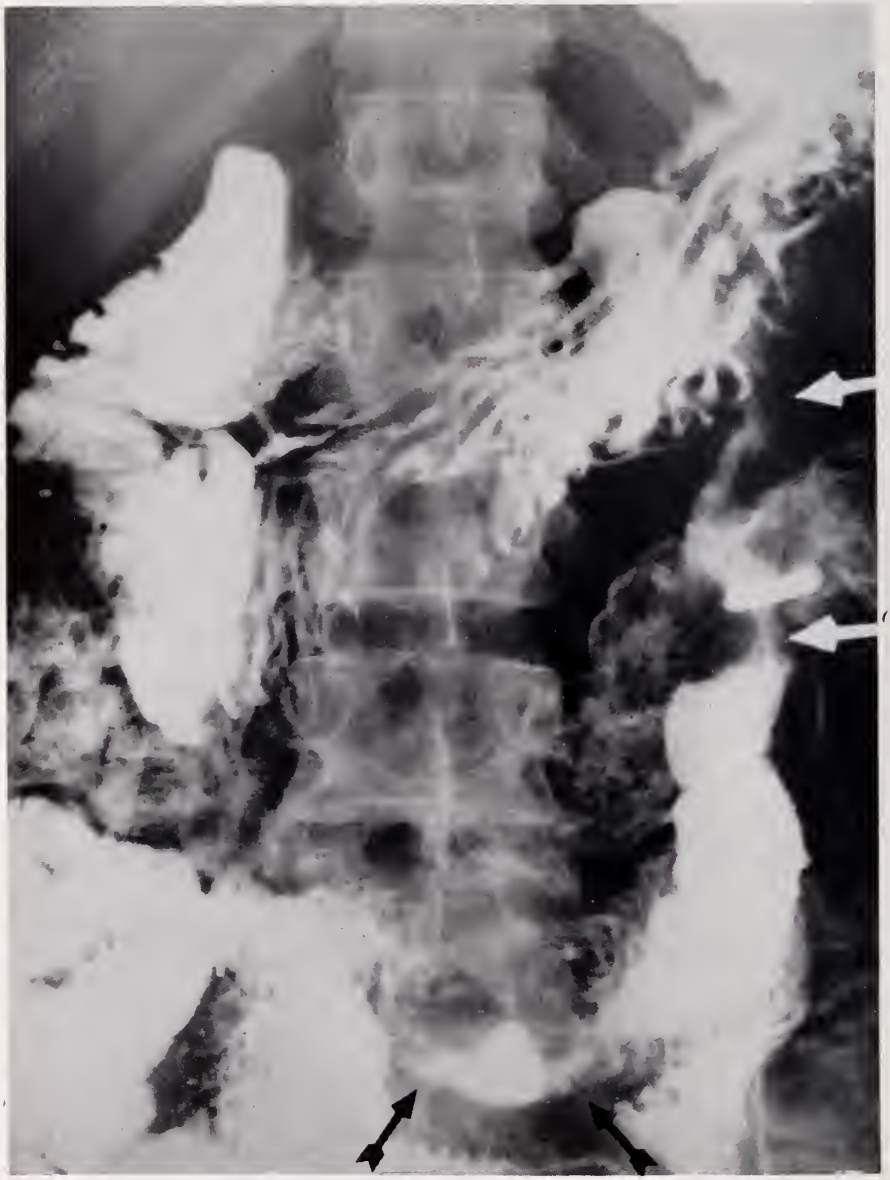


FIG. 1A. Gastro-intestinal series showed marked gastric and duodenal dilatation with an irregular markedly stenotic segment just beyond the ligament of Treitz (upper arrows on left side of patient). In addition, the jejunum showed three skip areas of narrowing with intervening dilatation. The appearance was interpreted as granulomatous jejunitis.

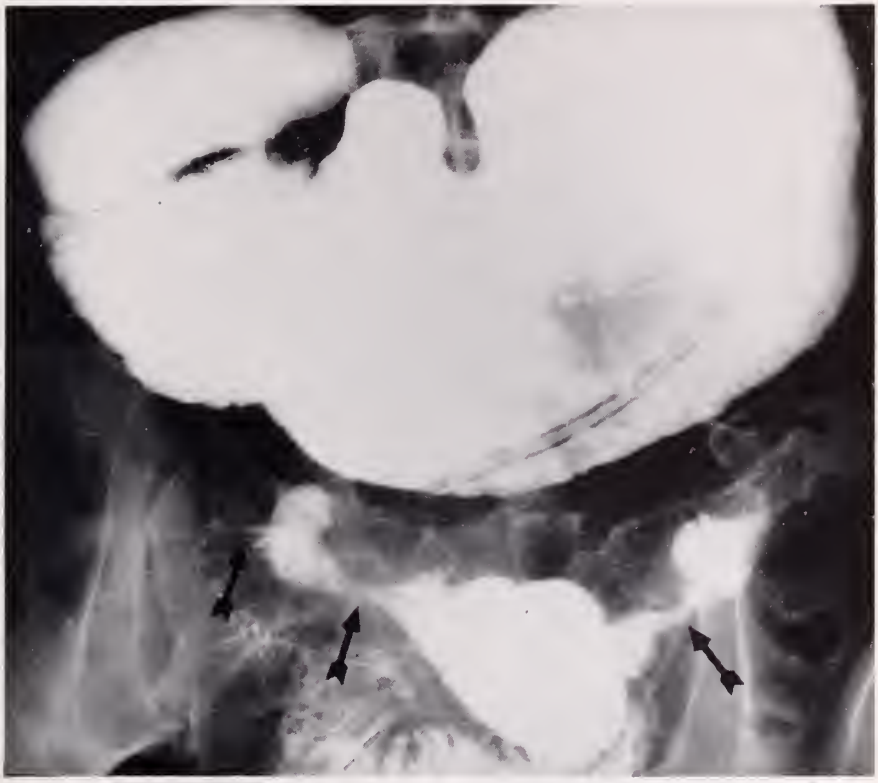


FIG. 1B. Findings similar to Fig. 1A. confirming multiple skip areas.

FIG. 1C. Terminal ileum was narrowed with spiculated contours and irregular distensible segments. Region of ileocecal valve was flattened and valve appeared to gape. Appearance is typical of terminal ileitis.

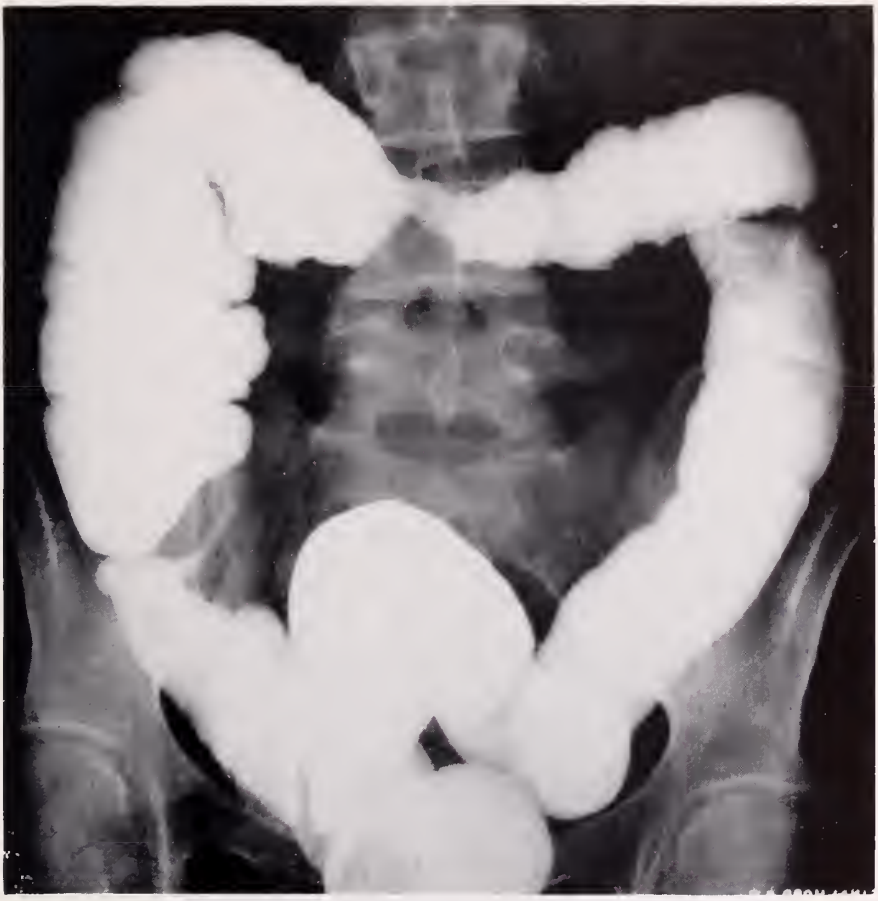
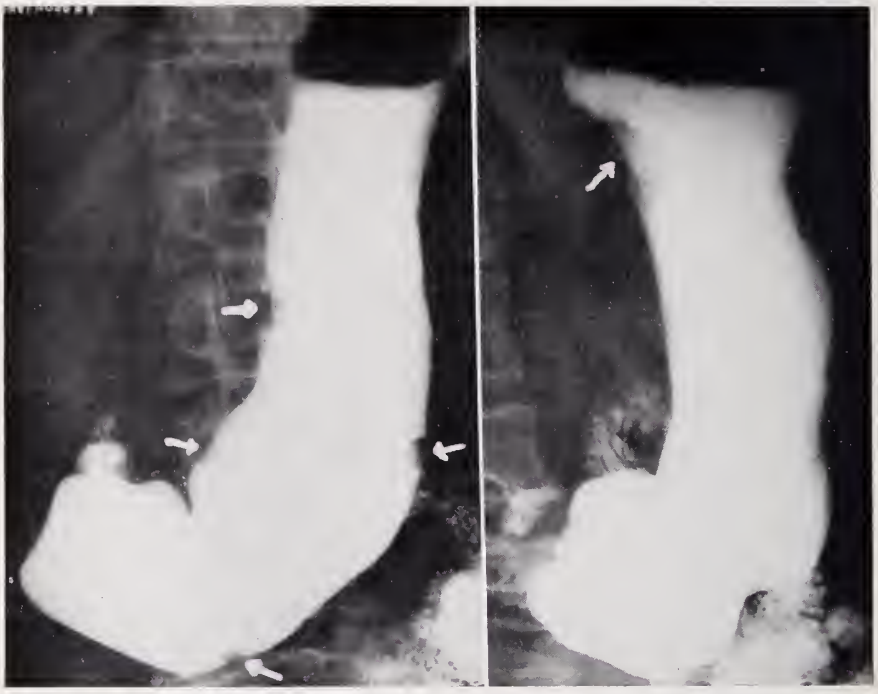


FIG. 2. Barium enema showed narrowed segment in mid-transverse colon with irregular limited distensibility and coarse mucosal pattern of the distal transverse colon and splenic flexure. Changes in the terminal ileum also were well seen. The lesion in the colon was interpreted as a segmental colitis, probably also granulomatous. At necropsy, granulomatous ileojejunitis was confirmed but the most proximal narrowed segment in the jejunum showed a large adenocarcinoma as well as evidence of jejunitis. Multiple metastases were present in the liver and lungs.

CASE OF MULTIPLE MYELOMA WITH INNUMERABLE MYELOMATOUS TUMORS IN THE VISCERA INCLUDING THE GASTROINTESTINAL TRACT

A. K., a male of 56 with known Multiple Myeloma was admitted for gastrointestinal bleeding (Drs. S. H. Averbuck and R. L. Rosenthal).



A B

FIG. 1A. Postero-anterior projection of filled stomach shows multiple sharply demarcated nodular filling defects with flattened or unbilicated tops.

FIG. 1B. Right anterior oblique projection reveals large lesion near cardia with flat crescentic excavation of its surface.

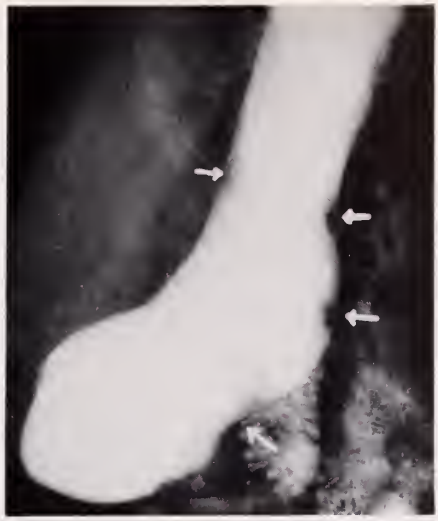


FIG. 1C. Left anterior oblique projection with similar findings. Along distal part of the greater curvature (lowest arrow) there was a large defect obscured by barium but indicated in profile by flattening of the contour and adjacent decreased density.

FIG. 2. Loops of small bowel showing innumerable discrete nodular or sessile filling defects. The larger lesions are flat-topped.

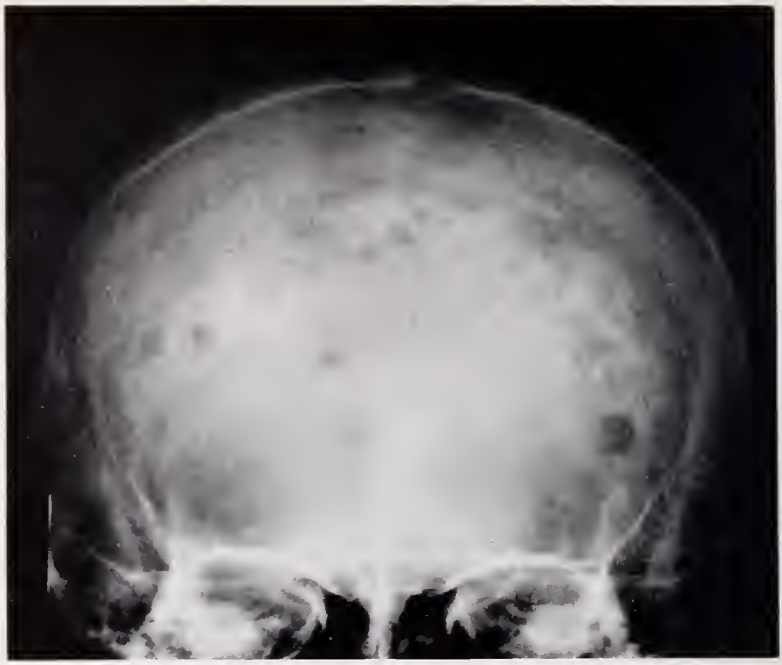


FIG. 3. Myelomatous defects in calvarium have typical appearance. At necropsy, there was diffuse bone involvement and the umbilicated or flat-topped character of the larger lesions in the stomach and small bowel was confirmed. Similar lesions were present through out the colon.

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