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SMALL BOWEL TUMORS

A Clinical Study of 109 Cases

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Tumors of the small intestine are uncommon, but the available literature on the subject is voluminous. It is difficult, however, for the interested clinician to formulate an accurate impression of the over-all frequency of these tumors, the relative frequency of the various types, and the spectrum of clinical features which these neoplasms present. The confusion arises for several reasons: many of the reports describe one case or a small series of cases; some authors have collected and reported tumors of only one microscopic type; others have concerned themselves with tumors of one section of the small intestine; still others have reviewed either benign or malignant tumors only. Carcinoids, lymphomas and Hodgkin's disease have usually been considered separately. Thus, although new relevant articles augment the American literature at the rate of about 25 per year (1), the clinician's perspective of these lesions as a unified problem may well be distorted or fragmentary. To compound the confusion, the criteria for the diagnosis have been highly variable in the innumerable case reports, and the precision of histological diagnosis has sometimes been less than optimal. Indeed, some reviews and case reports have not mentioned or clearly delineated diagnostic criteria at all.

PURPOSE AND METHOD

Stimulated by experience with five recent cases, the authors believe that there is need for a comprehensive clinico-pathological survey and analysis of all types of small bowel tumors as they occur at a large general hospital. The surgical pathology and autopsy records of The Mount Sinai Hospital for the last 25 years contain 109 cases of small intestinal neoplasms on which there are satisfactory clinical and pathological data. We excluded cases for which sufficient information was not available. The clinical chart of each patient was studied and either the operative note or post mortem protocol reviewed. All but a few unavailable histologic slides were collected and reviewed by the authors.

We have included all primary benign and malignant tumors of the small intestine. Cases of lymphoma and Hodgkin's disease have been included where the small bowel involvement was the only manifestation or predominant clinical feature of the disease. A few metastatic sarcomas have been included where the primary site was not apparent clinically. Metastatic tumors and lymphomas were excluded if the small intestinal lesion was a part of obvious metastatic or gen-

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eralized disease. We have also included, as will be discussed subsequently, cases of small intestinal carcinoma in which it was impossible to determine whether the tumors were primary or secondary.

It is not our purpose to review the literature. In the discussion of each section, however, some principal comparisons of our experience with that of others will be made. Clinical features of the entire series and of each group will be emphasized with particular attention to the difficulties of diagnosis. The diagnosis of small bowel tumors by x-ray is an extremely important aspect of this problem but is beyond the scope of this paper (2–8). We will discuss only how the x-ray was used and when it was successful.

MATERIAL

The types of tumors, their relative incidence and how the cases were found are indicated in Table I. Seventy cases were found at operation and 39 cases were found at post mortem examination. Since methods of case selection vary, incidence figures in the literature are not directly comparable to ours. Autopsy series of malignant lesions of the small intestine have been reported many times since 1876. Early autopsy figures reveal that small intestinal malignancies comprised one-tenth of one per cent or less of all gastrointestinal malignancies. Some ratios, however, have been as high as six per cent (9–13). Fifty-eight of our cases were males and 51 were females. Fifty-six cases had malignant tumors and 53 benign. Elias et al (14) found 32 malignant tumors and 57 benign in the surgical pathology and autopsy files of the Boston City Hospital over a 20-year period. Weibel et al (15) collected 100 malignant and 65 benign tumors from four hospitals over 16 years. Of the 39 cases found at autopsy in our series, eight were malignant and 31 benign. Elias et al (14) found 16 malignant and 46 benign. Buckstein's autopsy series (8) contained 30 malignant tumors and 35 benign out of 22,810 autopsies.

Many reviews separate autopsy and surgical cases completely for fear of losing clinical perspective by mixing together symptomatic and incidental cases. In our series, cases were found incidentally both at operation and at post mortem examination (Table I). There will be, therefore, no separate treatment of the surgical and post mortem material. Over-all, the tumors were clinically symptomatic, i.e. important or predominant in the clinical problem, in 74 cases and were found incidentally in 35 cases. Thirty-one of the 35 were benign tumors. As indicated in Table I, 52 of the 56 malignant tumors but only 22 of the 53 benign tumors were clinically symptomatic.

CARCINOMA

Fifteen cases of carcinoma of the small intestine were found during the reporting period. Elias et al (14), whose method of case selection was similar to ours, found 20 carcinomas out of 89 tumors of all types except carcinoid. Most authors (6, 14, 16, 17, 18) have found carcinoma to be more common than sarcoma, grouping lymphomas with the sarcomas. Less than a third, however, of our group of malignant tumors were carcinomas. One reason for the low propor-

tion of carcinomas may be the proper reluctance of the Pathology Department of The Mount Sinai Hospital to accept the diagnosis of primary carcinoma of the small intestine unless all possibility of another primary origin has been ruled out. Regarding duodenal lesions, clear evidence is required that the primary site is definitely not the pancreas, the stomach, or the ampulla of Vater. This may be impossible to determine. Kleinerman et al (19) "accepted" 453 cases of primary duodenal carcinoma out of 743 reported cases in 1950, and Brenner and Brown (20) added 21 others including 15 of their own in 1955. Experience of the Pathology Department has shown that carcinomas of the jejunum and ileum cannot be definitely designated as primary, regardless of their anatomic characteristics, unless the possibility of any other primary site is precluded by a surgical follow-up of at least five years or an autopsy study. Even a meticulous autopsy study may not remove the possibility of metastasis to the small bowel if hematogenous dissemination of an anaplastic carcinoma is found.

Thirteen of our 15 cases of carcinoma were operated on and two of these were later examined at post mortem. Two other cases were found at post mortem examination. In one of the latter two, the carcinoma was an incidental finding in a patient who died of congestive heart failure and pneumonia. Using the rigorous criteria outlined above, only one of the 15 can be considered a 'proven primary' neoplasm. This was a surgical case of a 55-year-old man with an annular scirrhous adenocarcinoma who was known to be alive and well five years and two months after operation.

In 13 other cases, the pathologic diagnosis of primary small bowel carcinoma was considered probable. Because the orientation of this study is clinical, data on these 13 cases have been included. Precision, however, requires brief ex-

TABLE I

Distribution of 109 Cases of Small Bowel Tumor

Distribution	Found at operation		Found at post mortem		Total	
	Symptomatic	Incidental	Symptomatic	Incidental	Symptomatic	Incidental
Malignant:						
Carcinoma	13		1	1	14	1
Lymphosarcoma and Hodgkin's Disease	16		3		19	
Sarcoma	15	1		1	15	2
Carcinoid	3		1	1	4	1
Total	47	1	5	3	52	4
Benign:						
Carcinoid	1	1	1	10	2	11
Other	17	3	3	17	20	20
Total	18	4	4	27	22	31
Total Benign and Malignant Tumors:	65	5	9	30	74	35

planation of why these 13 did not deserve classification as 'proven primary' carcinomas.

The slides of two post mortem cases which were reported as primary carcinoma 18 and 25 years ago could not be located. Since we were unable to study the sections of these two cases and since only one other case could be considered a 'proven primary', we must classify these as 'probable primary' tumors. Another case whose surgical specimen revealed immature anaplastic carcinoma of the jejunum showed at autopsy widespread hematogenous metastases. Thus doubt exists as to whether the jejunal lesion was actually primary. The fourth case examined at post mortem was a case of carcinoma of the duodenum. Review of the sections reveals microscopic involvement of the ampulla of Vater. Although this appears to be direct extension of a duodenal carcinoma, we believe the possibility of a primary ampullary carcinoma—a far more common lesion—has not been excluded.

Eight surgical cases had inadequate follow-ups. One of these was a pedunculated lesion believed to be a benign duodenal polyp at operation. A ninth surgical case had microscopic ampullary involvement which duplicates the condition in the autopsy case mentioned above. In one duodenal lesion, though there was marked mucosal involvement with a deep ulceration, it was impossible to tell whether the primary site was the duodenum itself or the pancreas. This case is designated 'possible primary.'

1. Location

Of the 15 carcinomas, nine arose in the jejunum and six in the duodenum. We did not find any carcinomas of the ileum. In fact, seven of the nine jejunal lesions were located within one foot of the ligament of Treitz. The generally accepted distribution figure for location is that of Hoffman and Pack (21) based on 228 collected autopsy cases. Approximately 45 per cent were found in the duodenum and 55 per cent in the jejunum and ileum. Bockus (16) and other reviewers have accepted these authors' finding that the second most common site was the lower ileum. Our failure to find any ileal lesions corresponds to the finding of Elias et al (14) of only two out of 20. Carcinoma of the duodenum has often been considered separately because of its special therapeutic implications. Silvis (22) compiled a lengthy bibliography which emphasizes surgical considerations.

2. Clinical Features

The group of 15 cases was composed of 11 males and four females. The age range was 40 to 72 with a mean of 56 years. The duration of symptoms was extremely variable, from one month to three years. Of the 14 symptomatic cases, six presented abdominal pain. In one of these, the pain was epigastric and relieved by food and alkali. This was an ulcerated jejunal carcinoma near the ligament of Treitz. The pain was not characteristically described in the other five. Three of the five had epigastric pain, one had left lower quadrant pain, and one had generalized abdominal pain. Two other patients, both with carcinomas

of the second portion of the duodenum, presented painless jaundice. Three patients presented a hypochromic anemia. The three other symptomatic cases—all carcinomas of the duodenum—presented as a chief complaint: epigastric distress, in two, and vomiting without pain, in one.

Bockus (16) and others follow Mateer and Hartman (23) in describing three recognizable clinical syndromes of carcinoma of the duodenum according to location—supra-ampullary, peri-ampullary, and infra-ampullary. This classification is still employed by some (20, 22, 24). All six of our carcinomas of the duodenum arose in the second portion. The above classification did not seem to be pathologically convenient or even possible in these cases nor did it seem to have clinical significance. A few of the lesions seemed to arise from almost the same location, yet the clinical picture varied considerably. Dixon et al (25) correlated symptomatology with morphologic characteristics and also found this classification unsatisfactory. None of the seven cases had the ulcer-type pain, back pain or fluctuating jaundice described by Bockus (16).

Other noteworthy clinical features included intussusception and mechanical obstruction in two cases. A mass was palpable in only three of the 14. One case, a duodenal carcinoma, had hematemesis and another had a moderate fever. Melena was definitely observed in nine cases and was probably present in three others although a stool guaiac report could not be found. None of the cases perforated.

Pridgen et al (26) found a palpable mass in 41 per cent of jejunal lesions and 48 per cent of ileal lesions. One of our six duodenal cases had a palpable mass as did two of the nine jejunal carcinomas. Our finding of only two clear cases of obstruction out of 14 is also less than the literature usually records. The common clinical features of this group of carcinomas are occult bleeding and nondescript abdominal pain.

3. Clinical and X-ray Diagnosis

Bleeding and pain are scarcely sufficient to suggest a diagnosis of small intestinal carcinoma, nor are many of the other clinical findings noted above more helpful. The difficulty in making this diagnosis preoperatively or ante mortem

TABLE II

Pre-operative or Ante Mortem Diagnosis in 14 Symptomatic Small Intestine Carcinomas

Correct	5
Carcinoma of pancreas	1
Carcinoma of ampulla	1
Infectious hepatitis	1
Carcinoma of stomach	1
Regional enteritis	1
Benign duodenal polyp	1
Cholecystitis	1
Not specified	2

TABLE III

Results of X-ray Examinations in 13 Cases of Carcinoma

	Jejunum (9)	Duodenum (4)
G.I. series	5	4
Small bowel series	4	
Abnormality noted	2	3
Diagnosis made	2	1

is indicated in Table II. The usefulness of x-ray examinations in this group is also tabulated (Table III). For a radiologic diagnosis to qualify as correct, we have arbitrarily accepted any x-ray report of "small bowel tumor," and have not demanded that the type of tumor be specified. We wish to stress that many of the x-ray examinations of the patients in the entire study were not carried out by the X-ray Department of The Mount Sinai Hospital. X-ray results and preoperative diagnoses are included to impress upon the reader the diagnostic difficulties of small bowel tumors. Far from disparaging the role of x-ray examination, it is our hope that the clinician may become more alert to the possibility of these diagnoses and pursue them with more frequent and careful x-ray studies.

In this group, no x-ray examination at all was done on one patient who had a duodenal carcinoma with painless jaundice. Death, however, was attributed to acute yellow atrophy due to infectious hepatitis. The other four duodenal lesions all disclosed some abnormality on upper gastrointestinal series. Five of the nine jejunal carcinomas had no x-ray examination of the small intestine. Weber and Kirklin (4) reported a correct diagnosis in 94 per cent of duodenal neoplasms, 85 per cent of jejunal, and 65 per cent of ileal neoplasms. Golden and Morales (5) found an abnormality in 17 out of 19 cases of small bowel carcinoma which were studied by small intestine series. By comparison, they found an abnormality in 13 out of 13 lymphomas, seven out of eight carcinoids, five out of six other malignancies, and 11 out of 15 benign tumors. Keats and Sakai (6), however, reported a lower over-all accuracy rate of 59 per cent.

4. Results of Treatment

Follow-up of this group of patients was poor. Of the 13 surgical patients, three died at or shortly after operation. Three died of cancer within a year. Eight of the 13 had metastases at the time of operation. A patient with a scirrhous annular lesion of the jejunum was known to be alive and well five years after operation. The fate of the other six is not known.

LYMPHOSARCOMA AND HODGKIN'S DISEASE

Nineteen cases of lymphosarcoma and Hodgkin's disease were found in which the small intestinal involvement was the predominant or only manifestation of the disease. These cases represent one-third of the malignant tumors in the series. According to Allen et al (27), lymphomas make up 39.7 per cent of small intestinal

malignancies. The literature on this subject is confusing because the histological classification of tumors of lymphoid and reticulum tissue has been subject to change. There has been a trend away from the elaborate classification of Robb-Smith (28). Even the simplified systems of Gall and Mallory (29) and Jackson and Parker (30) are more clinically relevant in an abbreviated form. The system employed by the Pathology Department of The Mount Sinai Hospital, similar to that used by other current authors (31, 32, 33), is a simplified division of lymphomas into lymphosarcoma, reticulum cell sarcoma (or large cell lymphosarcoma), and giant follicular lymphoblastoma.

The proper pathological classification of Hodgkin's disease has not been settled. The fact that we have considered lymphosarcoma and Hodgkin's disease together does not imply an etiological relationship between these two diseases. Their similarities, however, justify grouping them together for the purposes of a clinical study.

All four cases of Hodgkin's disease had unequivocal Reed-Sternberg cells on microscopic section. Cases in which the surgical pathology slides merely revealed changes "suggestive" of lymphosarcoma or of Hodgkin's disease were not included. A few of our cases appeared in a previous discussion of lymphosarcoma of the small and large intestine by Winkelstein and Levy (34).

Burman and van Wyk (32) collected, over an undisclosed period, 25 cases of lymphosarcoma of the small intestine and cecum, which included seven reticulum cell sarcomas, 18 lymphosarcomas of various sub-types, and no cases of Hodgkin's disease. Marcuse and Stout (33) reviewed 179 cases of small intestinal lymphosarcoma from the literature and 13 cases treated at Presbyterian Hospital over 15 years. They make no mention of Hodgkin's disease. Faulkner and Dockerty (31) reported 33 surgical cases from the Mayo Clinic. Their series included 11 lymphosarcomas ("small cell"), 16 reticulum cell sarcomas ("large cell"), three Hodgkin's disease, one giant follicular lymphoblastoma, and two "mixed" lymphomas. Usher and Dixon (35) studied 50 cases of lymphosarcoma of the small and large intestine and classified 25 as malignant lymphocytoma and 25 as reticulum cell sarcoma. Bockus (16) groups lymphosarcoma with other sarcomas according to Ewing's classification (36) of gastrointestinal sarcomas.

The general study of Hodgkin's disease by Hoster and Dratman (37) mentions only two reports of Hodgkin's disease limited to the small intestine (38, 39). Lumb's monograph (40) on lymphomas, based on a study of 410 cases of lymphoid tissue tumors, included 175 cases of Hodgkin's disease and 21 cases of reticulum cell sarcoma with no small intestinal involvement. On the other hand, seven of 75 cases of lymphosarcoma had small intestinal lesions.

In contrast to the distribution of small intestinal lymphomas in the above articles, four of our 19 cases were diagnosed as Hodgkin's disease. Warren and Littlefield (41) found ten out of 49 gastrointestinal lymphomas limited to the small bowel and two of the ten were Hodgkin's disease. The most inclusive study of this rare site of Hodgkin's disease was by Portmann et al (42). They reviewed the literature on gastrointestinal Hodgkin's disease from 1919–1953 and found approximately 200 cases in which the gastrointestinal tract was the principal or

TABLE IV

Types and Location of Small Intestine Lymphosarcoma and Hodgkin's Disease

Location	Hodgkin's disease	Lymphosarcoma	Total
Duodenum			
Duodenum and jejunum		1	1
Jejunum		8	8
Jejunum and ileum	3	2	5
Ileum		2	2
Entire small bowel	1	1	2
Not specified		1	1
Total	4	15	19

only site of involvement. Forty-five of their collected case reports were of Hodgkin's disease of the small bowel and they added one case of their own. Cases with coexistent gastric or colonic lesions were excluded.

1. Location

Location of the lesions is noted in Table IV. Bockus (16) states that the most common site of lymphosarcoma of the small bowel is the terminal ileum. This statement is supported by others (31, 32, 33, 35). Eighteen of the 33 cases of Faulkner and Dockerty (31) were limited to the ileum and five others involved both jejunum and ileum. Only two of our cases were confined to the ileum and six others had multiple lesions including the ileum. Portmann's figures (42) for 46 cases of small intestinal Hodgkin's disease were duodenum, 12.5 per cent; jejunum or proximal ileum, 55 per cent; terminal ileum, 20 per cent; and entire small bowel, 12.5 per cent.

2. Age and Sex

The age range of the 19 cases of lymphoma was 20 to 68 with a mean of 48 years. Nine cases were males and ten were females. The average age of the four cases of Hodgkin's disease was 53 years. One was a male and three were females. Marcuse and Stout (33) noted sex distribution in 134 out of 192 cases of primary lymphosarcomas collected from the world literature, 1932–1948. They found 104 cases in men and only 30 in women. This preponderance pervades the literature with a male-female ratio of 2 to 3.5:1. This ratio also seems to hold for gastrointestinal involvement of Hodgkin's disease (42, 43, 44), although involvement of the small intestine alone is too rare to warrant any statement.

3. Clinical Features

Sixteen of the 19 cases were found at operation. Three of these were later examined at post mortem. Three others were examined only at post mortem. All of the 19 cases were symptomatic.

The presenting symptom in 13 of the 19 cases was abdominal pain. This was frequently crampy in nature and associated with nausea and vomiting. Eleven

patients had a significant degree of mechanical intestinal obstruction. Interestingly enough, two of these 13 patients described epigastric pain relieved by food and alkali. One was a 52-year-old woman who had extensive infiltration of the jejunum by lymphosarcoma which had affected the cervical nodes two years earlier. The other was a 48-year-old man with a seven month's history of "ulcer-type" pain and lesions involving 40 cm. of jejunum and 3 cm. of ileum. Both patients had perforation and peritonitis and both came to post mortem examination. This striking feature of perforation will be discussed in detail.

Three of the 19 patients sought medical attention because of symptoms related to anemia. One patient found a palpable mass herself; another had had diarrhea; and the last in the series, a patient with perforation and peritonitis, had had a fever for three months.

In seven of the 19 cases a mass was palpable. Blood in the stool, almost always occult, was found in nine cases. Hematemesis was a feature of one patient who had gastric lesions. Prolonged weakness and weight loss, from four to 18 months, was present in seven cases. One case had ascites, one had clubbing, and one case of lymphosarcoma had eosiniphilia of three to 15 per cent. Intussusception was found in two of the 11 patients who had some degree of obstruction. Eight patients had fever and five of these had perforation or fistulization. Six patients had definite intestinal perforation into the peritoneal cavity or adjacent loops of bowel, and a seventh patient may have perforated.

One patient had a malabsorption syndrome. This was a 40-year-old man admitted in 1938 who had had episodes of abdominal pain and distension suggestive of partial intestinal obstruction for more than 18 months. For five months before his death, he had had steatorrhea and diarrhea. An oral glucose tolerance test was flat. No anemia was found. A small bowel series performed four months before his death revealed characteristic features of the sprue syndrome. A repeat examination one month before death showed more irregularity and some definite areas of ulceration. The first diagnosis was tuberculous enteritis, but lymphoma and regional ileitis were also mentioned. At post mortem examination the stomach, duodenum, and jejunum were diffusely infiltrated with lymphosarcoma and there were numerous foci in the mesenteric nodes, liver, and left kidney. Sleisenger, Almy, and Barr (45) have emphasized that this syndrome is probably not as rare in lymphoma or in unselected series of sprue as is generally believed. Including their own cases, only 17 instances of a malabsorption syndrome caused by lymphoma had been reported as of 1953.

Most authors agree that abdominal pain is the most common presenting symptom of small bowel lymphoma, but it has no special characteristics and is often caused by intestinal obstruction. There is disagreement as to the importance of anemia. Marcuse and Stout (33) and Burman and van Wyk (32) minimize the frequency of significant anemia but it is emphasized by some earlier writers (46, 47). Since symptoms develop late in proportion to the size of the tumors examined, it is not surprising that a palpable mass is common in other series as well as ours. In Burman and van Wyk's series (32) of 25 cases, 19 had a palpable mass Thirteen cases in that series had occult bleeding which compares well with nine

out of 19 in ours. In some series (32, 33, 47) change in bowel habits is stressed — either constipation, diarrhea, or alternating constipation and diarrhea This was not a prominent feature in our cases.

Intussusception has been reported in 18 to 50 per cent of various series. It was found in ten of the 33 surgical cases discussed by Faulkner and Dockerty (31). Gross (48) reports that two of his 702 cases of intussusception in children were due to lymphoma. Our two patients with intussusception were 20 and 41 years of age. The former had an 8 cm. intussusception which began 62 cm. beyond the ligament of Treitz and was led by a 3 cm. mucosal nodule of lymphosarcoma. The latter had a "golf-ball" size lymphosarcoma just proximal to the ileo-cecal valve with an ileo-colic intussusception which reached the mid-transverse colon.

Only two cases had either a suggestive or established history of lymphoma. One was the case of lymphosarcoma with prior cervical involvement, mentioned above, and the other was a 43-year-old woman who had a cervical node biopsy reported as giant follicular lymphoblastoma at The Mount Sinai Hospital two years before admission. She was treated with radiotherapy and was well until three months prior to admission when she developed weakness due to anemia. On post mortem examination, seven small gastric nodules of lymphosarcoma were found in the mucosa and submucosa, plus extensive nodular infiltration of all layers of the wall of the duodenum and jejunum by lymphosarcoma.

4. Perforation

Perforation of the bowel wall has been reported sporadically in cases of lymphosarcoma and has been estimated in one or two per cent of cases according to the older literature. This figure may have to be revised upward on the basis of some recent experience including our own. Skrimshire (49) reported that 20 per cent of a small series of lymphomas had a perforation. Portmann et al (42), in their review of gastrointestinal Hodgkin's disease, noted seven cases with perforation and peritonitis out of 39 case reports. One of the three cases of Hodgkin's disease included in the Mayo Clinic series (31) perforated. Irvine and Johnstone (50) collected 17 cases of lymphosarcoma of the small intestine over an eight-year period. Eight of the 17 had intestinal perforation. Furthermore, the authors described, but did not include, five other cases of perforation in lymphosarcoma. They found perforation related particularly to reticulum cell sarcoma. Two other recent series of lymphosarcoma (33, 32), found no perforations in 13 cases and five perforations in 25 cases. Marcuse and Stout (33) refer to other case reports of perforation and to instances in the foreign literature of perforation from one loop of bowel to another. They had one such case as did Burman and van Wyk (32).

In our series there were six definite cases of perforation or entero-enteral fistulization and another possible case. Two of these seven patients had Hodgkin's disease, including the case with possible perforation. In other words, two of the four patients with Hodgkin's disease of the small intestine had perforation. This is a finding of great rarity.

Four patients had frank peritonitis and a clearly visualized perforation. One of these four had Hodgkin's disease. In this case a "silver-dollar" size ulcer of the ileum had perforated. Post mortem examination revealed this ulcer as well as several other discrete plaques of the jejunum and ileum, many mesenteric nodes, and a 40 cm. strip of jejunum as sites of Hodgkin's disease. The three other patients all had multiple small intestinal lesions of lymphosarcoma. One had an obvious perforation of a necrotic ulcer; another had a very small sinus tract to the serosa. In the latter case the full thickness of the intestinal wall was involved with lymphosarcoma. The third had matted loops of small bowel resected. At least five openings were noted between two adjacent loops. In the center of an ulcerated area, there was a free perforation as well as a communication to an abscess in the mesentery.

Entero-enteral fistulae without free perforation were noted at post mortem examination in the patient with the sprue syndrome described above. The only patient in the series with large cell lymphosarcoma or reticulum cell sarcoma had involvement of many areas of the jejunum with several deeply ulcerated lesions and multiple fistulous communications.

Perforation was possibly present in a case of Hodgkin's disease, in which several hundred cc. of turbid fluid containing lymphocytes was found free in the peritoneal cavity at autopsy. The entire small intestine was infiltrated segmentally in all its layers by granulomatous Hodgkin's disease. Although several areas were deeply ulcerated, no perforation was seen.

Despite the fact that four authors (32, 46, 49, 50) have found perforation of small intestinal lymphomas in 18 to 47 per cent of their series, the frequency of the complication does not seem to be appreciated. It is hoped that our detailed discussion of six, or perhaps seven, cases of perforation out of 19 cases will help heighten general awareness of this problem.

5. Clinical Diagnosis

Clearly, lack of familiarity with perforation of lymphomas contributed to the low rate of accuracy in the pre-operative or ante mortem diagnosis of this group. These clinical impressions are listed in Table V. The two patients who were known to have had lymphoma previously were both diagnosed correctly. Aside from failure to consider lymphoma with perforation, the principal cause of diagnostic error was inadequate x-ray examination. Table VI indicates how often and how successfully x-ray examinations were used in the group.

No x-ray studies at all were made on four patients. The small bowel series was rewarding on all 11 patients on whom it was done. Indeed, in five of the 11, the correct diagnosis was made. In only one other case was the correct diagnosis made (Table V). Two barium enema studies showed an abnormality which was not diagnostic. One demonstrated an ileo-colic intussusception and the other revealed a soft tissue mass producing extrinsic pressure on the colon. The difficulties of distinguishing lymphoma from carcinoma by x-ray are discussed by Swenson (51) and others (3, 5, 7, 8, 31, 34).

TABLE V

Pre-operative or Ante Mortem Diagnosis in 19 Cases of Small Intestine Lymphoma

Correct diagnosis	6*	Carcinoma of colon	1‡
No clinical impression specified	2	Carcinoma of colon with perforation	1†
Sprue syndrome, possible tuberculous enteritis	1†	Carcinoma of stomach	1
Tuberculous enteritis and peritonitis	1†	Large bowel obstruction, cause unknown	1
Peritonitis, cause unknown	1†	Small bowel obstruction, cause unknown	1‡
Acute appendicitis	1	Regional ileitis	1
Acute appendicitis with perforation	1†		

* Two cases of definite perforation.
† Case of definite or possible perforation.
‡ Case of intussusception.

TABLE VI

Results of X-ray Examinations on 15 Cases of Lymphoma

Type of study	No. of cases	Abnormality seen	Diagnosis made
G.I. series	2		
Small bowel series	11	6	5
Barium enema	2	2	
Total	15	8	5

6. Results of Treatment

Of the 16 patients who underwent surgery, nine had multiple lesions or metastases at the time of operation. Three of the 16 died shortly after the operation; another died within four months. Seven of the 12 remaining patients are known to have lived at least one year after operation. The available information is summarized in Table VII.

Two patients with involved nodes at the time of operation lived six and eight years. Both were given post-operative radiotherapy. The former died of bronchogenic carcinoma and the latter died of leukemia. None of the other five patients had evidence of metastases and all are known to have lived one to six years. Three out of five patients with resectable lesions reported by Irvine and Johnstone (50) lived five to seven years. Eleven of the 25 patients in Burman and van Wyk's series (32) survived four years or more and three were living five years after the first symptom. Marcuse and Stout (33) found 23 cases out of a literature of 179 cases of small intestine lymphosarcoma who survived five years or more. Eighteen of these were treated with resection alone. Three were treated with resection and radiotherapy and two with radiotherapy alone. Six of these were reported to have had mesenteric node involvement at the time of operation. One patient with involved nodes lived more than eight years. Three out of 33 patients in the Mayo Clinic series (31) lived at least five years.

TABLE VII

Fate of Seven Patients with Small Bowel Lymphoma Who Lived More than One Year

Case	Metastases at time of operation	Post-operative Radiotherapy	Known Survival
1	yes	yes	8 years
2	no	yes	5 years or more
3	no	no	5 years or more
4	yes	yes	5 years or more
5	no	no	5 years or more
6	no	no	3 years or more
7	no	no	3 years or more

In an earlier paper, Stout (52) held that the disease is particularly malignant in children but now he and others have reported a few apparent cures. Usher and Dixon (35) studied 50 cases of lymphosarcoma of the entire intestine and found that patients with cecal lesions had a mean survival of eight years whereas patients with small intestine lesions had a mean survival of nine months.

If one removes the seven patients with definite or possible perforation from our series, the outlook appears far more optimistic. Of the remaining 12 patients, one died without operation. Seven of the 11 surgical patients who had no perforation are known to have lived three to eight years. One other patient died within 24 hours of the operation, and no follow-up information is available on the other three.

SARCOMA

Seventeen cases of various sarcomas have been grouped together, perhaps artificially, for consideration as a unit. We believe these tumors constitute a single diagnostic and therapeutic problem. There is an abundant literature of case reports and reviews of tumors of each histological type but it is more useful to stress similarities than differences. The collection of information along strict histologic lines has unfortunately emphasized the rarity of these tumors and may well have contributed to a diagnostic accuracy rate lower than that for the other malignant tumors.

These 17 cases comprise about 30 per cent of the malignant tumors in the series As one would expect, it is difficult to compare this incidence with previous experience because of the prevailing custom of reporting small bowel tumors by cell type or region. Our figure of 30 per cent of malignant tumors is certainly higher than in almost any other similar series and is about twice as high as in some (5, 6, 14). A partial explanation for this is the relatively low percentage of carcinomas in the total series of malignant tumors as compared with other series.

Of the 17 cases of sarcoma other than lymphoma in our series, ten were leiomyosarcomas, three were neurofibrosarcomas, three were melanosarcomas, and one was a fibrosarcoma (Table VIII). The age range of the group was 33 to 73 with a mean of 50 years. There were ten males and seven females. Seven tumors

TABLE VIII

Type and Location of Sarcoma Other than Lymphoma

Type	Duodenum	Jejunum	Ileum	Not specified	Total
Leiomyosarcoma		4	5	1	10
Neurofibrosarcoma		1		2	3
Fibrosarcoma			1		1
Melanosarcoma		2	1		3
Total	0	7	7	3	17

were located in the jejunum, seven in the ileum, and three were unspecified as to site. Sixteen of the 17 cases were found at operation, one incidentally. The 17th was an incidental finding at post mortem. One of the 15 symptomatic patients later died and was examined at post mortem.

The two tumors found incidentally were not small. One was a "peach-size," pedunculated, submucous leiomyosarcoma in a patient who was explored for carcinoma of the sigmoid colon with hepatic metastases. The other was an 8 x 10 cm. subserous neurofibrosarcoma of the jejunum found at autopsy in a patient who died of pulmonary embolism and had a negative gastrointestinal history.

1. Leiomyosarcoma

Nine of the 15 symptomatic cases were leiomyosarcomas. This tumor is generally agreed to be the most important in this group. Horsley and Means (53) found 108 cases of small intestinal leiomyosarcoma in the world literature as of 1955. Starr and Dockerty (54) reported 41 leiomyosarcomas and 35 benign leiomyomas from the surgical pathology files of the Mayo Clinic.

The following studies offer a comparison of the regional incidence of carcinoma and leiomyosarcoma. Kleinerman et al (19), as noted above, reported 453 "acceptable" cases of carcinoma of the duodenum in 1950, while Weinstein and Roberts (55) found only 27 cases of leiomyosarcoma of the duodenum up to 1953. Our entire series included seven carcinomas and no sarcomas of the duodenum. Ebert et al (56) found 12 carcinomas and three leiomyosarcomas of the duodenum in the autopsy records of the Boston City Hospital over 50 years. Mayo (57) reported that 10.8 per cent of 108 surgical cases of malignant duodenal tumors were leiomyosarcomas Marshall and Cherry (58) provide an extended discussion of gastrointestinal smooth muscle tumors.

2. Melanosarcoma

Melanosarcoma also deserves special mention. With our three cases, the total number of malignant small bowel melanomas recorded in the world literature is brought to 37. These three cases are the only ones in the entire series of 109 cases which are considered probably or definitely metastatic neoplasms. They are included because the relationship to a primary malignant melanoma at a distant site was not obvious and they presented diagnostic and therapeutic problems similar to primary small bowel tumors.

One case was that of a 51-year-old man who had blood-loss anemia intermittently for two years. A small bowel series revealed a local deformity. A very large, black 9 x 16 cm. deeply ulcerated tumor was removed. Many lymph nodes were involved. There is no mention that melanoma was known to exist elsewhere either at the time or in the past, nor is there any follow-up information.

A second patient, a 67-year-old man, had a malignant melanoma removed from his foot four years before admission. One year later a metastatic mass of nodes in his groin was resected. Five days before admission he developed acute intestinal obstruction. On operation, a 75 cm. intussusception of the jejunum was found led by a broad-based 2.5 cm. amelanotic, slightly ulcerated lesion. There is no note of observed metastases and again, no available follow-up information.

The third patient was a 42-year-old man who had a melanoma removed from the skin of his back five years prior to admission. He was admitted because of severe anemia and melena. A lesion was visualized in his ileum on a small bowel x-ray series. The correct diagnosis was suspected and, on operation, an ulcerated, fungating tumor encircling the bowel was found. The mass measured 10 x 8 cm. and severely encroached on the bowel lumen. Histologic diagnosis was amelanotic melanoma. Five months later the patient was seen and multiple abdominal masses were noted. No further information is known.

Beirne (59) found 33 cases of small bowel melanoma in the world literature and added one of his own, which appeared to be a primary lesion of the small intestine. Menne and Beeman (60) collected eight cases in which no primary locus could be found. Twenty-two of the 33 cases reported are definitely metastatic, as are two of our three cases. No final statement is warranted on the third. Willis (61), among others, contends that malignant melanoma is never primary in the small intestine.

3. Clinical Features

Of the 15 symptomatic cases of sarcoma, the presenting symptoms were those relating to anemia in six cases, abdominal pain in seven, and a palpable mass in two. Because of the rather low grade of malignancy, symptoms could often be traced back many months or years. One patient had had intermittent tarry stools for more than seven years There was no consistent relation between duration of symptoms and size of tumor, its location, or position in relation to the mucosa.

In addition to the two cases which presented with a palpable mass, this finding was a feature of six others, or more than half of the symptomatic cases. By comparison, a mass was noted in only four of the 14 symptomatic carcinomas and seven of the 19 lymphomas. Melena was present in eight cases and was characteristically of long duration, much longer than the melena described in our cases of carcinoma and lymphoma.

Intussusception was a feature of three cases. In one case, the tumor was an "apple-size," submucous, ileal fibrosarcoma—the only fibrosarcoma in our series. Another was a case of melanoma described above. The third was 7 x 5

cm. pedunculated leiomyosarcoma of the terminal ileum which intussuscepted as far as the splenic flexure. The diagnosis was made by barium enema.

Fever was present in only two cases. One case had a large intestinal neurofibrosarcoma with cystic degeneration. Its irregularly excavated center was continuous with an ostium lined by epithelium resembling intestinal mucosa. The second patient had multiple lymph node metastases from an infiltrating leiomyosarcoma of the jejunum.

Clubbing was marked in one 33-year-old woman who had a "tennis-ball" size leiomyosarcoma of the ileum attached to the serosa by a pedicle. She had no other cause for clubbing. Peritonitis was present in one patient who bled into the peritoneal cavity from a serosal leiomyosarcoma.

These clinical characteristics are not directly comparable to prior experience. Horsley and Means' review (53) of leiomyosarcoma alone has much the same distribution as our group of various sarcomas.

4. Clinical and X-ray Diagnosis

The correct diagnosis was made pre-operatively in only two of the 15 symptomatic cases. The tentative diagnoses (Table IX) included appendicitis, peptic ulcer, uterine fibroids, perforated Meckel's diverticulum, and urachal tumor. Both of the cases diagnosed correctly had intussusception. The diagnosis was made clinically without x-ray in one case, and by barium enema in the other. Four of the five cases on whom small bowel series were done showed some abnormality, but the diagnosis of small intestine tumor was made in only one (Table X). Four cases had an upper gastrointestinal series only and no abnormality was seen. Five others had no gastrointestinal x-rays at all.

5. Results of Treatment

No metastases were noted in the two cases in which the sarcoma was incidental. Six of the remaining 15 had metastases at the time of operation. One other had no metastases at operation but was re-explored a year later when a

TABLE IX

Pre-operative or Ante Mortem Diagnosis in 15 Symptomatic Cases of Small Bowel Sarcoma

Correct	2
Gastrointestinal bleeding, site unknown	2
Abdominal mass, cause unknown	2
Acute intestinal obstruction, cause unknown	1
Intussusception, cause unknown	1
Lymphosarcoma	1
Gastric ulcer	1
Duodenal ulcer	1
Uterine fibroids	1
Urachal tumor	1
Perforated Meckel's diverticulum	1
Acute appendicitis	1

TABLE X

Results of X-ray Examinations on Ten Cases of Small Bowel Sarcoma

Type of study	No. of cases	Abnormality seen	Diagnosis made
G.I. series	4		
Small bowel series	5	3	1
Barium enema	1	1	
Total	10	4	1

large retroperitoneal mass was found. Some information is available on the fate of four of the eight who had no metastases. These patients were known to be living two, three, five, and 15 years after admission.

BENIGN TUMORS

Forty of the entire series of 109 cases were primary benign tumors of the small intestine. Carcinoids which behaved like benign tumors have been reserved for consideration in a separate section. Raiford (62) stated that 8.9 per cent of all gastrointestinal neoplasms were benign and that 23.8 per cent of these were in the small intestine. The experience of other authors (8, 14, 15, 63) as well as our own indicates that about one benign tumor per year is found at large hospitals and about one to three per year at some of the largest medical centers.

A definitive review of benign small bowel tumors has recently been prepared by River, Silverstein and Tope (64). They reviewed 1,399 cases culled from the world literature and compiled a massive bibliography. Although we believe detailed information of each histologic type has limited clinical utility, the interested student is directed to their study. Of the 1,399 tumors, 72.4 per cent were found at operation, whereas 50 per cent of our 40 cases were found at operation (Table I). Three of these 20 surgical cases were incidental findings, while 17 of the 20 cases examined at post mortem were incidental findings. The types and location of the 40 tumors are charted in Table XI.

1. Incidence of Tumor Types

The most numerous group in the collection of River et al (64) consisted of adenomas, polyps, and polyposis (Peutz-Jeghers syndrome) which together numbered 456. Unfortunately, River et al do not specify how many of the 170 polyps were truly adenomatous nor what distinguishes intraluminal adenomas (209 cases) from polyps. Fifty-nine cases had polyposis associated with pigment deposition as described by Jeghers et al (65). We found six adenomas and all were reported as "adenomatous polyps." Two of the six cases had multiple polyps without abnormal pigmentation.

Lipomas, myomas, and fibromas followed in descending order of frequency in River's series (64) with 219, 179, and 163 cases respectively. We found 12 lipomas, 12 leiomyomas, and only one fibroma. The remainder of our series contains four neurofibromas, three hemangiomas, one lymphangioma, and one cystadenoma of

TABLE XI

Type and Location of 40 Benign Small Bowel Tumors

Type	No.	Location				Symptomatic	Incidental
		Duodenum	Jejunum	Ileum	Multiple		
Leiomyoma	12	2	7	3		8	4
Lipoma	12	2	6	3	1	4	8
Adenomatous polyp	6	1	1	2	2	3	3
Neurofibroma	4		1	1	2	2	2
Hemangioma	3		1		2	1	2
Lymphangioma	1		1				1
Fibroma	1			1		1	
Cystadenoma of pancreatic rest	1		1			1	
Total	40	5	18	10	7	20	20

a pancreatic rest. River et al collected 90 "neurogenic tumors," 127 angiomas and hemangiomas, and 18 lymphangiomas. Tumors of aberrant tissue were excluded. They also found 147 cases of ten other tumor types not represented in our series.

Before continuing with general considerations, a brief discussion of some of the tumor types is indicated. Eight of the 12 leiomyomas comprised 40 per cent of the 20 symptomatic cases in the group. This important type has been the subject of special interest (57, 58). None of the eight symptomatic cases exhibited a symptom complex suggestive of peptic ulcer as observed by Marshall and Cherry (58).

Three cases of vascular tumors were found. Two of these cases were multiple, of which one had multiple simple hemangiomata causing intestinal bleeding. The other had multiple cavernous hemangiomata, and the third had a single small serosal hemangioma. Henck and Lisa (66) and Gentry et al (67) have reviewed the literature. River et al (64) outline the vascular tumor classifications of Kaijser, Hansen, and Gentry et al.

A cystadenoma of a pancreatic rest of the jejunum is included in our series because it was clinically and surgically indistinguishable from other benign tumors. Horsley and Keasbey (68) discuss features of 328 cases of aberrant pancreatic tissue. Except for annular pancreas, these ectopic foci are almost always of little clinical significance. They occur least often in the jejunum. Cystadenomatous change of these rests is extremely rare. Such a lesion, however, was found in a 56-year-old woman who sought medical attention because she had noticed an abdominal mass for nine months with no other complaints. On operation, an "orange-size" (6 x 5 x 5 cm.) multilocular cystic mass was found beneath the serosa of the jejunum extending into the mesentery. The tumor was almost completely encapsulated and the mucosa and muscularis of the bowel were intact. Microscopic examination revealed a cystadenoma arising in intramural pancreatic tissue.

2. Location

It is generally believed that benign tumors, like malignant tumors, arise most frequently in the ileum and least frequently in the duodenum. Nearly half the cases in the collection of River et al (64) were found in the ileum. Table XI illustrates that a plurality of our benign tumors were found in the jejunum rather than the ileum. We have previously noted a similar distribution of malignant tumors.

3. Age and Sex

The age range of the whole group was six to 80 years with a mean of 51. The mean age of the 20 symptomatic cases was 46 years. Two patients of age six had multiple polyps. Another, age ten, had a myoma of the ileum which led an ileo-colic intussusception. Eighty-three of the cases of River et al (64) were less than ten years of age.

There were 18 males and 22 females in our series. River et al noted a slight preponderance of men to women, 685 to 638.

4. Clinical Features

Anemia was the presenting problem in ten of the 20 symptomatic cases. Two patients noticed an abdominal mass and eight patients reported pain as the cardinal problem. Five of these eight had intussusception with at least partial intestinal obstruction caused by the following intraluminal tumors: two myomas, one lipoma, one neurofibroma, and one fibroma. In a sixth case, partial intestinal obstruction was caused by a 4 x 3 x 3 cm. submucous lipoma of the terminal ileum.

The origin of pain was not clear in the other two patients. One had an ulcer-like syndrome and was apparently cured (five-year follow-up) by removal of a "pea-size" duodenal polyp which showed no evidence of ulceration. The other patient had no characteristic pain pattern, but a 4 x 2 x 2 cm. polyp on a long pedicle was removed from the proximal jejunum.

Melena was a presenting or additional feature of 14 of the 20 symptomatic cases. An abdominal mass was palpable in three cases other than the two mentioned above.

5. Clinical and X-ray Diagnosis

Only three of the 20 symptomatic cases were diagnosed correctly as neoplasms of the small bowel before operation or death (Table XII). In all three symptomatic cases examined at post mortem, pain or bleeding or both had been noted. One of these died of an unrelated condition which precluded investigation. The other two died of exsanguinating hemorrhage. One was the patient with multiple simple hemangiomata mentioned above. The second was a 72-year-old man who died of cardiac failure precipitated by massive hemorrhage from an ulcerated polypoid lipoma of the jejunum.

Intussusception was correctly diagnosed in three other cases but the underly-

TABLE XII

Pre-operative or Ante Mortem Diagnosis in 20 Symptomatic Cases of Benign Small Bowel Tumor

Correct	3
Gastrointestinal bleeding, site unknown	5
Abdominal mass, cause unknown	2
Intussusception, cause unknown	3
Intestinal obstruction, cause unknown	2
Diverticulitis	1
Carcinoma of the cecum	1
Gastric polyp	1
Symptoms noted but no gastrointestinal diagnosis entertained	2

TABLE XIII

Results of X-ray Examinations on 16 Cases of Benign Small Bowel Tumor

Type of study	No. of cases	Abnormality seen	Diagnosis made
G.I. series	9	4	3
Small bowel series	5		
Barium enema	2	1	1
Total	16	5	4

ing tumor was not suspected. Another case of intussusception was incorrectly diagnosed by barium enema as carcinoma of the cecum. Two cases with a palpable mass were operated on without x-ray examination.

Again, the low level of diagnostic accuracy is clearly related to an inadequate concern for the possibility of small bowel tumor. This unawareness is illustrated by the results of x-ray examinations of the symptomatic cases (Table XIII). Sixteen had gastrointestinal x-ray studies of which nine had upper G.I. series only, five had G.I. and small bowel series, and two had a barium enema only. In the latter two cases, both with ileo-colic intussusceptions, an abnormality was noted and the diagnosis of small bowel tumor was made in one. An abnormality was noted in four of the cases studied by upper G.I. series and a correct diagnosis suggested in three. These three were all duodenal lesions. In other words, small bowel x-ray examination revealed no abnormality in the five cases studied. But it is more significant that only five of 20 symptomatic cases were studied by the simplest type of small bowel examination.

CARCINOID

Tumors of the argentaffine cells in the gastrointestinal tract are of growing clinical interest and seem to be recognized with increasing frequency. Only 237 cases of carcinoids of the small intestine had been reported (69) as of 1939. A report (70) in 1956 reviews 438 cases. MacDonald (71) was able to collect 356 gastrointestinal carcinoids from the records of seven Boston hospitals. Ninety-

nine of these carcinoids were located in the small intestine. Humphreys (72) believed that carcinoids comprised 0.16 per cent of gastrointestinal tract tumors but more recently estimates (73) have risen to 0.4 per cent. The proportion of these tumors arising in the appendix has varied from 58 per cent to 75 per cent to 90 per cent (71, 70, 74).

In addition to increased recognition, there has been growing interest in the embryological origin of the argentaffine cell and the malignant potential of argentaffine tumors. The former topic has been discussed well elsewhere (70, 71, 75, 76). Although 30 years ago metastases from these lesions were considered rare, recent emphasis (71, 77, 78) has been on the frequency of local invasion and lymph node involvement. All agree that the distinction between benign and malignant lesions is histologically difficult or impossible. With this problem in mind, MacDonald (71) has chosen to avoid the designations "benign" and "malignant" and has graded his tumors on a four-degree scale of invasiveness. For the practical purpose of this paper, with its clinical orientation, we have included the non-metastasizing lesions with the benign group and the metastasizing lesions with the malignant. Although the pathological validity of this separation may be challenged we believe it is useful.

The final impetus to the study of carcinoids has been the description of the so-called carcinoid syndrome with its important physiologic implications (70, 79, 80, 81). We did not find one example of this syndrome, whereas MacDonald (71) found four examples out of 24 extra-appendiceal carcinoids with hepatic metastases.

Eighteen carcinoid tumors of the small intestine were found during the reporting period. The group represents 16 per cent of our entire series of small bowel tumors. Dockerty et al (82) have stated that carcinoids account for 23 per cent of small bowel tumors. As Table XIV shows, the most striking feature of the group was its low proportion of clinically significant lesions. Only six of the 18 tumors were symptomatic. Five of the 18 were found at operation and one of these was incidental. Thirteen cases had no metastases and were considered benign. Eleven of these 13 were found incidentally, ten at post mortem and one at operation. Five tumors had metastasized and one of these was an entirely incidental finding. Diffenbaugh and Anderson (70) state that 34.2 per cent of small bowel carcinoids metastasize, whereas only 3.5 per cent of appendiceal carcinoids metastasize. MacDonald (71) classified 30 of his 99 small bowel lesions in the

TABLE XIV

Distribution of Eighteen Carcinoid Tumors of the Small Intestine

	Found at operation		Found at post mortem		Total	
	Sympt.	Incid.	Sympt.	Incid.	Sympt.	Incid.
No metastases ("benign")	1	1	1	10	2	11
Metastases ("malignant")	3		1	1	4	1
Total	4	1	2	11	6	12

third or fourth degree of invasiveness, meaning that they involved local lymph nodes or had metastasized widely. He did not find one case with metastases out of 204 appendiceal carcinoids.

1. Location

Sixteen of the 18 arose primarily in the ileum and two in the jejunum. MacDonald's collection (71) included 74 tumors of the ileum, 17 in the jejunum and eight in the duodenum. He also noted that 16 per cent of the 149 extra-appendiceal tumors arose from multiple foci. This was true in five of the 18 in our series.

2. Age and Sex

The age range was 27 to 76 years with a mean of 60. The average age of the five symptomatic cases was 56 years. Most of the cases in the literature are of incidental tumors found in older people at post mortem examination. A case has been seen, however, in an infant ten days old (70). Ten of the patients were males and eight were females.

3. Clinical Features

Of the six symptomatic cases, two presented abdominal pain. One of these was a 27-year-old man who had complained of intermittent crampy periumbilical pain for ten years. On operation a small intramural carcinoid which had caused partial intestinal obstruction was found in the proximal ileum. No metastases were noted. The other patient was a 66-year-old woman who had had intermittent crampy epigastric pain for one year. Tarry stools had been noted for three months, and a tender mass was felt in the right lower quadrant Operation revealed a "silver-dollar" size mass, arising from the ileal lip of the ileo-cecal valve, which had caused partial intestinal obstruction. Local lymph nodes were involved. The patient died of a "stroke" three years later. These two patients were the only ones in whom intestinal obstruction was a significant feature. Earlier authors (83, 84) have estimated that 17 per cent or 50 per cent of small bowel carcinoids cause obstruction.

Bleeding with tarry stools was the presenting symptom in three patients and a prominent feature in another. Thus four of the six symptomatic cases had obvious intestinal bleeding. It is claimed (16) that ulceration is late and infrequent in carcinoid tumors and bleeding, therefore, infrequent. The sixth symptomatic patient, a 54-year-old man, had a chief complaint of diarrhea for 20 years. An "irregular" terminal ileum was seen on x-ray and a diagnosis of regional enteritis made. Operation showed eight inches of terminal ileum diffusely thickened and constricted. Multiple mucosal plaque-like lesions which infiltrated the submucosa and muscularis were noted. These lesions proved to be carcinoids. The tumor had spread to many lymph nodes. This patient was known to be alive ten years later.

4. Clinical and X-ray Diagnosis

Not one of the six symptomatic cases was diagnosed correctly as a small intestinal neoplasm. Bleeding in two cases was attributed to varices and leukemia.

Two cases were believed to be carcinoma of the cecum. One case was diagnosed as regional ileitis, and still another which had features of partial obstruction was diagnosed as acute appendicitis.

Only two of the six symptomatic cases had gastrointestinal x-ray examinations. One was studied by barium enema and was interpreted as carcinoma of the cecum. The other had a small bowel series and was interpreted as regional ileitis.

5. Results of Treatment

Little information on the notoriously languid course of malignant carcinoids can be gained from these cases. Reviewers often cite as an extreme Mallory's case (85), in which a patient with "inoperable" metastatic carcinoid survived 20 years. The course of the five malignant cases will be reviewed.

1) A 70-year-old man with known lymphatic leukemia had weakness, anemia, and tarry stools for a few weeks before admission He died and post mortem examination revealed a submucous carcinoid which had infiltrated the entire wall of the small bowel. Mesenteric nodes and the peritoneal surface of the bladder were involved.

2) A 63-year-old woman died of pulmonary edema after nephrectomy for an unrelated complaint. Five years previously she was explored for "inoperable carcinoma" of the cecum. A by-pass procedure around the cecum was done but no biopsy taken. At post mortem, a 2 x 4 cm. intraluminal mass covered with apparently intact mucosa was seen. Metastases were demonstrated in the mesenteric and portal nodes and the liver. There was invasion of the superior mesenteric and portal veins. This is our only case with hepatic metastases.

3) A 2 x 0.5 cm. submucosal carcinoid was found incidentally at autopsy in a 65-year-old man who died of thrombocytopenic purpura. Mesenteric nodes showed metastatic carcinoid.

4) A 54-year-old man with a 20-year history of diarrhea is known to have lived at least ten years after operation.

5) A 66-year-old man with symptoms of partial obstruction for one year died from an unrelated cause three years after resection of the lesion and involved nodes.

DISCUSSION

The correct diagnosis was made pre-operatively or ante mortem in 13 out of 52 symptomatic cases of malignant tumor, and in 3 out of 22 symptomatic cases of benign tumor. Over-all, 22 per cent of the 74 symptomatic cases were correctly diagnosed. The fact that the 58 remaining symptomatic cases were given 26 different diagnoses illustrates the degree to which small bowel tumors can mimic other conditions. It should be re-emphasized that to qualify as 'correct,' we arbitrarily decided that any mention of small bowel neoplasm was sufficient. We did not demand the correct tumor type or an opinion as to malignancy.

The principal clinical manifestations of the 74 symptomatic cases (Table XV) were abdominal pain in 36 (28 malignant and 8 benign), and symptoms related

TABLE XV

Presenting Symptom or Clinical Problem in 74 Symptomatic Small Bowel Tumors

Symptom	Malignant	Benign
Abdominal pain	28	8
Anemia	13	12
Palpable mass	3	2
Jaundice	2	
Epigastric distress	2	
Diarrhea	2	
Fever	1	
Vomiting without pain	1	
	—	—
	52	22

TABLE XVI

Results of X-ray Examinations on 56 Small Bowel Tumors

Type of study	No. of cases	Abnormality seen	Diagnosis made
G.I. series	24	7	4
Small bowel series	26	11	8
Barium enema	6	5	1
	—	—	—
Total	56	23	13

to anemia in 25 (13 malignant and 12 benign). The frequency of these symptoms underlines a cardinal objective of this study. Unexplained abdominal pain, particularly if associated with partial intestinal obstruction and unexplained gastrointestinal bleeding, demands investigation for tumors of the small bowel. We have noted other features, however, which may dominate the clinical picture in malignant tumors of the small bowel. Some of our patients have presented jaundice, diarrhea, fever, dyspepsia, or a palpable mass.

Fifty-six of the 74 patients with symptoms underwent some type of gastrointestinal x-ray study (Table XVI). Twenty-four had an upper gastrointestinal series only. An abnormality was noted in seven and the correct diagnosis was made in four others. An upper gastrointestinal series and small bowel series were done in 26 cases. An abnormality was found in 11 and the correct diagnosis was suggested in eight others. In five cases an abnormality was noted on barium enema, which showed either extrinsic defects or intussusception. In a sixth case, the correct diagnosis was made by barium enema. X-ray study, then, led to the correct diagnosis in 13 of the 56 cases and was useful in demonstrating an abnormality in 23 more. The examinations were done by various private physicians and hospital radiology departments as well as the X-ray Department of The Mount Sinai Hospital. If the cases are analyzed chronologically, it is encouraging to note that those examined in the last ten years show an accuracy rate significantly higher than the 64 per cent found for the entire series. The accuracy rates of other series have been mentioned previously (4, 5, 6).

Seventy-four symptomatic tumors of the small bowel were found at The Mount Sinai Hospital over a period of 25 years. A case rate of three per year is more common than that of other entities which the clinician considers more frequently in difficult gastrointestinal diagnostic problems.

SUMMARY

1) The clinical behavior of 109 small bowel tumors of various types has been analyzed.

2) The special problems in the clinical and pathologic diagnosis of primary carcinoma, particularly duodenal carcinoma, have been discussed.

3) Clinical observations in this series have been compared with studies of individual cell type tumors.

4) An important and unexpected feature of this study has been the striking tendency of small bowel lymphomas to perforate. Even though corroborated by other authors, this complication has been inadequately appreciated.

5) Three cases of malignant melanoma of the small intestine have been described, which augments the 34 cases previously reported in the world literature.

6) To stimulate awareness, the results of x-ray examination and the rate of diagnostic accuracy have been emphasized. The accrual rate of symptomatic cases has averaged three per year at The Mount Sinai Hospital.

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INFLUENZA—A CRITICAL REVIEW

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INTRODUCTION

Influenza is an old disease. It is said to have been introduced and spread throughout Europe by the Crusaders. In the Middle Ages it was often called the "sweating sickness" (1). In the 1562 epidemic in Scotland, it was referred to as the "newe acquayantance" (2). It was not until 1580 that it was given its present name, "influenza," by the Italians who thought that it was the result of a "celestial influence" (1).

Influenza was often taken lightly and this is reflected in various popular names that have been used such as "the jolly rant," "the new delight," "gallant's disease," and "the fashionable illness" (2). Because of the explosive character of its onset, it has also often been the cause of considerable concern, although perhaps never so far in advance of an outbreak as now, thanks to our modern communications, world-wide chain of influenza "listening post" laboratories, and the many who recall the pandemic of 1918.

The purpose of this paper is to review some of what is now known and what is speculation about this disease so that we may approach the problems inherent in the present so called "Asian flu epidemic" more rationally.

VIROLOGY

It is less than 25 years since influenza has been proven to be caused by a virus. We now recognize at least four immunologically distinct types of influenza virus and many subtypes or strains. These strains show a progressive shift in antigenic composition away from the parent type. This is especially true with Type A. In Chart I are summarized the pertinent facts (3–5).

A great deal of our present knowledge of influenza is a testimonial to a readily available, susceptible laboratory animal, the chick embryo, and to a relatively simple serological test, the hemagglutination-inhibition (H-I) test (6).

A diagnosis of influenza can only be confirmed in a virology laboratory. This is done conclusively by recovery of the virus from a patient's throat washings and the demonstration of a rise in titer of antibody to this virus during convalescence. A presumptive diagnosis may be made by just demonstrating a rise in antibody titer to a currently epidemic strain. The isolation of virus is carried out most frequently in the amniotic sacs of 10-day-old chick embryos. The antibody rise is demonstrated most conveniently with the H-I test by using as antigens currently epidemic strains. This is illustrated in Chart II which is from a study of an influenza A-prime outbreak at The Mount Sinai Hospital in 1951. Sera from two patients were tested in the hemagglutination-inhibition test

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CHART I

The Influenza Viruses

I. Are all *grouped together* because they—
   1. have same *clinical syndrome*
   2. have same *animal pathogenicity*
   3. *multiply* rapidly
   4. are good *antigens*
   5. *agglutinate* and *elute* from red blood cells
   6. have same *size and shape.*

II. Are *separated on immunologic basis* into—
   1. *Types* (on basis of complement fixing antigens) and within each Type into
   2. *Strains* (on basis of more or less sharing of antigens best shown in hemagglutination-inhibition tests).

   Thus:

   Type *A*—4 sets of strains: Swine (1919–1929?)
   PR-8 (1933–1943)
   A-prime (1946–1956)
   F.E. (1957–)

   Type *B*—2 main strains:
   Lee (1940)
   Bon (1943)

   Type *C*—(1950)

   Type *D*—Sendai (1952)

CHART II

Typical Influenza Serology in Outbreak of March 1951

		Virus		
		PR-8	FM-1	Kummel
Carr	3/7	80*	80	20
	3/16	80	160	20
	3/22	80	640**	80
Taylor	3/10	160	80	40
	3/21	80	160	160

* Reciprocal of highest dilution of serum giving inhibition.

** Only a 4-fold or greater rise in titer is considered significant.

against the classical A (PR-8) and A-prime (FM-1) viruses, and the Kummel virus which was recovered during the outbreak. It will be seen that if only the classical strains had been used as antigens, the diagnosis could not have been made in the second patient.

As has just been implied, the clinical illness stimulates the rapid production by the patient of specific antibodies, and this in a crude way parallels his immunity to that strain. We know that after a few years this immunity will wane, but we do not know at what level of antibody he will again be susceptible. We do know that this varies from individual to individual. Indeed, as might have been anticipated, the circulating antibody level can *only* be a *crude* measure of resistance to a virus which does not cause a viremia, but which is essentially a surface infection—spreading from one respiratory epithelial cell to the next. It

has been suggested by Burnet (7) that antibody protection is important in influenza only when secondary inflammatory changes are produced as a result of primary necrosis. The faster the spread, the more virulent the virus, the less effective the antibody; and conversely the lower the virulence, the more obvious the effect of antibody.

CLINICAL PICTURE

The classical clinical description of influenza—abrupt onset, prostration, temperature for two to three days, headache with ocular pain, myalgia, cough and sore throat—is seen in only about one-half of all patients with serologic evidence of this infection. Conversely, many patients suspected on clinical grounds as having influenza, even during an epidemic period, may have some other respiratory infection. In 1943 and 1944 on the West Coast, we studied sera from 119 soldiers diagnosed clinically as having influenza. In only about 40 per cent of these patients could we demonstrate a rise in antibody titer for influenza (6).

In 1943, the U. S. Army Commission on Acute Respiratory Diseases studied an epidemic of influenza Type A at Fort Bragg, N. C. (8). This study had the benefit of the most modern laboratory technics. The influenza epidemic was followed very closely by an epidemic of acute respiratory disease (A.R.D.) which we now recognize as being caused by an adenovirus. The Commission compared the cumulative frequency of a variety of signs and symptoms in 79 proven cases of influenza A with 113 cases of A.R.D. It was found that constitutional symptoms (feverishness, chilliness, malaise, headache, anorexia and weakness) and signs and symptoms involving the nose occurred more frequently in influenza, while sore throat and hoarseness were more frequent in A.R.D. Cough occurred with about equal frequency (70%) in both syndromes. Nevertheless, in individual instances these syndromes may be indistinguishable without the aid of a virology laboratory.

A clinical sign which may be of value in infants and children with influenza is a biphasic temperature curve (9). This is rarely seen in adults.

The routine laboratory studies in patients with influenza are mostly of negative value. The white blood cell count is more often normal than leukopenic. However, if some secondary bacterial infection is superimposed, leukocytosis is found. Fortunately, the rate of secondary infection is usually low. The few deaths that have been reported in the current outbreak appear to have been due principally to staphylococcal and streptococcal infection of the lungs. Because of this, when a decision is made to use antibiotics, erythromycin has been recommended for older children and adults. Because of the additional threat of H. influenza infection in infants, it has been suggested that one of the tetracyclines be given along with erythromycin (10).

EPIDEMIOLOGY

The epidemiology of influenza has been so characteristic that it has been possible to trace this disease in Europe back to 1510. We know that influenza has a one to two day incubation period, that effective immunity is type and to

a degree strain specific, and that it is of relatively short duration. This would seem to make understandable why epidemics in any one area appear to be explosive, to spread rapidly through susceptibles, to be over in a few weeks and to recur periodically. Pandemics, which are epidemics over a wide area, are characterized by the occurrence of secondary or even tertiary waves of disease. Epidemic influenza is characterized by a high morbidity rate (between 10–30 per cent of a population may be infected at one time) and a low mortality rate.

Because of the difficulties in accurately diagnosing and reporting this disease, statisticians have resorted to studying the excess mortality from respiratory disease in any one year, as a base for charting epidemics of influenza and grading their severity. When this is done, as in a recent paper on influenza in the United States by Collins and Lehman (11), one can clearly see the multiple waves in the pandemic of 1918 and 1919 in contrast to the single peaks of subsequent epidemics. There were 21 such peaks since 1919 with major ones showing an excess annual death rate of at least 200 per 100,000 in 1920, 1922, 1923, 1926, 1929, 1932, 1937 and 1943. When the etiology of epidemics which are known is added, it is seen that A epidemics occurred in 1932, 1935, 1937, 1939, 1941 and 1943; A-prime epidemics occurred in 1947, 1950, 1951 and 1953; and B epidemics occurred in 1936, 1940, 1945 and 1952. Thus, although influenza epidemics occur periodically, this periodicity is quite irregular.

All the factors which are responsible for the spread of influenza are not known. In the 1943 Fort Bragg study (8) it was shown that the virus of influenza could be recovered from throat washings most often on the first and second days of illness and never after the sixth day. It was also found in that study that many soldiers apparently had subclinical influenza, since they showed a good rise in antibody to the prevalent virus. Human contact and routes of travel have been carefully studied without adequately accounting for the frequent simultaneous appearance of peaks of incidence in widely separate areas of the world. One frequently quoted hypothesis is that there is first a widespread seeding of the virus without too many clinical cases, and that the sudden appearance of an epidemic reflects the introduction of some second factor not yet understood; perhaps having to do with climate (12) or perhaps "celestial influence."

The actual immunity from an attack of influenza is of short duration, however serologic evidence of it usually persists for life and provides an interesting recapitulation of past infections. Thus an individual during his life time may be exposed to many influenza viruses, yet the dominant antibody remains that of the initial infection. This has been called the "doctrine of original antigenic sin" (13). For example, it has been recently shown in a survey of sera from infants, children and adults living in the United States (14) that the youngest children had highest titers to A-prime strains, the young adults had their highest titers to PR-8 like Type A strains, and that older adults had a broad spectrum of Type A antibodies which even included swine influenza (which is thought to be related to the virus of 1918). In Holland, it has been found that antibodies to the newly recovered F.E. or Asian strains could be detected in the sera of people who were alive during the pandemic of 1890 (5).

What has just been said about the epidemiology of influenza applies at the present only to Types A and B. Types C and D outbreaks have not yet been sufficiently studied, indeed they would seem at present to be usually associated with endemic rather than epidemic disease.

PROPHYLAXIS BY VACCINATION

The appearance of specific antibodies and immunity following an attack of influenza early prompted investigation of the possibilities of vaccination for prophylaxis. At the present time it is clear that killed influenza virus injected into patients will also stimulate the production of specific antibodies and some degree of immunity. However, a number of practical difficulties have arisen. One is unable to translate the actual level of antibody into terms of degree of immunity. This is not surprising in light of the pathogenesis of influenza, and the unclear role of circulating antibody in a cellular disease not associated with a viremia. However, it is known that, in a general way, higher levels of antibody are associated with greater degrees of immunity. Higher levels of antibody result when more antigen is injected, although this is not a proportionate increase—e.g., a 200-fold increase in amount of antigen may lead to only a 5-fold increase in antibody level (15). Even given the same amount of antigen, all strains are not equally good antigens. There is a practical limit to the amount of antigen that can be given. After a certain point there is a sharp rise in the incidence of systemic reactions with even small increments in virus (15). These reactions which appear six to eight hours after the giving of killed vaccine are characterized by influenza-like symptoms. They have been related to the virus particles themselves, and not to an impurity in the vaccine. This type of reaction occurs more frequently in younger individuals. The reason is not clear. It is not entirely neutralized or prevented by circulating antibody since individuals who have had such reactions to first injections may also get them with subsequent ones, tho to a lesser extent. It has been suggested that these reactions may be the result of some primary pharmacologic toxic effect of the virus, or a sensitization to the protein of the virus. The current F.E. or Asian strains are said to have especially potent toxic properties (16). Although we do not know the cause, the problem of these severe reactions is real. These reactions may occur in at least ten per cent of individuals inoculated with large doses. Consequently, limitations have to be placed on the amount of vaccine that can be given at any one time. It is interesting that there is no correlation between the severity of these reactions and the amount of antibody produced.

The vaccine is made from egg-grown virus and egg sensitivity allergic reactions have been reported. These take place almost immediately in contrast to the toxic reactions. They are less frequent than the toxic reactions but may be terrifying in severity. Like other allergic reactions, they may occur after even very small amounts of vaccine. Since the vaccine may be irritating when injected intradermally, it should not be used to test for egg sensitivity; the egg white scratch test material has been recommended for this purpose (17).

The optimal amount and number of injections necessary for protection is not

yet known although it is under study. It would seem, however, that if the vaccine contains antigens closely related to those with which the individual has had some previous experience, only a single injection would be sufficient to elicit an amnestic or recall response and a high antibody level. However, if it is a rather different antigen, similar to the F.E. or Asian strains to which serologic surveys indicate very little previous experience (except perhaps in very old people); then two or more injections would seem to be required to get a good antibody response.

The best route of inoculating vaccine would seem to be subcutaneously although there is some evidence that smaller doses given intracutaneously may be effective for production of antibodies (18).

The duration of effective immunity following vaccination with saline antigens such as we are now using is also not known. It has been said to vary from four to twelve months. In the 1943–44 experience with vaccinating college students across the country, the least convincing results were obtained on the West Coast where the vaccine was given about six weeks before the start of the epidemic. There, four per cent of those vaccinated and six per cent of the controls developed influenza (19). The best results were shown when the vaccine was not given until after the epidemic had already started. At one such institution, only 1.7 per cent of those vaccinated became ill in contrast to eight per cent of the controls (20). This is in young adults. It is still not clear as to whether vaccination in infants and children does more than produce an antibody response. There is still no really good evidence on the protective effects of vaccination in infants and children.

Immunity following any vaccination reflects the antigenicity of the strains used, the dosage and frequency of injections, their route, and the individuals. It is consequently very difficult to project from past experience with other *similar, but not identical vaccines.* We must await the results of actual field trials with the current influenza vaccine before we can say how effective it is or for how long.

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NALORPHINE IN THE TREATMENT OF MORPHINE-INDUCED BILIARY COLIC

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The effects of therapeutic doses of morphine on the biliary tract have been studied and described in detail (1, 2). In brief, morphine produces a spasm of the choledochal sphincter with a resulting rise in common bile duct pressure. This increased intraductal pressure may be associated with symptoms varying from mild epigastric discomfort to acute and severe biliary colic. This explains the occasional failure of morphine to relieve the pain of biliary colic.

Schapiro and Beal (3) studied the effect of nalorphine (n-allylnormorphine) on choledochal sphincter action in patients who had choledochostomy tubes. These workers demonstrated that nalorphine, when given prior to morphine, prevents the rise in intraductal pressure. Also, when nalorphine was administered during a morphine-induced rise in intraductal pressure, a prompt fall in common duct pressure resulted. These studies suggested to us that nalorphine might be a useful agent in the treatment of morphine-induced biliary colic. The following reports illustrate dramatically the therapeutic value of nalorphine in such cases:

CASE I

A 33 year old woman who had had a cholecystectomy four years before admission, was brought to the operating room for a hemorrhoidectomy. She was given morphine sulfate, 15 mg., and atropine sulfate, 0.4 mg., 30 minutes prior to her arrival on the operating floor. Shortly after her arrival on the floor, the patient experienced very severe epigastric pain with some radiation to the substernal region. Her pulse and blood pressure were unchanged. After 30 minutes of constant distress she was given 5 mg. of nalorphine intravenously. There was dramatic and complete disappearance of pain within three minutes. There were no untoward reactions to nalorphine. A hemorrhoidectomy was performed uneventfully under spinal analgesia and the patient made a satisfactory recovery. On further questioning, the patient recalled that, prior to her cholecystectomy, morphine gave no relief in her episodes of biliary colic and appeared, at times, to aggravate the pain.

CASE II

A 51 year old white woman was brought to the operating floor for a cholecystectomy with the diagnosis of chronic cholecystitis and cholelithiasis. Thirty minutes earlier she had received morphine sulfate, 10 mg., and atropine sulfate, 0.4 mg., by hypodermic injection. Shortly after her arrival on the operating

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floor, the patient developed severe right upper quadrant pain with radiation to the back, nausea and retching. The patient volunteered the statement that she was having "a gall bladder attack". Ten minutes after the onset of pain, nalorphine, 10 mg., was administered intravenously. Within three minutes there was dramatic and complete cessation of pain, nausea and retching; there were no side-effects to the drug. A cholecystectomy was performed under cyclopropane-ether anesthesia without incident.

DISCUSSION

A variety of drugs have been employed in the treatment of narcotic-induced biliary colic. These include anticholinergic agents, synthetic antispasmodics, ganglion blocking drugs and smooth muscle relaxants.

Anticholinergic agents, as atropine and methantheline (Banthine®), have been shown to have little effect on the choledochal sphincter. Also, synthetic antispasmodics (syntropan, pavatrine) and ganglion blocking agents (tetraethylammonium) are ineffective (4).

Smooth muscle relaxants, such as amyl nitrite, glyceryl trinitrate and theophylline, have been found to be effective (5). However, these drugs may have certain undesired side effects, such as vertigo, headache, hypotension, nausea and emesis (6).

Although nalorphine was introduced as a specific narcotic antagonist with emphasis on its respiratory effects, it has been shown to prevent or counteract morphine side effects as vasomotor depression and intestinal and biliary spasm. It appears to be the agent of choice in the treatment of narcotic-induced biliary colic. The experimental studies of Schapiro and Beal and the cases herein reported support this contention.

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AURAL CHOLESTEATOMA: PARTICULAR REFERENCE TO PATHOGENESIS AND TREATMENT

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Cholesteatomata of the middle ear and the mastoid have been known for over a hundred years and much has been observed and written on this subject. However, their characteristics are often misunderstood and the theories of their origin are still confusing and contradictory. The term cholesteatoma, as it is commonly applied to the ear, is in reality a misnomer, for it implies neoplasm. The English have recently suggested that the name cholesteatosis be used for this condition.

The term cholesteatoma was applied by Johannes Muller over a century ago (in 1838) and Virchow in 1855 (1) assumed its origin to be the same as cholesteatoma of the brain. Toynbee, on the other hand (2) stated in 1860 that "these lesions" probably originated in the external auditory canal. It was not until 1880 that Bezold and Siebenmann (3) first considered them to be a product of inflammation and not a true neoplasm.

Histologically, a cholesteatoma can be described as a mass of tissue consisting of concentrically arranged polygonal lamellas, and of epidermal cells and cholesterin crystals. The entire mass is surrounded by a membrane, a matrix, which is composed of an outer layer of connective tissue and an inner layer of stratified squamous epithelium.

Histogenesis—A sharp distinction must be made between two types of cholesteatoma. The first type develops on the basis of a necrotic otitis media and is usually associated with the acute exanthemeta such as scarlet fever and measles or with tuberculosis. This type is not seen nearly so frequently at present as it was prior to the advent of the antibiotics. The second type, encountered more often, is the one usually associated with tiny perforations in Shrapnell's membrane or in the superoposterior margin of the drum. This type seems to have been less influenced by the antibiotics, since infection is not an immediate factor in its etiology.

In the *first type*, that associated with necrotic otitis, it has been observed that the drum usually has been previously destroyed to a great extent and a large perforation exists. Instead of the necrotic mucosa becoming lined by the adjacent healthy epithelium of the middle ear and eustachian tube, as takes place in the usual healing process of middle ear infections, very early in the disease there is evidence of a strong tendency for the epidermal layer of the external canal or tympanic membrane to grow around the margins of the perforation and to enter the tympanic cavity. The proliferating epidermis replaces the necrotic mucosa and ultimately lines the cavity (Fig. 1). It has been maintained by some that a prerequisite for such an ingrowth is the presence within the tympanum

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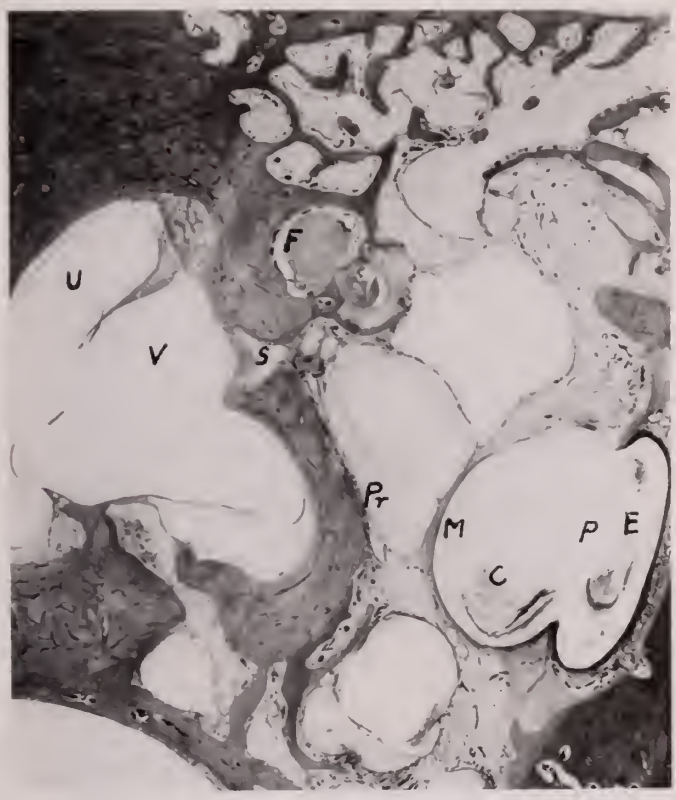

FIG. 1. Vertical section through the tympanum showing a large central perforation of the tympanic membrane. The cholesteatomatous matrix has grown around the margin of the perforation and has come into close proximity to the inner tympanic wall. C represents cholesteatoma; E, external auditory canal; F, facial nerve; M, matrix of cholesteatoma; P, perforation of tympanic membrane; Pr, promontory; V, vestibule and U, utricle.

of a hyperplastic type of mucosa, since it serves as a good supporting tissue for the advancing epidermis. I do not entirely agree with this concept. I believe that the epidermal ingrowth can take place in the presence of any type of a mucosa providing it has previously undergone necrotic changes (Fig. 2 A & B). It is doubtful that normal healthy mucous membrane can be replaced by epidermis. The epidermis continues to desquamate as it invades the middle ear cavity. The accumulated waste products act as irritants to the mucous membrane and eventually destroy it. In this manner, almost the entire middle ear and mastoid cavity may become lined by epidermis. This invasive character of the epidermis appears to be so strong at times that it actually displaces the tympanic membrane inward in its attempt to line the middle ear cavity (Fig. 3). We have seen instances in which the high columnar epithelium of the eustachian tube, a structure well known to offer great resistance to the invading epidermis, had eventually succumbed to it (Fig. 4). This ingrowth of the epidermal layer, in reality, is evidence of nature's attempt to heal a chronically infected middle ear by providing the cavity with a covering that is more protective to the out-

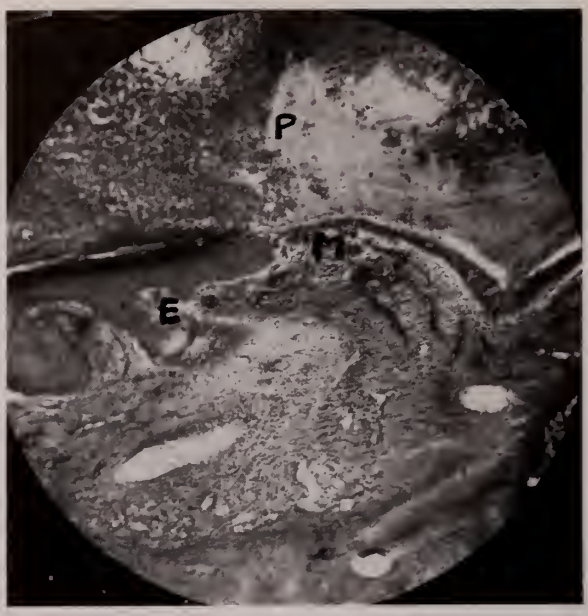

FIG. 2A. The epidermis can be seen extending into the tympanic cavity and replacing the diseased mucosal lining. E represents epidermis; M, mucosa and P, purulent exudate. (Courtesy Arch. Otolaryng., Druss, J. G., April, 1933.)

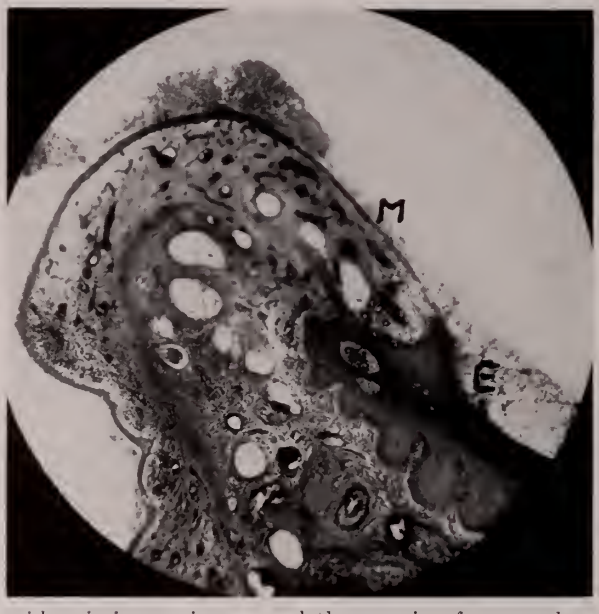

FIG. 2B. The epidermis is growing around the margin of a granulomatous polyp replacing the unhealthy mucous membrane lining. E represents epidermis; and M, mucous membrane. (Courtesy Arch. Otolaryng., Druss, J. G., April, 1933.)

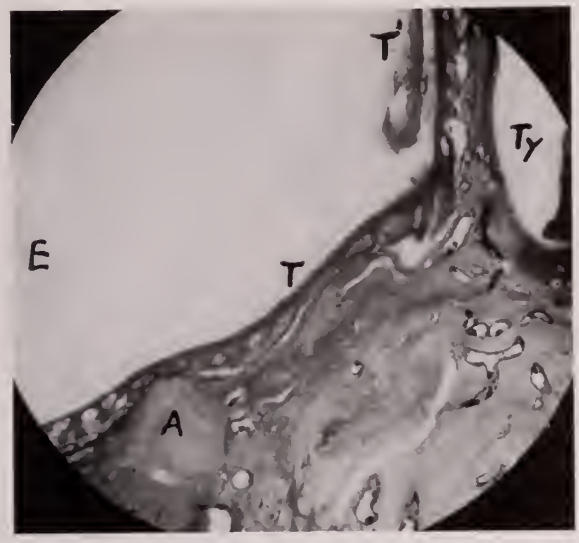

FIG. 3. Displacement of the tympanic membrane by cholesteatoma. The lower part of tympanic membrane has become bound down to the floor of the tympanum and a secondary tympanic membrane has been formed at a site medial to the original one. A represents annulus of tympanic membrane; E, external auditory canal; T, tympanic membrane and Ty, tympanic cavity. (Courtesy Arch. Otolaryng., Druss, J. G., April, 1933.)

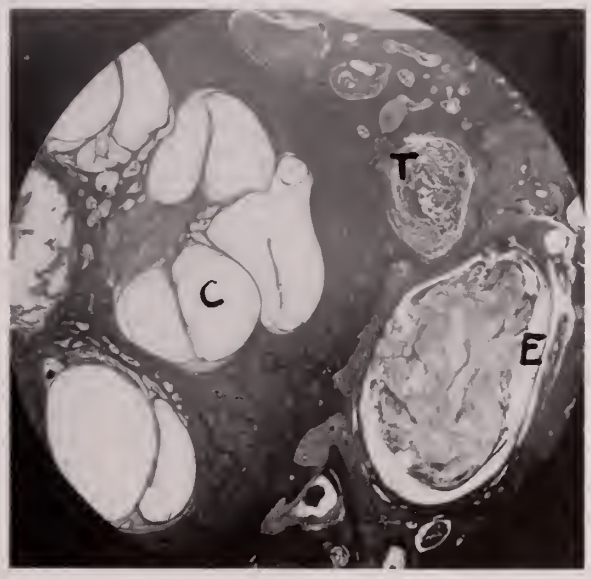

FIG. 4. Section through the cochlea showing cholesteatoma in the eustachian tube. C represents cochlea; E, eustachian tube with cholesteatoma and T, tensor tympani muscle.

side elements than it originally had; and it is the same principle that is utilized when a skin flap is turned in during a radical mastoidectomy. Under favorable conditions after the epidermis has lined the middle ear cavity, the inflamed underlying subepidermal connective tissue begins to contract down and healing takes place. However, under less favorable conditions, where the infection persists, the subepidermal connective tissue with its rich blood supply becomes activated and gradually erodes the adjacent bone and other vital structures. At the same time the epithelial layer continues to desquamate and to produce the typical concentric lamellas of the cholesteatoma. Occasionally, on histologic examination, the epidermal tissue itself can be seen to proliferate in the form of fingerlike projections and invade the underlying structures. Clinically, the picture observed in this type of cholesteatoma is that of an extensive destruction of the tympanic membrane and in advanced cases of the malleus and incus as well.

The second type of cholesteatoma, that associated with attic or marginal perforations, is poorly understood and often mismanaged. It has been stated that cholesteatoma is associated in about 90% of the cases with perforations of this kind.

Three main theories have been offered to explain the formation of this type of cholesteatoma:

1. The primary or neoplastic theory—The cholesteatoma arises from congenitally misplaced epidermal cells in the attic region (sponsored by McKenzie) (4) (Fig. 5).

2. The metaplastic theory—The mucosal epithelium of the middle ear under the influence of chronic suppuration undergoes biologic changes and takes on

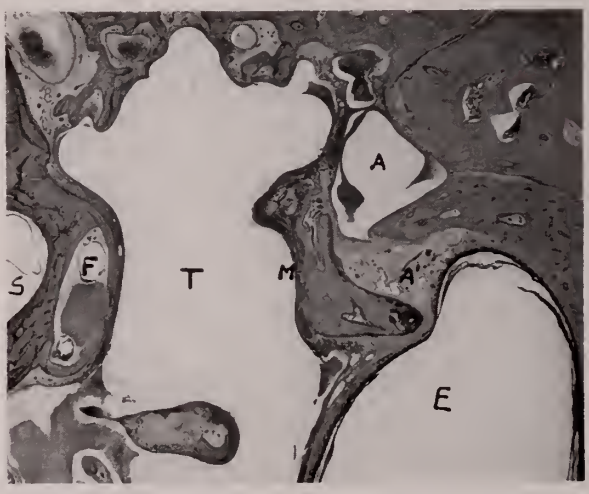

Fig. 5. Section through the tympanum showing presence of fibrous tissue in the attic. The remnants of embryonal tissue are not infrequently seen at this site in the adult temporal bone. A represents attic with fibrous tissue A'; E, external auditory canal; F, the facial nerve; M, the malleus with short process; T, tympanum and S, semicircular canal, external.

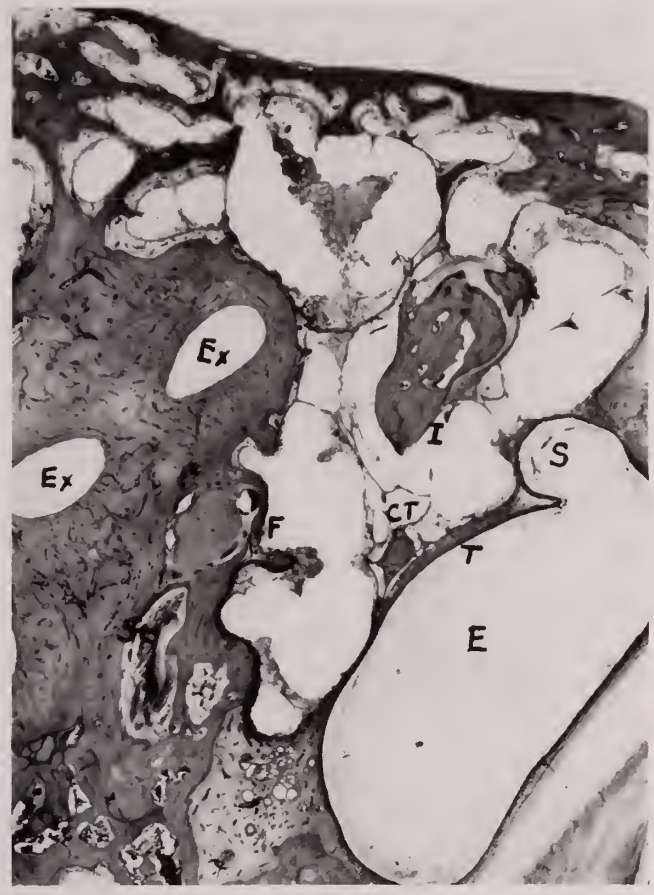

FIG. 6. Section through the antrum showing marked invagination inward of Shrapnell's portion of tympanic membrane at S. If this process continues, rupture of tympanic membrane at this site will probably take place. CT represents chorda tympani nerve; E, external auditory canal; Ex, external semicircular canal; F, Fallopian canal; I, incus; St, stapedeus muscle; and T, tympanic membrane.

the characteristics of squamous epithelium. The desquamative inflammatory reaction results in the formation of a cholesteatoma. This was first introduced by Wendt in 1873 (5).

3. The ingrowth or migration theory—The epidermis from the external canal extends into the attic to line the cavity (Fig. 6). Bezold (3) and Politzer (6) et al.

Of these three theories, the third or ingrowth theory received greatest acceptance.

In a paper, "The Role Which the Epidermis Plays in Suppurations of the Middle Ear", published in the Archives of Otolaryngology in 1933 (7), I presented histologic data in support of the ingrowth theory. A number of cases were reported therein which demonstrated quite clearly the process of sinking in of Shrapnell's membrane into the attic or Prussacks space as the possible beginning

or forerunner of cholesteatoma formation in this region. It was my contention at that time that this inward dimpling of Shrapnell's progressed and gradually continued until rupture of the drum membrane finally occurred. The cause for this peculiar inpouching of Shrapnell's could not be determined then and is not definitely known now. It has been suggested by Bezold (3) and later by Lederer (8), Day (9) and others, that it is due to a previous sealing off of the eustachian

FIG. 7. Section through the attic showing perforation of tympanic membrane at A with ingrowth of epidermis and cholesteatoma formation. C represents cholesteatoma; E, external auditory canal; F, facial nerve; I, incus; M, malleus; S, semicircular canal, external; S′, semicircular canal, posterior and T, tympanic membrane. (Courtesy Arch. Otolaryng., Druss, J. G., April, 1933.)

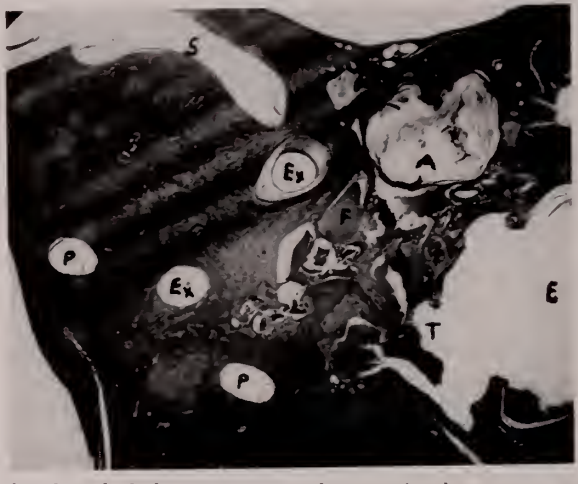

FIG. 8. A well developed cholesteatoma can be seen in the antrum at A. E represents external auditory canal; Ex, external semicircular canal; F, facial nerve; P, posterior semicircular canal; S, superior semicircular canal; T, tympanic cavity with perforation in the tympanic membrane. (Courtesy Arch. Otolaryng. Druss, J. G., April, 1933.)

tube or of the attic from the middle ear by means of traversing fibrous tissue bands, these bands having resulted from latent inflammation of the middle ear in the past. When the attic is thus separated from the middle ear, the air within the attic is gradually resorbed and is replaced by a transudate. The negative pressure that is produced within the attic results in a sucking in of the thin Shrapnell's membrane just above the short process. This is aided by the fact that Shrapnell's membrane lacks the dense middle connective tissue layer present in the pars tensor portion of the tympanic membrane. This cul de sac or pronounced retraction in Shrapnell's area is not infrequently seen clinically on otological examination. It is obvious that as the negative pressure persists, rupture of the drum will finally take place. The epitympanic cavity becomes secondarily infected and begins to discharge. The epidermis now has an opportunity to grow in around the margins of the perforation, replacing the inflamed mucosa, and to line the cavity. A typical cholesteatoma with its lining matrix and desquamating epithelium is thus formed (Figs. 7 & 8). The cholesteatoma may gradually increase in size, occupy the entire tympanic and mastoid cavities or even invade the intracranial contents, destroying in its path the preexisting connective tissue bands and adjacent bony structures. All this is accomplished in a manner quite similar to that previously outlined with the first type of cholesteatoma (Fig. 9).

The ingrowth of epidermis is not always preceded by the formation of a cul de sac in Shrapnell's membrane. It may occur with a relatively flat Shrapnell's

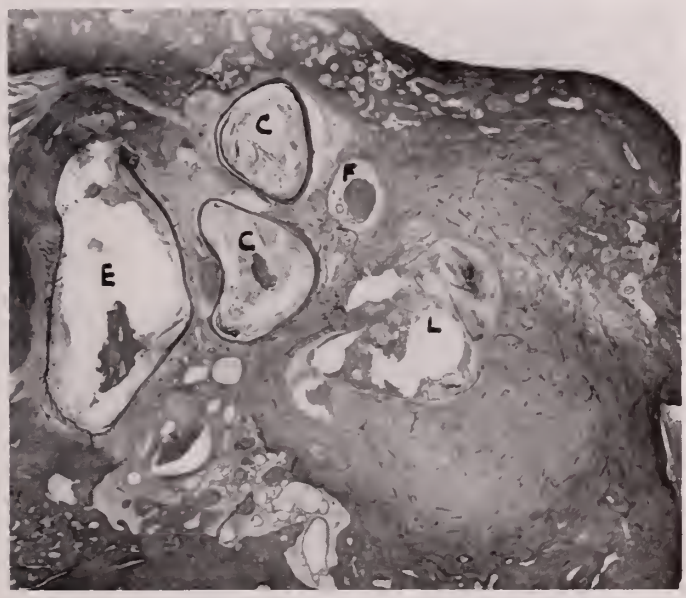

Fig. 9. Section through tympanum showing a cholesteatoma within, dividing into two portions. A diffuse purulent labyrinthitis secondary to the infection can be seen. C represents cholesteatoma; E, external auditory canal, F, facial nerve and L, labyrinth, purulent exudate within.

membrane. Here, for some unknown reason, the epidermal layer begins to proliferate and gradually infiltrates the subepidermal tissue as a solid column of cells (Fig. 10).

Of course, not in every instance of chronic middle ear suppuration with a perforation in Shrapnell's, does the epidermis invade the epitympanum; in some cases, the epidermis shows no tendency whatever to act in this manner (Fig. 11). It has been stated in the literature (8) that the anatomic prerequisite for the inward growth of the epidermis is not only the presence of a hyperplastic mucosa lining the epitympanic cavity, but also the presence of a restricted pneumatization of the temporal bone. In my opinion, while these conditions are most favorable for the growth of cholesteatoma, they are not absolutely essential. Cholesteatomata can and do occur in pneumatized temporal bones far more often

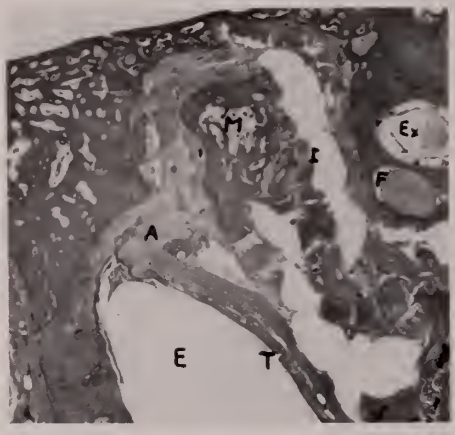

Fig. 10. The epidermal cells lining the external canal and tympanic membrane in the region of Shrapnell's are proliferating and are advancing in a finger-like projection into the attic A. E represents external auditory canal; Ex, external semicircular canal; F, facial nerve; I, incus; M, malleus; T, tympanic membrane.

Fig. 11. A granuloma G arising from Shrapnell's membrane. Note that the epidermis of the tympanic membrane does not line the granuloma. C represents chorda tympani nerve; E, external auditory canal; M, malleus and T, tympanic membrane.

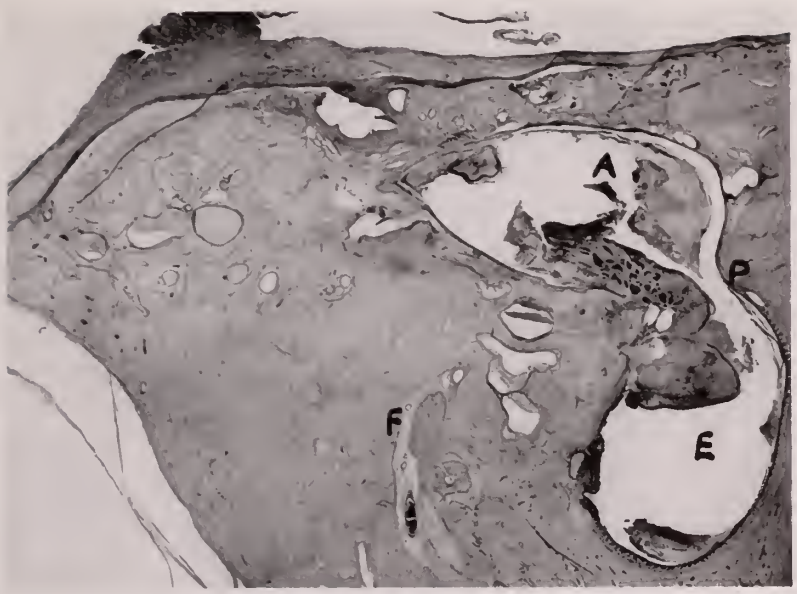

FIG. 12. The granuloma G has almost entirely occluded the perforation P in the attic region. A large cholesteatoma can be seen within the antral cavity. A represents antrum containing cholesteatoma; E, external auditory canal and F, facial nerve.

than is commonly believed. The writer has seen their formation both clinically and histologically in a number of relatively well pneumatized bones. Cases of this character have also been reported by Wittmaack, Bezold and others.

Diagnosis—A careful history of the aural symptoms, particularly of a discharge in the past, is most important. Not infrequently a simple mastoidectomy is undertaken because of a faulty history and during the operation a cholesteatoma is discovered. An accurate history would have established a diagnosis of an acute exacerbation of a chronic middle ear suppuration with every indication existing for a modified radical or a radical mastoidectomy.

In the examination of the ears, Shrapnell's area should be very carefully scrutinized for the presence of a perforation. A tiny perforation may be present at this site; it may be covered by a small granuloma or by a small crust, making it almost imperceptible to the examiner's eyes. The patient may have been unaware of discharge at any time. Nevertheless, in spite of this, a large cholesteatoma may exist that has eroded the ossicles and adjacent bone (Figs. 12 & 13). It has been suggested, in cases with perforation and questionable discharge, to keep for a period of 24 hours, a small pledget of cotton at the site of the perforation after thorough cleansing. If, at the end of that time, there is a fetid discharge on the cotton, one can assume that a cholesteatoma is present. The fetid odor commonly observed with cholesteatoma may disappear during an acute exacerbation. Hearing impairment may be so slight that the patient is unaware of it. Symptoms of labyrinthitis, facial paralysis or other intracranial complications may be present.

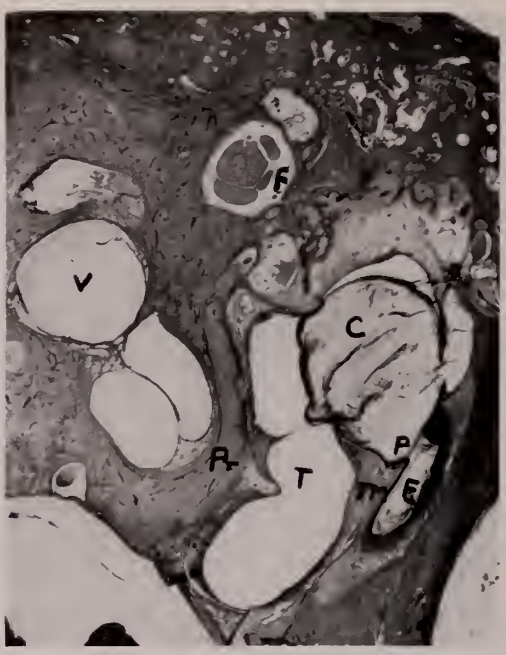

FIG. 13. Vertical section through the middle ear showing the presence of a fine fibrous tissue band sealing off the perforation in the tympanic membrane at P and concealing a large cholesteatoma within the tympanic cavity. C represents cholesteatoma; E, external auditory canal; F, facial nerve; Pr, promontory; T, tympanic cavity; TM, tympanic membrane and V, the vestibule.

X-ray examination is of considerable diagnostic value. It may show the presence of sclerosis in the bone and not infrequently outline a cholesteatomatous process. It should be made in every instance before operation is undertaken. Nevertheless, the x-ray examination may be entirely negative in a case in which there is extensive deep seated osseous destruction with or without cholesteatoma. It has been my experience to find cholesteatoma at operation in a number of instances which were not demonstrated on x-ray examinations made by very competent roentgenologists. One must not rely on x-ray findings as the sole guide to a correct diagnosis.

Prognosis—Cholesteatoma is a constant source of danger to life because of the insidious nature of its growth, because of its tendency to destroy bone and other contiguous structures, and to produce intracranial complications. The occurrence of an acute exacerbation in the presence of a cholesteatoma presents a more serious situation than that which is encountered with the usual mastoiditis. A cholesteatoma in the epitympanic region with a small perforation is more liable to be responsible for complications than a cholesteatoma located in other parts of the middle ear associated with large perforations (Fig. 14).

Indications for operation—Once a diagnosis of cholesteatoma of the middle ear has been established operative interference is generally indicated. A continuous foul smelling discharge which persists in spite of diligent local treatment with

or without cholesteatoma is indicative of necrosis of bone within the tympanum or mastoid. Cholesteatosis must be considered a menace to the life of the patient which can be removed safely only by operation. Moreover, in our present state of knowledge, we should not be content only with saving the life of the individual but we must realize that surgical intervention is also indicated as a means of preserving practical serviceable hearing or even improving the hearing.

Type of operation—In considering the type of operation required, the primary objective of the surgeon is to remove the source of danger to the patient, and then if possible, to conserve the hearing. Since it is almost impossible to predict before the operation the extent of the diseased process, the type of procedure to be done should be decided on only at the time of operation after the extent of the disease has been accurately determined. The surgeon should always be prepared to do the classical modified radical or the radical operation. In the event that the patient has good practical, serviceable hearing and the necrotic process has not involved the middle ear, a modified radical, the so-called Bondy procedure, is the operation of choice. This decision can usually be made after the antrum has been widely opened and the outer attic wall completely removed. The incus and head and neck of the malleus are then fully exposed to view. In the presence of extensive disease within the middle ear with little or no practical hearing a complete radical mastoidectomy is definitely indicated. If there is any

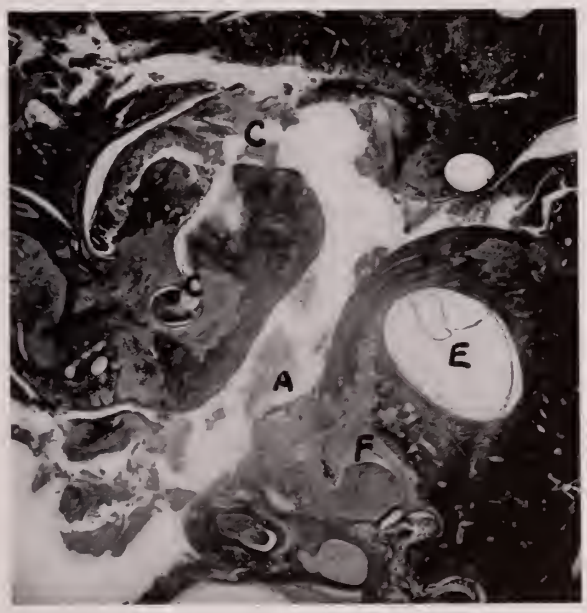

FIG. 14. Vertical section through the attic region showing the presence of necrosis of the ossicles by cholesteatomatous invasion. It is obvious that under such circumstances the ossicles cannot be preserved at operation and a radical mastoidectomy would be indicated. A represents matrix of cholesteatoma (epidermal lining); C, cholesteatoma; E, external semicircular canal; F, facial nerve and M, malleus. Note that the bony fallopian canal has been necrosed and the necrotic process is extending to the external semicircular canal with impending fistula formation.

question as to type of procedure to be used, it is safer to do a radical mastoidectomy. In performing the modified radical or radical mastoidectomy either the post auricular or the endaural approach will usually give satisfactory exposure. I believe that the otologist who has been trained in both approaches and has had experience with the fenestration operation technique, will prefer the endaural route. Whether a dental drill or an osteotome with mallet is used, is a matter of personal preference. The use of the Zeiss magnifying lenses also has been of inestimable value at operation. With their aid, the important structures can be identified more readily and are less liable to be injured.

The problem whether or not to remove the cholesteatomatous matrix during the operation has been a controversial one for many years. Some otologists (10, 11, 12) have favored its removal in every case, while others (13), on the other hand, have felt that under certain circumstances it is not only safe but it is advisable to leave the matrix untouched. In my report (7) published in 1933, histologic evidence was presented which demonstrated the potential dangers should the matrix of the cholesteatoma be left at the time of operation. Photomicrographs of cases then presented showed that though the inner tympanic wall had apparently been lined postoperatively by normal squamous epidermis, active bone necrosis with erosion of the fallopian canal and labyrinthine capsule was taking place beneath this epidermis. The mere presence of an epidermal lining does not negate the possibility that a pathological process is going on beneath it (Fig. 14). This pathological process apparently can take place not only as a result of pressure from a tightly packed cholesteatoma but also may occur even in the presence of a wide open wound in which drainage of exfoliated matter is adequately afforded. Thus there are undoubtedly factors other than pressure of the cholesteatoma which are responsible for the destruction of the underlying structures, such as biochemical or enzymatic action, presence of moisture, etc. Because of this innate biological activity of the cholesteatomatous matrix, I previously advocated and now still advocate the removal of the matrix wherever possible. Also, one should stress the importance of a continued follow up in all post radical and modified radical mastoidectomies during which the wound can be carefully inspected and the patient questioned for untoward symptoms.

In conclusion, the following points should be emphasized:

1. The otologist should be on the constant look-out for the presence of cholesteatoma.

2. The x-ray should not be relied upon as the sole means of making the diagnosis of bone necrosis.

3. Once the diagnosis is established, operative interference is usually indicated.

4. It is safer to remove the matrix of the cholesteatoma during the operation than to leave it undisturbed.

5. While elimination of the pathological process during operation is of primary importance, due consideration must be given to the question of restoration and preservation of hearing.

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A SURVEY OF CURRENT BACTERIAL SUSCEPTIBILITY TO ANTIMICROBIAL AGENTS

Comparison with Previous Surveys

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Selection of chemotherapeutic agents for the treatment of infections often poses considerable difficulty especially when such bacterial species as Staphylococci, Enterococci and the Coliform bacteria are involved, due to wide variations in antibiotic susceptibility among individual strains within these groups. Where time permits, this dilemma may be resolved by the performance of *in vitro* sensitivity tests. In acute or fulminating infections, however, prompt treatment is essential and any delay in instituting treatment to await laboratory reports might prove dangerous and invite disaster. In an attempt to establish a rational basis for the selection of the most promising antibiotics in such situations, the results observed with a large number of antibiotic sensitivity determinations recently performed in the Chemotherapy Laboratory upon different bacteria isolated from a variety of clinical sources have been compiled and tabulated with a view to ascertaining the proportion of strains of each bacterial specias currently amenable to the action of each available chemotherapeutic agent, thereby providing a guide for the selection of drugs most apt to prove efficacious in the treatment of specific infections.

The period under consideration covers one year and includes the last six months of 1956 and the first half of 1957. In addition, the present findings with respect to group antibiotic susceptibility were compared with those observed in previously undertaken surveys in order to determine whether or not any changes in the pattern of antibiotic susceptibility for any particular bacterial group had taken place during the intervening periods. No new procedural changes for the performance of sensitivity tests were instituted in the laboratory during the periods under comparison so that the findings are directly comparable.

METHOD

The procedure employed in this laboratory to test bacterial sensitivity to antibiotics is the tube-dilution method. The type and pH of the medium, preparation of standard antibiotic stock solutions, age and size of the inoculum, and the temperature and duration of incubation are all carefully controlled. Fresh veal extract broth, pH 7.2, is the medium. The test is performed in 2 ml. amounts, by adding 1 ml. of a 10^{-6} dilution of a six hour broth culture to a series of tubes containing varying concentrations of standard antibiotic in 1 ml. of broth. The end point is read after 18 hours incubation at 37° C. This is the first clear tube, indicating complete visual inhibition of growth, containing the

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least amount of drug. A growth control tube containing the test inoculum without antibiotic is used with each determination.

RESULTS

All bacterial strains inhibited by concentrations of standard antibiotic up to or less than 0.5 units of penicillin, 1 mcg of erythromycin, 5 mcgs of tetracycline 10 mcgs of chloramphenicol, 5 units of bacitracin, 5 mcgs of streptomycin, 5 mcgs of neomycin, 25 mcgs of nitrofurantoin, 20 mgm % of sulfonamides, 5 mcgs of novobiocin, 2 mcgs of oleandomycin and 5 mcgs of polymyxin per ml were classified as sensitive and those requiring larger amount to effect growth

TABLE I

Antibiotic Susceptibility of Gram Positive Microorganisms

		Staphylococcus aureus	Staphylococcus albus	Enterococcus	Pneumococcus	Beta Hemolytic Streptococcus	Streptococcus viridans
Penicillin	Total Tested	646	40	24	61	81	35
	# Sens.	389	32	2	60	80	30
	% Sens.	60.2	80.0	8.3	98.4	98.8	85.8
Erythromycin	Total Tested	696	45	467	57	83	33
	# Sens.	571	38	358	57	82	30
	% Sens.	82.0	84.4	76.7	100.0	98.8	90.9
Tetracycline	Total Tested	274	18	183	16	35	20
	# Sens.	139	13	45	15	31	18
	% Sens.	50.7	72.2	24.6	93.7	88.6	90.0
Chloramphenicol (Chloromycetin)	Total Tested	346	13	96	7	12	10
	# Sens.	261	11	84	7	11	10
	% Sens.	75.4	84.6	87.5	100.0	91.7	100.0
Bacitracin	Total Tested	49	3	4	0	0	2
	# Sens.	45	2	3	—	—	2
	% Sens.	91.8	66.7	75.0	—	—	100.0
Streptomycin	Total Tested	29	5	21	2	1	8
	# Sens.	15	5	3	2	1	7
	% Sens.	51.7	100.0	14.3	100.0	100.0	87.5
Neomycin	Total Tested	36	4	79	0	0	2
	# Sens.	35	4	78	—	—	1
	% Sens.	97.2	100.0	98.7	—	—	50.0
Nitrofurantoin (Furadantin)	Total Tested	22	2	429	0	0	1
	# Sens.	22	2	426	—	—	1
	% Sens.	100.0	100.0	99.3	—	—	100.0
Sulfonamides	Total Tested	20	1	19	1	0	0
	# Sens.	3	1	1	1	—	—
	% Sens.	15.0	100.0	5.3	100.0	—	—
Novobiocin	Total Tested	63	6	11	1	1	2
	# Sens.	51	5	0	1	1	1
	% Sens.	80.9	83.3	0.0	100.0	100.0	50.0
Oleandomycin	Total Tested	15	0	3	0	0	0
	# Sens.	12	—	1	—	—	—
	% Sens.	80.0	—	33.3	—	—	—

TABLE II

Antibiotic Susceptibility of Gram Negative Microorganisms

		E. Coli	Aero-bacter aero-genes	B. Proteus	B. pyo-cyaneus	Salmo-nella	B. Fried-lander	B. alkali-genes fecalis
Tetracycline	Total Tested	151	148	101	103	12	5	4
	# Sens.	89	48	5	25	11	2	3
	% Sens.	58.9	32.4	5.0	24.3	91.7	40.0	75.0
Chloramphenical (Chloromycetin)	Total Tested	395	391	314	269	13	6	7
	# Sens.	327	260	228	43	12	4	4
	% Sens.	82.8	66.5	72.6	16.0	92.3	66.7	57.1
Streptomycin	Total Tested	17	21	20	24	3	1	0
	# Sens.	12	5	10	7	2	0	—
	% Sens.	70.6	23.8	50.0	29.2	66.7	0.0	—
Neomycin	Total Tested	158	169	194	180	1	2	0
	# Sens.	154	168	180	153	1	2	—
	% Sens.	97.5	99.4	92.8	85.0	100.0	100.0	—
Nitrofurantoin (Furadantin)	Total Tested	369	383	296	212	12	5	7
	# Sens.	359	355	289	49	12	5	5
	% Sens.	97.3	92.7	97.6	23.1	100.0	100.0	71.4
Sulfonamides	Total Tested	13	21	12	18	4	0	1
	# Sens.	1	1	6	1	1	—	0
	% Sens.	7.7	4.8	50.0	5.6	25.0	—	0.0
Novobiocin	Total Tested	2	7	10	8	0	0	0
	# Sens.	0	0	3	0	—	—	—
	% Sens.	0.0	0.0	30.0	0.0	—	—	—
Polymyxin	Total Tested	11	26	22	59	0	0	0
	# Sens.	11	23	0	52	—	—	—
	% Sens.	100.0	88.5	0.0	88.1	—	—	—

inhibition as resistant. The proportion of strains of each bacterial species, both Gram positive and Gram negative, found sensitive to each antibiotic are contained in Tables I and II, respectively.

The relative effectiveness of different antibiotics against particular bacteria species are graded numerically in Table III, according to the following criteria:

1—Over 90 % of strains sensitive
2—76–90 % of strains sensitive
3—51–75 % of strains sensitive
4—25–50 % of strains sensitive
5—Less than 25 % of strains sensitive

Species in which less than five strains were tested against any antibiotic are not listed in the table. Utilization of this table as a guide for the selection of antibiotics most apt to prove effective against particular bacterial species may prove of service in attaining therapeutic success in the treatment of infections more certainly and more rapidly.

Considering possible changes in antibiotic susceptibility patterns over the course of years, relative sensitivities of a variety of bacteria to tetracycline and

TABLE III

Comparative Efficacy of Various Antibiotics Against Different Microorganisms in vitro

Organism	Penicillin	Erythromycin	Tetracycline	Chloramphenicol	Bacitracin	Streptomycin	Neomycin	Nitrofurantoin	Sulfonamides	Novobiocin	Polymyxin	Oleandomycin
Staphylococcus aureus	3*	2	4	3	1	3	1	1	5	2	—†	2
Staphylococcus albus	2	2	3	2	—	1	—	—	—	2	—	—
Enterococcus	5	2	5	2	—	5	1	1	5	5	—	—
Pneumococcus	1	1	1	1	—	—	—	—	—	—	—	—
Beta Hemolytic Streptococcus	1	1	2	1	—	—	—	—	—	—	—	—
Streptococcus viridans	2	1	2	1	—	2	—	—	—	—	—	—
E. coli	—	—	3	2	—	3	1	1	5	—	1	—
Aerobacter aerogenes	—	—	4	3	—	5	1	1	5	5	2	—
B. proteus	—	—	5	3	—	4	1	1	4	4	5	—
B. pyocyaneus	—	—	5	5	—	4	2	5	5	5	2	—
Salmonella	—	—	1	1	—	—	—	1	—	—	—	—
B. Friedlander	—	—	4	3	—	—	—	1	—	—	—	—
B. alkaligenes fecalis	—	—	—	3	—	—	—	3	—	—	—	—

* 1. Over 90% of strains sensitive 2. 76–90% sensitive 3. 51–75% sensitive 4. 25–50% sensitive 5. Less than 25% sensitive.

† Microorganisms with fewer than 5 strains tested against a particular antibiotic are not graded.

chloramphenicol in the years 1949–51 (1) are compared with those now being found, in Table IV. With respect to the tetracyclines, it is of interest to note that with the passage of time the proportion of strains found sensitive out of the total number tested has remained fairly constant with E. coli and B. proteus, has risen with B. pyocyaneus and the Salmonella, and has fallen significantly with Aerobacter aerogenes, Staphylococcus aureus and albus, and Enterococcus. Likewise the proportion of strains of E. coli, Aerobacter aerogenes, Salmonella and Enterococcus sensitive to chloramphenicol has remained fairly constant, has increased with B. proteus, B. pyocyaneus, Staphylococcus albus and has decreased with B. Friedlander and Staphylococcus aureus. By and large, strains of Streptococcus viridans, Beta Hemolytic Streptococcus and Pneumococcus have remained highly susceptible to both antibiotics with but very rare exceptions.

The proportion of strains of Staphylococcus aureus found sensitive to penicillin 1953 and 1954 (2) as compared to those isolated during the period covered by the present report is noted in Table V. From the table it may be observed that the percentage of strains proven sensitive to penicillin has remained relatively constant and appears to have become stabilized throughout the years investigated. This coincides with the experience of Needham and Nichols (3) who noted that following the initial period of increasing resistance to penicillin, the ratio of penicillin-resistant to penicillin-sensitive strains of staphylococci for a given institution finally stabilizes and remains relatively constant so that a

TABLE IV

Bacterial Susceptibility to Chlortetracycline and Chloramphenicol in 1949–1950–1951 and at Present

Organism	Chlortetracycline						Chloramphenicol					
	1949–1950–1951			1956–7*			1949–1950–1951			1956–7		
	Total Tested	# Sens.	% Sens.	Total Tested	# Sens.	% Sens.	Total Tested	# Sens.	% Sens.	Total Tested	# Sens.	% Sens.
Esch. coli	271	148	54.6	151	89	58.9	237	189	79.7	395	327	82.8
Aerobacter aerogenes	82	48	58.5	148	48	32.4	57	43	75.4	391	260	66.5
B. proteus	125	7	5.6	101	5	5.0	143	60	41.9	314	228	72.6
B. pyocyaneus	132	3	2.3	103	25	24.3	140	8	5.7	269	43	16.0
Salmonella	21	15	71.4	12	11	91.7	19	18	94.7	13	12	92.3
B. Friedlander	20	18	90.0	5	2	40.0	18	17	94.4	6	4	66.7
B. alkaligenes fecalis	18	11	61.1	4	3	75.0	16	8	50.0	7	4	57.1
Staphylococcus aureus	236	222	94.1	274	139	50.7	95	90	94.7	346	261	75.4
Staphylococcus albus	61	53	86.9	18	13	72.2	20	15	75.0	13	11	84.6
Enterococcus	164	95	57.9	183	45	24.6	171	154	90.1	96	84	87.5
Pneumococcus	32	32	100.0	16	15	93.7	7	7	100.0	7	7	100.0
Beta hemolytic streptococcus	67	67	100.0	35	31	88.6	13	13	100.0	12	11	91.7
Streptococcus viridans	107	104	97.2	20	18	90.0	31	30	96.8	10	10	100.0

* Organisms were tested for their sensitivity to tetracycline during this time. Since there is a high degree of cross resistance between chlortetracycline and tetracycline, results obtained with both are comparable.

TABLE V

Susceptibility of Staphylococcus Aureus to Penicillin in 1953–1954 and at Present

Year	Total Tested	# Sensitive	% Sensitive
1953	175	113	64.6
1954	330	215	65.1
1956–7	646	389	60.2

rough equilibrium between both is finally established. Our proportion of Staphylococcal strains sensitive to penicillin is somewhat higher than that reported in the literature (3–7). This may be due to technical reasons rather than represent an actual difference in experience since the tube-dilution method for performing sensitivity tests was employed exclusively for the series reported upon whereas the results obtained in most of the reports cited are based upon methods that utilized a solid medium technique, either partially or exclusively.

Present susceptibility of bacterial species to erythromycin as compared to the period 1953–1954 (8) is presented in Table VI. As may be observed from the table, although a high degree of sensitivity has been maintained by organisms within the recommended spectrum, some lessening in the percentage of strains sensitive to this antibiotic has been noted with Staphylococcus aureus and albus, Enterococcus and with Streptococcus viridans while all pneumococcal strains

TABLE VI

Bacterial Susceptibility to Erythromycin in 1953–1954 and at Present

Organism	1953–1954			1956–7		
	Total Tested	# Sens.	% Sens.	Total Tested	# Sens.	% Sens.
Staphylococcus aureus	559	509	91.1	696	571	82.0
Staphylococcus albus	79	76	96.2	45	38	84.4
Enterococcus	256	223	87.1	467	358	76.7
Pneumococcus	22	22	100.0	57	57	100.0
Beta hemolytic streptococcus	46	46	100.0	83	82	98.8
Streptococcus viridans	63	61	96.8	33	30	90.9

TABLE VII

Bacterial Susceptibility to Nitrofurantoin in 1953–1954 and at Present

Organism	1953–1954			1956–7		
	Total Tested	# Sens.	% Sens.	Total Tested	# Sens.	% Sens.
Esch. coli	281	278	98.9	369	359	97.3
Aerobacter aerogenes	223	223	100.0	383	355	92.7
B. proteus	237	237	100.0	296	289	97.6
B. pyocyaneus	101	45	45.6	212	49	23.1
B. Friedlander	3	3	100.0	5	5	100.0
B. alkaligenes fecalis	2	2	100.0	7	5	71.4
Staphylococcus aureus	6	6	100.0	22	22	100.0
Enterococcus	160	160	100.0	429	426	99.3
Salmonella	—	—	—	12	12	100.0

and all strains of Beta Hemolytic Streptococcus except 1 out of 83 strains tested have been found universally sensitive to erythromycin at the present time as they were during 1953 and 1954.

Finally, regarding nitrofurantoin, as may be seen in Table VII, with the exception of B. pyocyaneus and B. alkaligenes fecalis, all microbial species tested are currently highly sensitive to nitrofurantoin as they were in 1953–1954 (9). However, only 23.1 % of B. pyocyaneus strains are now susceptible to its action as compared to 45.6 % earlier and 71.4 % of strains of B. alkaligenes fecalis as compared to 100.0 % formerly. However, too few strains of the latter species were tested during both periods to draw any significant conclusions. In addition, whereas all of a large number of strains of Aerobacter aerogenes, B. proteus and Enterococcus were previously found to be universally susceptible to nitrofurantoin, 28 out of a total of 383 strains of Aerobacter aerogenes, 7 out of 296 strains of B. proteus and 3 out of 429 strains of Enterococcus are presently resistant to its antibiotic effect in the present survey.

SUMMARY

1. Results found with a large number of antibiotic sensitivity determinations performed on microorganisms isolated from a variety of clinical sources have

been compiled and tabulated in an effort to ascertain the proportion of strains of each microbial species currently sensitive to available chemotherapeutic agents.

2. Based upon the above data, antibiotics have been graded numerically in Table III according to their relative effectiveness against different bacterial species in order to provide a guide for the selection of antibiotics for the treatment of specific infections.

3. Current antibiotic sensitivity findings were compared with those observed in previously undertaken surveys in an effort to ascertain and note whether or not the pattern of antibiotic susceptibility of any bacterial groups had changed during the intervening periods.

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A METHOD OF ANALYZING ELECTROCARDIAC ENTITIES IN SPACE

III. The Electric Axis and Ventricular Gradient as Determined from the Twelve Lead Electrocardiogram

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We have seen that the spherical coordinates of a vector in space are readily extracted from its projections (1, 2). An ideal system of electrode placement displays equal lead vectors on mutually perpendicular axes. Until such a system is unanimously or "officially" adopted, it may be useful to examine the time-integrals of the cardiac cycle as obtained from the twelve-lead electrocardiogram. The ventricular gradient ($\overline{VG}$), electric axis ($\overline{QRS}$), and the angle subtended by these forces ($\overline{QRS}$-$\overline{VG}$ angle) were therefore determined in 49 normal subjects. Six females and forty-three males in an age range of 21 to 58 years were studied. All were asymptomatic. The presence of heart disease was excluded by history, physical examination, and fluoroscopy. Ballistocardiograms were taken on 38 subjects and were normal.

METHOD

The net area of PQRST (3) is measured by counting squares in leads I and II, and the frontal projection of the gradient determined on the triaxial frame (4). Only the upper edge of the tracing is considered, and a line joining the T-P segments before and after the complex is taken as the isoelectric level. The area above this is positive; that below, negative. In counting squares, it is useful to place the edge of a piece of paper on this line, as illustrated in figure 1a, which demonstrates the positive area in the second complex and the negative in the third. The value is that which would be obtained if the area of PQRST were measured algebraically in one sweep of a planimeter (3).

It is essential that the transverse component of the horizontal projection be equal to that of the frontal. The horizontal projection cannot therefore be obtained by vectorial summation of two precordial leads, as this condition would obtain only by coincidence. A combination of leads I and V_2 is also not feasible as the V_2 electrode is much nearer to the dipole-center than are the arms. The horizontal projection is therefore found by an indirect method. It is assumed that the precordial leads lie on a horizontal plane at the level of the dipole-center and that their axes are separated from the frontal plane by angular distances estimated to be $-15°$, 17°, 56°, 72°, 92°, and 124° for V_6 through V_1 respectively,

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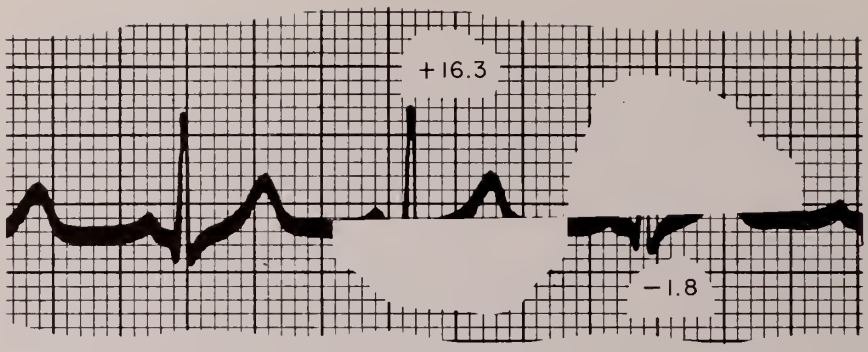

Fig. 1a

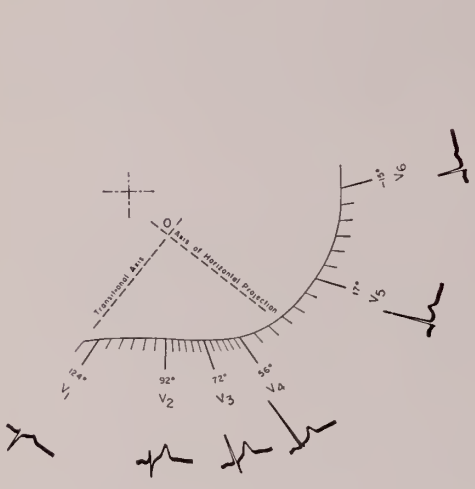

Fig. 1b

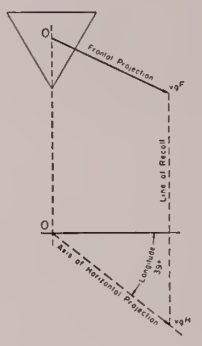

Fig. 1c

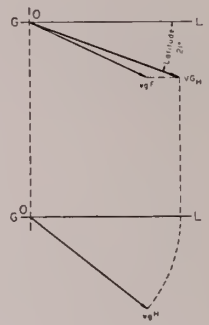

Fig. 1d

Fig. 1a. Measurement of areas for determination of the ventricular gradient. The area of PQRST is measured in a manner simulating that of planimetry. Only the upper edge of the tracing is considered, and the level of the T-P interval is taken as the isoelectric line. It is useful to place the edge of a piece of paper on this line. Areas above it are positive; those below are negative. The positive area is shown in the second complex; the negative in the third.

Fig. 1b. Determination of the axis of the horizontal projection. The horizontal projection is perpendicular to that axis on the horizontal plane on which its derivative is equal to zero. The precordial leads are therefore examined to determine the axis on which the area of PQRST equals zero. This is the transitional axis, and the axis of the horizontal projection is drawn perpendicularly to it.

Fig. 1c. Determination of the terminus of the horizontal projection. The areas of PQRST are measured in leads I and II, and the frontal projection determined in the usual manner. The line of recall is then dropped from its terminus (vg^F) to the axis of the horizontal projection. The point of intersection is the terminus of the horizontal projection (vg^H).

Fig. 1d. Latitude and magnitude are then determined by revolution. In practice the entire procedure is conveniently performed on the chart of the orthovectorcardiogram (1). The illustration is included for purposes of exposition.

FIG. 2. Having determined the spherical coordinates of the gradient, it is represented by a spot on the surface of a sphere.

as shown in figure 1b. These values were obtained by drawing the fifth interspace chest perimeter of a normal subject and positioning the dipole-center to the left of the mid-sagittal line by 9.4% of the thorax width and anterior to a line joining the mid-axillary points by 14.8% of the thorax depth (5). The transitional axis is determined. For our purpose it is considered to be that axis on which the net area of PQRST is equal to zero. It is possible to divide the angular distances between adjacent leads into six divisions with reasonable accuracy. Thus in the V_1–V_2 interval, the axis may be estimated to lie midway between the leads, to the left or right of midway, to the left of V_1, or to the right of V_2. Differences in lead vectors precludes exact interpolation. As the derivative of the horizontal projection on the transitional axis is zero, or a point, the horizontal projection is obviously perpendicular to this axis, and a perpendicular is therefore drawn, as in figure 1b. It is the axis of the horizontal projection and supplies the longitude of the gradient, which in the figure is 39°. To mark the terminus, vg^H, of the horizontal projection, the line of recall (1) is dropped from the terminus, vg^F, of the frontal projection, as in figure 1c. Latitude and magnitude are then obtained by revolution, as in figure 1d. In this case the former is 21°, and the axis is represented by a point in figure 2. $\overline{QRS}$ is determined in a similar manner.

RESULTS

The results are listed in Table I and graphically presented in figure 3. The spherical surface is most suitable for the application of statistical techniques to groups of spatial axes. To determine the angular deviation of, for example, a gradient axis from the mean gradient axis of the series, the arc distance between the points representing these axes is measured with a pair of dividers. The value, along with those of the remainder of the series, is then subjected to the usual statistical techniques.

TABLE I

		Mean	Mean Deviation	Standard Deviation	Range	Range of Deviation (from mean)
$\overline{QRS}$	Magnitude in microvolt-seconds	22.0	8.4	10.0	4.8 to 51.2	0.8 to 29.6
	Axis	Longitude −18° Latitude 46°	23°	26°	97° (solid angle)	2° to 55°
$\overline{VG}$	Magnitude in microvolt-seconds	54.0	14.0	18.4	16.8 to 118.8	0.4 to 64.8
	Axis	Longitude 23° Latitude 38°	20°	22°	81° (solid angle)	3° to 47°
$\overline{QRS}$-$\overline{VG}$ angle	Magnitude	32°	13°	16°	8° to 74°	1° to 42°
	Bearing	NW88°				

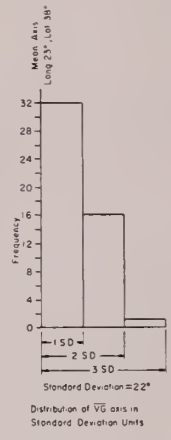

Fig. 3a

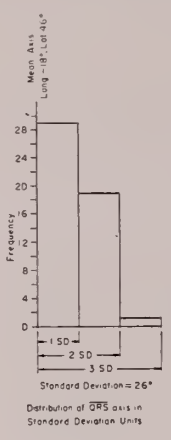

Fig. 3b

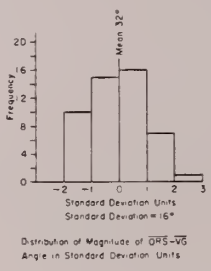

Fig. 3c

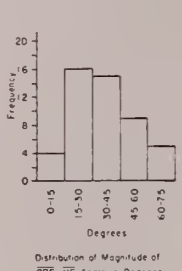

Fig. 3d

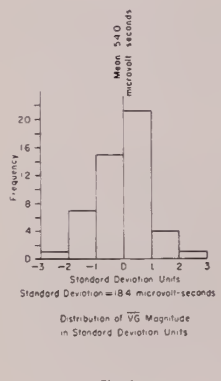

Fig. 3e

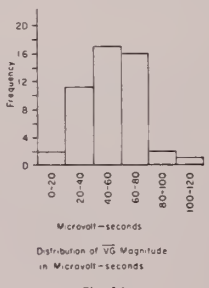

Fig. 3f

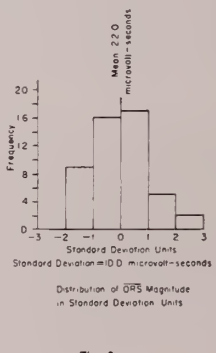

Fig. 3g

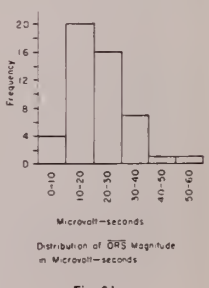

Fig. 3h

FIG. 3

FIG. 4. Ventricular gradients of 49 normal subjects. The star is at the mean axis. The circles centered on it have radii of 1, 2, and 3 standard deviations. The standard deviation equals 22°. The area of each spot is proportionate to the magnitude of the vector it represents. The posterior hemisphere is shaded.

FIG. 5. $\overline{QRS}$ vectors of 49 normal subjects. The triangle is at the mean axis. Standard deviation equals 26°.

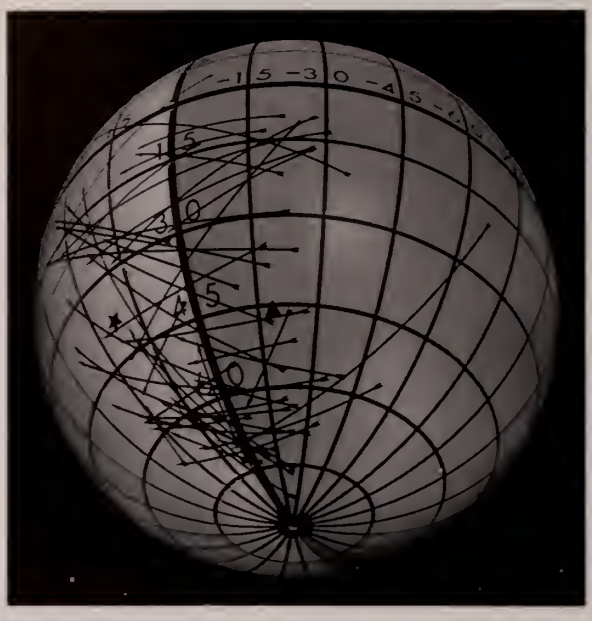

FIG. 6. $\overline{QRS}$-$\overline{VG}$ angle in 49 normal subjects. Each subject is assigned an arrow. Its tail is at the $\overline{QRS}$ position; its head, at the $\overline{VG}$ position. Its length equals the angular distance between the forces. As it has magnitude, direction, and sense, it may be taken as a vector on a spherical surface. The mean $\overline{QRS}$-$\overline{VG}$ angle equals 32° and bears NW88°, or N8°; W41°.

The angular deviation of the gradient axes from the mean gradient axis is charted in standard deviation units in figure 3a. This differs from the usual type of standard deviation histogram, such as that of figure 3c, in that all values are positive. It is, of course, drawn on a flat surface. An interesting and useful spatial counterpart may be displayed on a spherical surface. This is shown in figure 4, which presents the 49 gradients. Here the area of the spots is proportionate to magnitude. The posterior hemisphere is shaded. The mean axis is represented by a star, and the concentric circles have radii of 1, 2 and 3 standard deviations (22°), respectively. The $\overline{QRS}$ vectors are similarly illustrated in figure 5, in which the mean axis is represented by a triangle.

The $\overline{QRS}$-$\overline{VG}$ angles are presented in figure 6. Each subject is assigned an arrow. The tail of the arrow is at the $\overline{QRS}$ position, and the head at the $\overline{VG}$ position. The length is an arc distance equal to the magnitude of the subtended angle, and the orientation is the bearing of $\overline{VG}$ from $\overline{QRS}$. The arrow may be considered to represent the vector of the $\overline{QRS}$-$\overline{VG}$ angle (angular distance); it has magnitude, direction, and sense. It bears NW in 31 instances, SW in 16, NE in 1, and N in 1.

DISCUSSION

If the precordial leads lay on a horizontal plane through the dipole-center, the derivative of a vector on a precordial axis would equal the derivative of its horizontal projection on that axis. As these leads do not lie on such a plane, a

source of error is introduced. This could be overcome by determining the transverse level of the dipole-center by the method of Frank (5) and positioning the electrodes at this level. The nature of the Burger triangle (6) and its backwards tilt (7) have not been considered.

SUMMARY

1. A method of determining the ventricular gradient ($\overline{VG}$), electric axis ($\overline{QRS}$), and $\overline{QRS}$-$\overline{VG}$ angle from the twelve lead electrocardiogram is presented.

2. These are obtained in 49 normal subjects.

3. The spherical coordinates of the mean ventricular gradient are: magnitude 54.0 micro-volt seconds; longitude 23°; latitude 38°. Those of $\overline{QRS}$ are: magnitude 22.0 microvolt-seconds; longitude −18°; latitude 46°. The mean $\overline{QRS}$-$\overline{VG}$ angle is 32° and bears NW88°.

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ADDENDUM

A Rapid Method of Determining Space-Polar Coordinates

A method of determining the spherical coordinates (magnitude, azimuth and elevation) of vectors in space has recently been advanced (1–4). It has further been demonstrated that a spatial axis may be represented by a point on the surface of a sphere (2–4). The angular distances between this point and the cardinal planes and axes may then be measured with a pair of dividers or a calibrated meridian. It is intended here to present a method of rapidly determining these angles on paper and to propose criteria of range and polarity.

There are three cardinal planes: the frontal (F), the horizontal (H), and the sagittal (S). There are three cardinal axes: the transverse (X), the vertical (Y), and the sagittal (Z). The angles subtended by a vector with these coordinates of reference shall be annotated as $<$F, $<$H, $<$S, $<$X, $<$Y, and $<$Z, respectively. The determination of $<$H has already been presented (1–4). For reasons that will become apparent it shall be repeated here. An acquaintance with the principles by which spatial entities are represented by and visualized from their projections is requisite to a proper understanding of the exposition that follows.

The interested reader who lacks this qualification is referred to Part I of this Series (3).

METHOD

Let us assume the vector $\overline{OM}$ with frontal projection Om^F and horizontal projection Om^H as in figure 1a. Vector $\overline{OM}$ is shown pictorially in figure 1b. If a plane be passed between the vector and its horizontal projection, this plane, MOm^H, is perpendicular to the horizontal plane and is called a horizontal projecting plane. It may be revolved into the frontal plane, on which it is represented in figure 1b as M_HOm_H. OM_H is then the true length of the vector and $<M_HOm_H$ is the angle it subtends with the horizontal plane ($<H$), as these have not changed during the revolution. To perform the revolution orthographically, an arc centered at 0 is drawn from m^H to the ground-line, and at the point of intersection a perpendicular is erected to the altitude of m^F, as in figure 1c. M_H then represents the position of the vector terminus, M, after its revolution. As it is determined by revolution of a horizontal projecting plane and supplies the angle with the horizontal plane, it has been termed the *horizontal revolute* (1–3).

The revolution may conveniently be performed on the polar coordinate chart of figure 1d. The projections are obtained oscilloscopically in the case of instantaneous vectors or by areal measurements of components in the case of mean vectors, or time integrals. They are then positioned on the chart, the revolution is performed, and the horizontal revolute, M_H, annotated as a point. $<H$ is its angular distance from the line of abscissa and ranges from 0° to ±90°. As the Y axis is perpendicular to the horizontal plane, $<Y$ is the complement of $<H$. It is therefore equal to the angular distance of the horizontal revolute from the line of ordinate. Inferiorly oriented vectors subtend positive angles; superiorly oriented vectors, negative angles with both the horizontal plane and the Y axis. In figure 1d $<H = -17°$ and $<Y = -73°$.

Every vector has three projecting planes: the horizontal, frontal and sagittal. These intersect on the axis of the vector, as in figure 2a. The frontal projecting plane extends between the vector and its frontal projection and is perpendicular to the frontal plane; the sagittal projecting plane extends between the vector and its sagittal projection. To obtain $<F$, the angular distance from the frontal plane, the frontal projecting plane is revolved into the horizontal plane, as in figures 2b and 2c.

In this case M_F is obtained by revolution of a frontal projecting plane and furnishes the angle with the frontal plane. It may therefore be called the frontal revolute and is shown on the chart of figure 2d. $<F$ ranges from 0° to ±90° and is measured from the line of abscissa. As the Z axis is perpendicular to the frontal plane, $<Z$ is complementary to $<F$ and is measured from the line of ordinate. Both $<F$ and $<Z$ are positive in the case of anteriorly directed vectors and negative in that of posteriorly directed vectors. In this case $<F = 44°$, and $<Z = 46°$.

To determine $<S$, the sagittal projecting plane is revolved into the frontal plane. The sagittal projection is obtained from the frontal and horizontal in

figure 3a. In this case it is viewed from the subject's right, but a view from the left does not affect the construction, which is shown pictorially in figure 3b, and orthographically in figure 3c. M_S is the sagittal revolute. Its angular distance from the line of ordinate in figure 3d is equal to $<S$. As the X axis is perpendicular to the sagittal plane, $<X$ is the complement of $<S$ and is measured from the

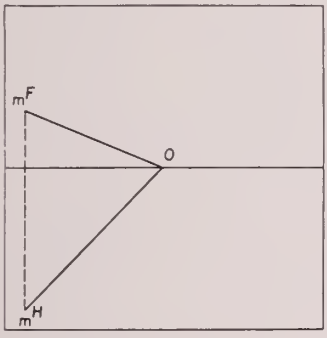

Fig. 1a

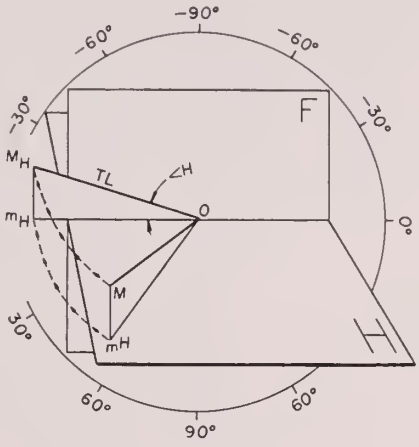

Fig. 1b

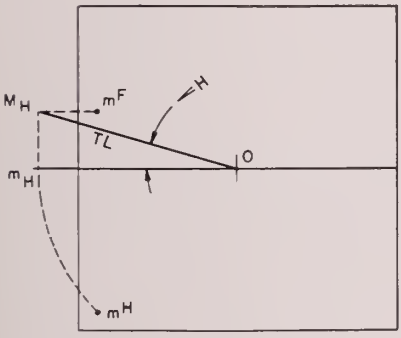

Fig. 1c

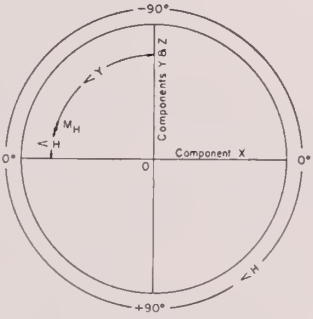

Fig. 1d

FIG. 1a. Orthographic representation of vector $\overline{OM}$.

FIG. 1b. Vector $\overline{OM}$ shown pictorially. The plane subtended by the vector and its horizontal projection, Om^H, is perpendicular to the horizontal plane and is called a horizontal projecting plane. When revolved into the frontal plane, the polar coordinates of the vector terminus, M, on the horizontal projecting plane appear on the frontal plane. These are its true length (TL), or magnitude (M°), and $<H$. M_H, the position of the vector terminus after revolution, is called the horizontal revolute.

FIG. 1c. The revolution is performed orthographically. An arc of radius Om^H is drawn to the ground-line (intersection of frontal and horizontal planes) and a perpendicular erected to the altitude of m^F.

FIG. 1d. The revolution can be performed on a polar coordinate chart, and the position of M_H noted. $<H$ then equals the angular distance of M_H from the line of abscissa. Angles below this line are positive; those above, negative. $<Y$ is the complement of $<H$ and is measured from the line of ordinate. It bears the same polarity as $<H$. The dial applies only to $<H$.

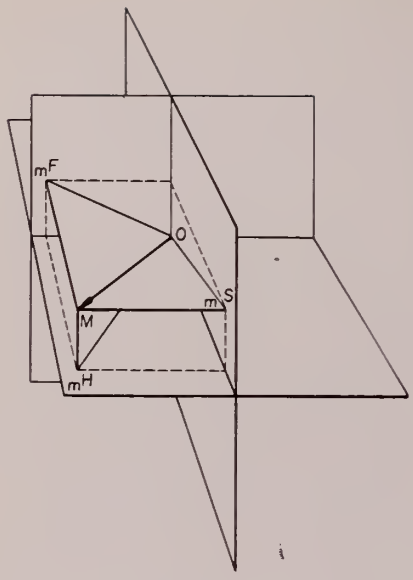

Fig. 2a

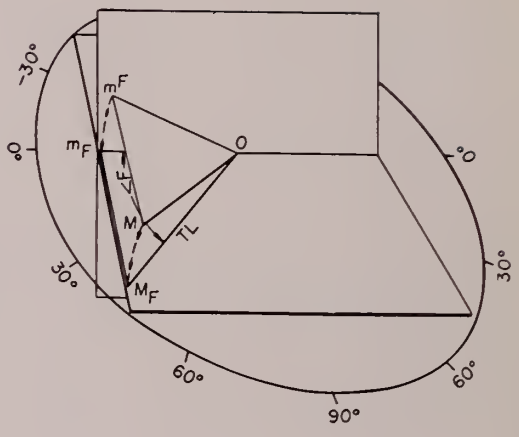

Fig. 2b

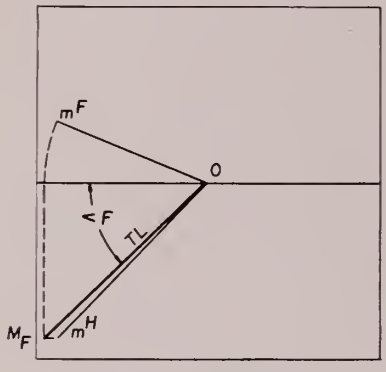

Fig. 2c

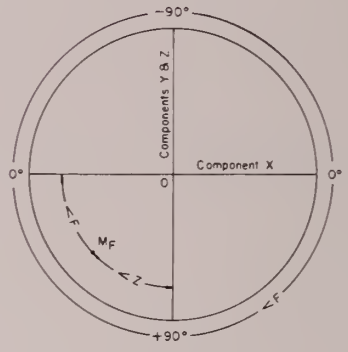

Fig. 2d

Fig. 2a. Six principal planes intersect on the axis of a vector. Three of these are illustrated; the horizontal, frontal, and sagittal projecting planes. The frontal projecting plane extends between the vector and its frontal projection and is perpendicular to the frontal plane; the sagittal projecting plane extends between the vector and its sagittal projection and is perpendicular to the sagittal plane. The planes subtended by the vector and the three cardinal axes, X, Y, and Z, are not shown.

Fig. 2b. To determine $<F$, the frontal projecting plane is revolved into the horizontal plane. The final position of the vector terminus is now termed the frontal revolute (M_F). $<F$ is the angle between OM_F and the frontal plane as measured against the dial on the horizontal plane. TL has the same value as in Figure 1.

Fig. 2c. Orthographic revolution of frontal projecting plane. An arc of radius Om^F is drawn to the ground-line, and a perpendicular erected to the distance of m^H from the ground-line.

Fig. 2d. After positioning M_F, the frontal revolute, on the polar-coordinate chart, $<F$ equals the angular distance of M_F from the line of abscissa. $<Z$ is the complement of $<F$, bears its polarity and is measured from the line of ordinate. The dial applies only to $<F$.

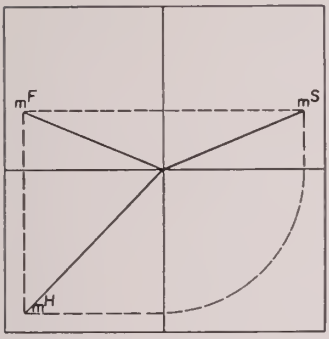

Fig. 3a

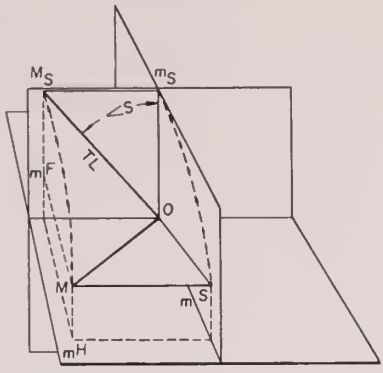

Fig. 3b

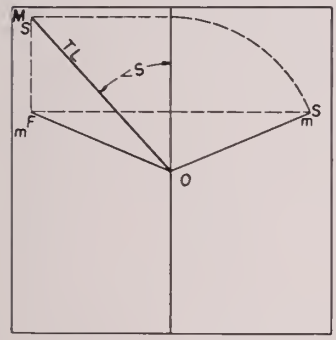

Fig. 3c

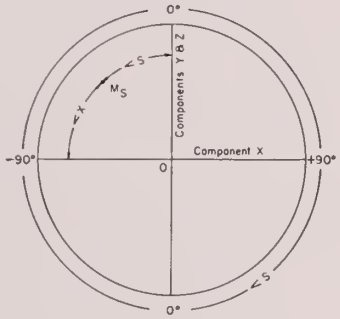

Fig. 3d

FIG. 3a. The sagittal projection, m^S, is derived from the frontal and horizontal.

FIG. 3b. $<S$ is obtained by revolution of the sagittal projecting plane, OMm^S, into the frontal plane. M_S is the sagittal revolute.

FIG. 3c. Orthographic revolution of the sagittal projecting plane. An arc of radius Om^S is drawn to the line of ordinate, which represents the intersection of the frontal and sagittal planes. A perpendicular is then drawn to the distance of m^F from the line of ordinate.

FIG. 3d. After performing the revolution on the polar-coordinate chart, $<S$ is the angular distance of the sagittal revolute, M_S, from the line of ordinate. Angles to the left are positive; those to the right, negative. $<X$ is the complement of $<S$, bears its polarity, and is measured from the line of abscissa. The dial applies only to $<S$.

line of abscissa. Both $<S$ and $<X$ range from 0° to $\pm 90°$ and are positive when the vector points to the left, negative when it points to the right.

The three revolutes can be obtained from two projections by use of a simple stratagem. Let us assume that M_H has been obtained from the frontal and horizontal projections. M_H and m^H are shown as points in figure 4a. The distance of the three revolutes from 0 is a constant as it equals the magnitude of the vector. M_F and M_S therefore lie on an arc through M_H. From figure 3b it is seen that the sagittal revolute and the horizontal projection are equidistant from the sagittal plane. M_S therefore lies on a parallel to the line of ordinate through m^H, and at the intersection of this parallel with the arc. In figures 2a, b, and c, the frontal

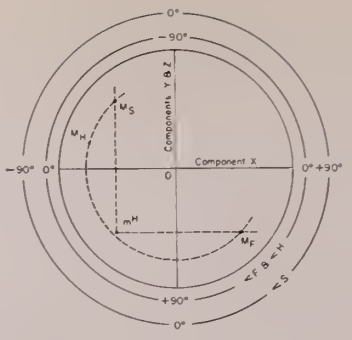

Fig. 4a

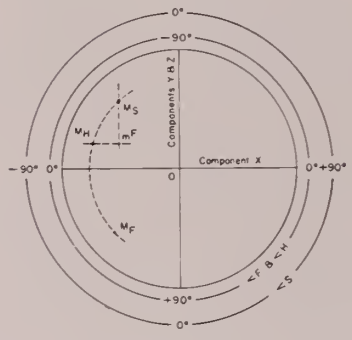

Fig. 4b

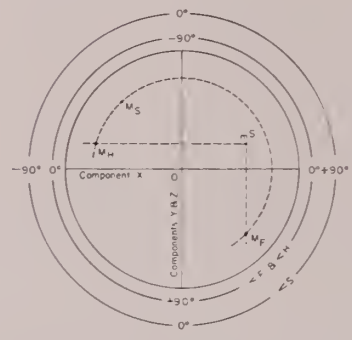

Fig. 4c

Fig. 4a. Scheme for rapid determination of angles X, Y, Z, F, H, and S starting with M_H, the horizontal revolute, and m^H, the horizontal projection. An arc is drawn through M_H. Its radius is equal to the magnitude of vector $\overline{OM}$. The three revolutes therefore lie on this arc. As the frontal revolute, M_F, and m^H are equidistant from the frontal plane, M_F will lie at the intersection of the arc and a parallel to the line of abscissa through m^H. As the sagittal revolute, M_S, and m^H are equidistant from the sagittal plane, M_S will lie at the intersection of the arc and a parallel to the line of ordinate through m^H.

Fig. 4b. Scheme starting with M_F, the frontal revolute, and m^F, the frontal projection. The arc is drawn through M_F. As m^F and M_S are equidistant from the sagittal plane, M_S will lie at the intersection of the arc and a parallel to the line of ordinate through m^F. As M_H and m^F are equidistant from the horizontal plane, M_H will lie at the intersection of the arc and a parallel to the line of abscissa through m^F.

Fig. 4c. Scheme starting with M_S, the sagittal revolute, and m^S, the sagittal projection. The arc is drawn through M_S. As M_H and m^S are equidistant from the horizontal plane, M_H will lie at the intersection of the arc and a parallel to the line of abscissa through m^S. As M_F and m^S are equidistant from the frontal plane, M_F will lie at the intersection of the arc and a parallel to the line of ordinate through m^S.

revolute and horizontal projection are equidistant from the frontal plane. M_F therefore lies at the intersection of the arc and a line through m^H parallel to the line of abscissa. Given m^F and M_F, the two remaining revolutes can be found, as in figure 4b. Given m^S and M_S, the remaining revolutes are found as in figure 4c.

Six principal planes intersect on the axis of a vector, the three projecting planes, which are shown in figure 2a, and the three planes subtended by the vector and and the cardinal axes. The polar coordinates of the vector terminus, M, on each of these planes are space-polar coordinates. Thus, on the horizontal projecting plane, these are magnitude (M°) and <H; on the frontal projecting plane, M° and <F, etc. In extra-medical fields, it is customary to refer to M° and <X, <Y, and <Z as coordinates of the space-polar coordinate system, although these are sometimes called spherical coordinates. The latter is, however, more applicable to the azimuth, elevation system as it is useful for annotating axes as points on the surface of a sphere (2, 4).

From the revolutions the following relationships can be derived:

$$<X = \cot^{-1} \frac{X}{\sqrt{Y^2 + Z^2}}$$

$$<Y = \cot^{-1} \frac{Y}{\sqrt{X^2 + Z^2}}$$

$$<Z = \cot^{-1} \frac{Z}{\sqrt{X^2 + Y^2}}$$

$$<F = \tan^{-1} \frac{Z}{\sqrt{X^2 + Y^2}}$$

$$<S = \tan^{-1} \frac{X}{\sqrt{Y^2 + Z^2}}$$

$$<H = \tan^{-1} \frac{Y}{\sqrt{X^2 + Z^2}}$$

These values should satisfy the equations:

$$(\cos <X)^2 + (\cos <Y)^2 + (\cos <Z)^2 = 1$$

$$(\sin <F)^2 + (\sin <H)^2 + (\sin <S)^2 = 1$$

The arithmetic sum of the six angles is, of course, 270° (three pairs of complements).

In our 49 normal subjects, the mean angles, X, Y, Z, S, H, and F, were found to be 49°, 44°, −78°, 41°, 46° and −12°, respectively, in the case of the electric axis, and 44°, 52°, 70°, 46°, 38°, and 20°, respectively, in the case of the ventricular gradient.

DISCUSSION

A point in space can only be fixed relative to pre-determined points, lines, or planes. It is natural and useful to elect the null-point and the cardinal planes and axes as coordinates of reference. Designation of range and polarity of angles is, however, arbitrary. As Einthoven has assigned positive values to manifest angles directed below the horizontal plane, this tradition has been expanded to its spatial expression, Einthoven's α is the frontal projection of $<$H. The latter has been given the polarity of its projection. When directed inferiorly, $<$H is therefore positive; when superiorly, negative.

Azimuth is the manifest angle on the horizontal plane. The Einthoven dial has been imposed on this plane and serves for azimuth (1–3). As this is the horizontal projection of $<$F, the polarity of $<$F has been chosen to correspond to that of azimuth. Anteriorly directed angles are therefore positive; posteriorly, negative.

The spatial angles have been given a range of 0° to ±90° rather than 0° to ±180° and are a measure of the acute angles subtended with the cardinal planes and axes. Adoption of the broader range would have introduced a source of misconception. Thus if $<$H were measured from the left half of the frontal plane and extended through ±180°, its value could alter drastically as a vector traversed the sagittal plane. This is illustrated in figure 5. The two vectors shown, $\overline{OA}$ and $\overline{OB}$, are near each other but separated by the sagittal plane. Both subtend equal angles with the horizontal plane, −15°, as seen on the inner dial. Were they measured from the left half of the horizontal plane, $<$H of one would be −15°, of the other, −165°, as seen on the outer dial. When we consider that the same considerations apply to the remaining angles, it becomes evident that employment of the broader range would readily lead to confusion, as angular coordinates

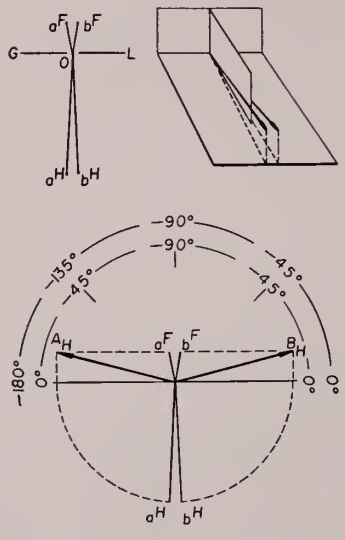

Fig. 5

that are widely dissimilar may represent vectors that lie in close proximity. Determination of angles X, Y and Z from the simple complementary relationships with angles S, H and F, respectively, would also be needlessly complicated. The adopted range is in addition preferable for statistical purposes. The mean of $-15°$ and $-15°$, for example, is $-15°$, whereas that of $-15°$ and $-165°$ is a misleading $-90°$.

It may be argued, with justification, that a range of $0°$ to $+180°$ for angles X, Y, and Z is to be preferred. The considerations demonstrated in figure 5 do not apply to these angles, and signs could be eliminated. Furthermore, statistical calculations would seem at first glance to be simplified. Thus angles X of vectors $\overline{OA}$ and $\overline{OB}$ are found to be $-87°$ and $+87°$, respectively, in the range adopted but the mean is $0°$. Reason tells us that the mean is $90°$, and this would be our value if the $0°$ to $+180°$ range were chosen. We need only remember, however, that $<X$ is the complement of $<S$, and the mean $<X$ is therefore the complement of the mean $<S$. Angles S of $\overline{OA}$ and $\overline{OB}$ are $-3°$ and $+3°$, respectively. The mean is $0°$, and the complement of this, or mean $<X$ is $90°$, as expected. In using this scheme, therefore, the angle with the cardinal plane is first determined, and the angle with the corresponding cardinal axis is then assigned a complementary value. The need of additional dials is thus obviated and the simple complementary relationship maintained.

The use of Greek letters to symbolize coordinates has been avoided. These needlessly tax the memory and have been interchangeably employed in graphic descriptions of various spatial systems.

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AN UNUSUAL CASE OF ACUTE ESOPHAGITIS

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Esophageal lesions are becoming more easily recognized as techniques for their diagnosis are perfected, and their recognition is becoming more significant as means of therapy are developed.

This case is presented to demonstrate an unusual type of acute esophagitis which presented a diagnostic and therapeutic problem.

CASE REPORT

P. M., a 56 year old white male, was first admitted to the Medical Service of The Mount Sinai Hospital on April 15, 1954 with a chief complaint of nausea of one month's duration.

The patient admitted that during his adult life he indulged in a heavy intake of alcohol associated with a poor dietary intake. He had spent his youth in Puerto Rico, in an area endemic for Schistosoma mansoni. In 1939 he was told that he had syphilis and was treated with injections. At the completion of treatment his serological test for syphilis was negative. He denied jaundice, clay colored stools, dark urine, or exposure to hepatotoxins. One year prior to admission he observed the onset of loss of libido. One month prior to admission he developed nausea, vomiting of coffee-ground material, and passage of tarry stools. This ceased spontaneously after three days and was followed by ankle edema.

On admission, physical examination revealed a chronically ill appearing white male. The axillary hair was sparse and chest hair was absent. The pubic hair was of female distribution. There was no spider angiomata, gynecomastia, or testicular atrophy. The heart was slightly enlarged and presented a faint apical systolic murmur. The liver edge was felt three finger breadths below the right costal margin. No ascites was present. There was four plus pitting edema of the ankles. Neurological examination was normal.

Laboratory examination revealed the hemoglobin to be 7.5 gm. per 100 ml. and a normal white blood cell count. Urinalysis, blood urea nitrogen, and fasting blood sugar, serum bilirubin and cholesterol were normal. Alkaline phosphatase was 26.5 units, cephalin cholesterol flocculation was negative, and the total protein was 6.6 gm. per cent (albumin, 3.3 gm. per cent; globulin, 3.3 gm. per cent). BSP retention in 45 minutes was 16 per cent. Blood Wassermann was negative. Stool quaiacs were negative for occult blood. Rectal biopsy revealed no schistosoma ova.

Gastrointestinal x-rays showed esophageal varices with normal filling of the upper esophagus. Chest x-ray demonstrated faint apical densities.

The patient received 500 cc. of whole blood and was given a high protein, high carbohydrate diet, and iron therapy.

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He was discharged on May 3, 1954 with a diagnosis of Laennec's cirrhosis and esophageal varices. Thereafter he resumed his previous habits of heavy alcoholic intake and inadequate diet. He did well, however, except for intermittent ankle edema.

One day prior to the patient's second admission he became nauseated after drinking several glasses of beer. On January 19, 1957 he passed several tarry stools and came to the emergency room.

He appeared to be an acutely and chronically ill white man. During the examination the patient regurgitated 500 cc. of dark red blood and collapsed. His blood pressure was 50 0; his pulse was 100 per minute. The physical examination was unchanged from the previous examination in 1954. The patient was immediately intubated with a Sengstaken tube, and the shock was treated with plasma expanders and whole blood. Several minutes after the onset of therapy the blood pressure was 110 70 and the patient appeared to be out of shock.

On the morning after the day of admission, it was observed that the Sengstaken tube had been regurgitated, and the gastric balloon was lodged in the esophagus. The tube was removed and the bleeding did not recur.

The laboratory work revealed a hemoglobin ranging from 10 to 14 gm. per 100 ml. and a normal white blood count. Urinalysis was normal. Blood urea nitrogen, fasting blood sugar, and serum electrolytes were normal. Serum bilirubin ranged from 2.66 to 0.77 mg. per cent. Alkaline phosphatase was 25 units. Serum albumin was 3.0 gm. per cent and serum globulin was 3.4 gm. per cent. Cephalin cholesterol flocculation varied between 0 and 2 plus. BSP retention in 45 minutes was 18 per cent. The serologic test for syphilis gave a negative result.

On January 20, 1957 the trachea was observed to be shifted to the right, the temperature was 102° F., and chest x-ray revealed a right upper lobe pneumonia. Treatment with antibiotics was instituted and by February 2, 1957 the pneumonia had cleared.

In view of the fact that this was the second episode of bleeding from varices in this patient, and considering his relatively good parenchymal function, it was decided to evaluate the patient for a portal-caval shunt operation to relieve the portal hypertension.

Esophagram performed on February 1, 1957 revealed the following surprising findings. In the upper third of the esophagus there was a large intraluminal mass over which the mucosa appeared to be distorted and perhaps destroyed (Fig. 1). This indented the contour of the esophagus for a distance of approximately 15 cm., ending in the lower third of the esophagus. It was widest at its cephalad end and tapered irregularly down to its distal end. It appeared on the right side of the esophagus, but the left side of the esophagus was similarly indented although more irregularly. The middle third of the esophagus therefore was not as easily distended with barium or air as the more proximal or distal portions. There were also discrete, irregular filling defects seen in the lower half of the esophagus which gave the appearance of varices. In addition there was a pulsion type of hiatal hernia. Peristalsis was poor in the esophagus and a small amount of barium was retained at the cardio-esophageal junction for ten min-

utes. There was no evidence of reflux of barium from the stomach into the hernia or esophagus in the Trendelenburg position. The remainder of the stomach showed no evidence of intrinsic organic abnormality. The duodenal bulb was deformed at its apex, but no ulcer niche was seen. The appearance of the filling defect in the esophagus was suggestive of carcinoma.

On February 7, 1957 another esophagram again revealed this mass in the esophagus which gave the impression of a carcinoma.

On February 12, 1957 the patient began to complain of dysphagia and was unable to swallow solid food. On February 14, 1957 esophagoscopy revealed, at 25 cm. from the upper incisors, almost complete occlusion of the esophageal lumen by the bulging mass of the esophageal wall. The mass felt firm and bled easily. Biopsy of the mass revealed fragments of esophageal wall, peri-esophageal soft tissue, and fat containing nerve bundles. No evidence of tumor was seen.

FIG. 1. Esophagram revealing a large intraluminal mass in the upper third of the esophagus.

FIG. 2. Esophagram revealing a disappearance of the previous defect.

On February 15, 1957 intensive antibiotic therapy was begun. The dysphagia and inability to swallow solid foods persisted.

On February 21, 1957 esophagoscopy revealed, beginning at 20 cm. from the upper incisors, a gray, flat mass on the posterior and right lateral walls of the esophagus which extended downwards and bled readily. This was removed for histological examination. The endoscopist remarked that he could not be certain as to whether this tissue was grossly tumor or inflammatory exudate. The pathological report of the tissue obtained at biopsy was fragments of completely necrotic tissue and inflammatory exudate. No tumor was seen in the specimen.

On February 27, 1957 an esophagram showed no change in the ovoid filling defect of the esophagus.

On March 5, 1957 the patient suddenly became nauseated and regurgitated 10 cc. of bright, red blood. The dysphagia persisted subsequently. Two days later he was esophagoscoped. 25 cm. from the upper incisors, there was projecting into the lumen a small amount of irregular pink tissue suggestive of

granulation tissue. The ulcerative masses seen at the previous examination had disappeared although the membrane appeared rough and congested. This was suggestive of a healing esophagitis. There was no evidence of a bulging mass at any point.

Following the procedure the dysphagia rapidly disappeared. Esophagram on March 13, 1957 showed a disappearance of the previous filling defect (Fig. 2). Directly below the area where the defect had been present there was a slight, relative narrowing of the esophagus and slight irregularity of its contours.

The patient has remained asymptomatic, and it is felt that the lesion was an esophagitis.

COMMENT

The etiology of esophagitis is not at all clearly defined. The most common explanation of the cause of esophagitis is the bathing of esophageal mucosa in corrosive gastric juices which gain access to the esophagus via an incompetent cardia due to a sliding hiatal hernia or the presence of an indwelling gastric tube (1–5). However there is evidence which does not support this view. Palmer (6) states that the disease is primarily subepithelial, that the esophageal mucosa is normally resistant to acid digestion, and that esophagitis ensues only when the esophageal tissues are devitalized. Penner and Bernheim (7) point out in their series of esophagitis at post mortem examination that the common factor in acute esophagitis is the clinical syndrome of shock. They found that most of the esophagitis they encountered occurred in patients who had undergone major surgical procedures or had died after being in a state of shock.

Bartels (5), in his series of 82 cases of esophagitis, found at post mortem examination that 55 cases occurred in patients who had undergone major, extensive surgical procedures. Bloch (8) in his series of 20 cases of esophagitis points out again that most of his cases were those in which the patients had been in shock. Furthermore, one encounters esophagitis in achlorhydric patients, and medical measures to control gastric acidity do not ameliorate esophagitis (9).

It would seem then that the most likely sequence of events in acute esophagitis is first the clinical syndrome of shock with contraction of esophageal arterioles. The subsequent tissue anoxemia is followed by increased capillary permeability, transudation of plasma, and escape of cellular elements with hemorrhage leading finally to necrosis and pseudomembrane formation (7). Once the tissue is devitalized then the regurgitation of acid gastric juices may help to digest the necrotic tissue (6).

In the case presented, the patient had obviously been in shock. He had regurgitated gastric contents and had had ample opportunity for trauma to the esophageal mucosa from an indwelling Sengstaken tube. Following this course of events however, instead of developing the usual erosive esophagitis that one might expect, he developed a profuse proliferation of granulation tissue which on x-ray could not be distinguished from a carcinoma of the esophagus. On esophagoscopy the lesion was seen to almost completely occlude the esophageal lumen. Biopsy revealed chronic inflammatory exudate. At the time, with these

facts in mind, a possibility was that the lesion represented a carcinoma of the esophagus with superimposed infection on the tumor tissue. However, the complete clearance of the lesion on antibiotic therapy confirmed the diagnosis of esophagitis.

The distinction between an inflammatory lesion of the esophagus which can and does respond to antibiotic and conservative therapy, and neoplasm of the esophagus which requires prompt, radical surgical therapy is patently of crucial significance. In the literature I have been able to locate only two cases of inflammatory lesions of the esophagus with mass formation which on endoscopy and x-ray resembled carcinoma. One case of Adams and Luria (10) on x-ray revealed a mass protruding into the esophagus which was confirmed at esophagoscopy. Biopsy of the lesion showed chronic inflammation. Esophagogastrectomy was performed with excision of the mass. Pathological examination of the mass revealed an inflammatory diverticulum of the lower esophagus with chronic suppuration and granulomatous periesophagitis.

The second case is reported by Kampmeier and Jones (11). In this case, a 48 year old woman with a positive blood Wassermann and Kahn complained of dysphagia. Esophagram demonstrated almost complete obstruction at about the midpoint of the esophagus with an irregular canalization through the area of obstruction suggestive of carcinoma. Esophagoscopy revealed constriction at the mid point of the esophagus by a band of scar tissue below which was observed a granular tumor that resembled carcinoma. Biopsy revealed a chronic inflammatory reaction. The lesion was assumed to be a gumma, and was treated with bismuth, potassium iodide, neoarsphenamine, and dilatations with a bougie. The lesion responded well, and dysphagia disappeared after four weeks. At follow-up, $2\frac{1}{2}$ years after the onset of treatment, examination revealed slight stricture at the site of previous obstruction with a small traction diverticulum. The patient remained asymptomatic (11).

Our case, after the discovery of the esophageal mass, presented a therapeutic problem. If this was a carcinoma then radical surgery was indicated, and if this was an inflammatory lesion then antibiotics and conservative therapy would be the treatment of choice. The biopsies of the lesion revealed inflammatory exudate, but this could be compatible with inflammation overlying a tumor. It was decided to give the patient a trial on antibiotics and conservative therapy. After three weeks of antibiotic therapy the lesion had disappeared, thus confirming its inflammatory nature.

SUMMARY

A case of esophagitis is presented in which the x-ray and endoscopic findings were indistinguishable from those seen in carcinoma of the esophagus. The lesion responded to antibiotics and conservative management.

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Radiological Notes

CASE NO. 26

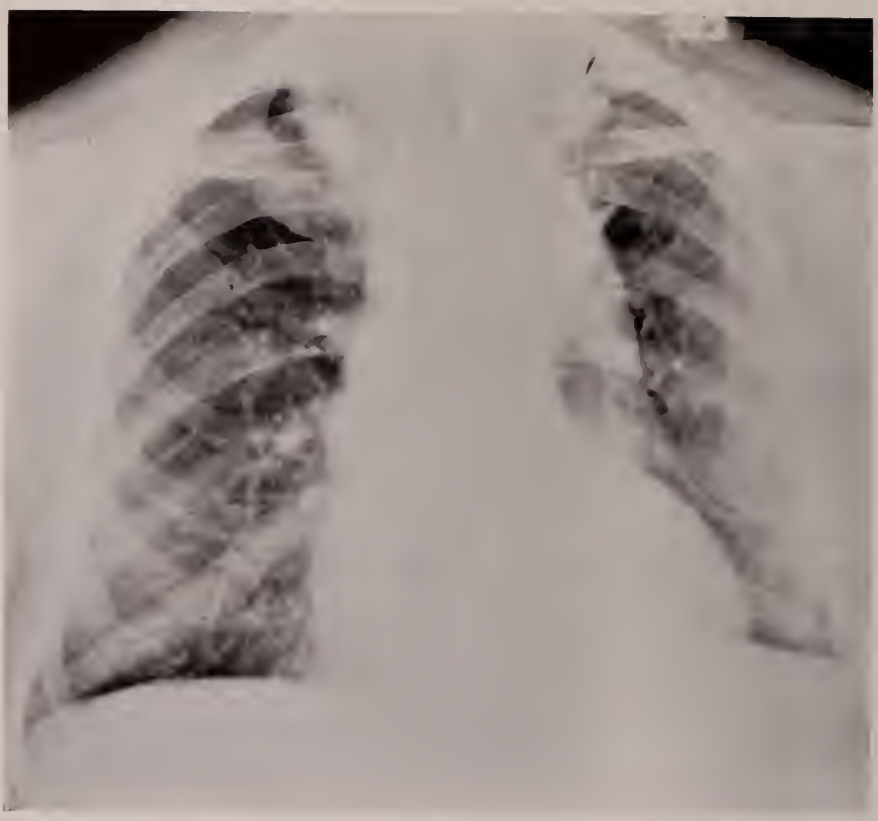
A 77 year old male was admitted with a history of sudden severe low back pain. The patient was a known hypertensive for at least five years with recurring episodes of confusion and memory defects. A reliable history could not be obtained.

Physical examination showed a blood pressure of 210/130 with a pulse rate of 100 per minute. The temperature was 101.6°F. The heart was enlarged to the left. Regular sinus rhythm was present. A2 was loud and booming. The abdomen was soft. No masses or organs were palpable. Ten or 15 RBC pre high power field of centrifuged urine were present, with clumps of WBC. The prostate was enlarged to twice the normal size. The possibility that the pain was on the basis of a urinary calculus was considered but a G.U. work-up was negative. During the course of the patient's hospital stay, the pain diminished over a period of two weeks but it became evident that the patient was hoarse and, on laryngoscopy, an immobile left vocal cord in the cadaveric position was noted. The patient's mental state continued to be confused and he was finally discharged without a definite diagnosis to explain the low back pain.

Examination of the chest in the PA projection (Fig. 1) about two weeks after admission showed a moderate increase in the transverse diameter of the heart. The left leaf of the diaphragm was somewhat elevated and straightened but there was no definite evidence of any pleural effusion. The ascending aorta did not appear remarkably prominent. However, the aortic knob was extremely wide with a deep identation on the esophagus, and in addition extended unusually high, above the level of the sternoclavicular articulations. The descending aorta beyond the arch showed a marked bulge into the left lung field. In the left oblique projection (Fig. 2), there was slight prominence of the ascending aorta but the posterior bulging of the descending aorta beyond the arch was very marked. The esophagus was displaced posteriorly with the aorta. There was no definite evidence of calcification within the dilated aorta. The roentgen features described above were considered consistent with a simple arteriosclerotic aneurysmal dilatation.

Two and a half years after the above admission to the hospital, the patient was readmitted in a markedly cachetic and confused condition and died suddenly with massive bleeding from the nose and mouth. Necropsy examination demonstrated the presence of a dissecting aneurysm beginning in the region of the arch of the aorta and extending downwards well into the abdominal aorta. The cause of death was a perforation of the thoracic false sac into the lung.

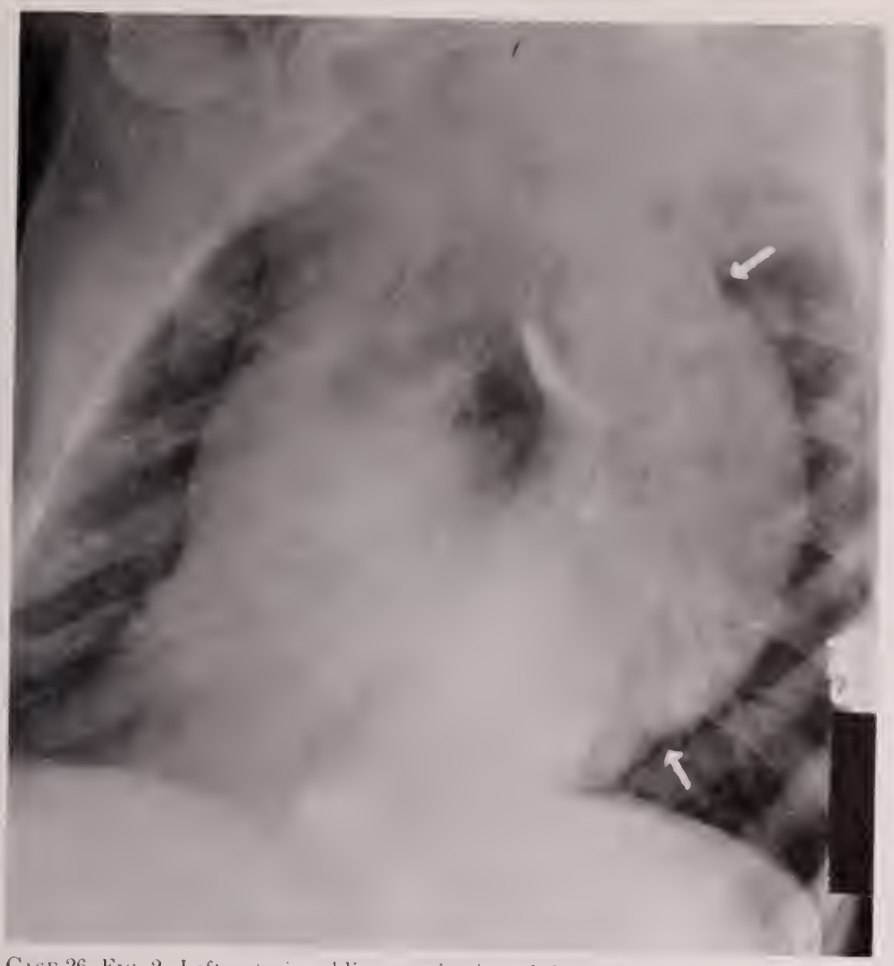
Review of the chest films taken on the first admission indicate that the possibility of dissection might at least have been suggested on the basis that the



Case 26, Fig. 1. PA projection of the chest shows moderate increase in the transverse diameter of the heart with a globular configuration of the left ventricular contour. The ascending aorta is slightly prominent. The arch of the aorta, however, is markedly increased in both the transverse and vertical directions. The descending aorta swings far into the left pulmonic field in a continuous convex line. The left leaf of the diaphragm is somewhat elevated and straightened. The left costophrenic sinus is obliterated but there is no evidence of pleural fluid. This film was taken two weeks after the onset of low back pain.

posterior prominence of the thoracic aorta, particularly in the left oblique projection, is not only quite marked but also rather well localized with slight notches above and below where it joins the aortic arch and descending aorta. The discrepancy between the large calibre of the aortic arch and the descending aorta and the relatively normal size of the ascending aorta probably also deserves emphasis. While these findings are not completely diagnostic, nevertheless the suggestion of dissection should be made in order that clinical confirmation might be obtained. Roentgen evidence of dissection is more easily demonstrable in the thoracic than in the abdominal aorta. The acute onset of back pain which may be the only prominent clinical finding must then be recognized as extension of dissection into the abdomen.

Final Diagnosis: Dissecting aneurysm of aorta.

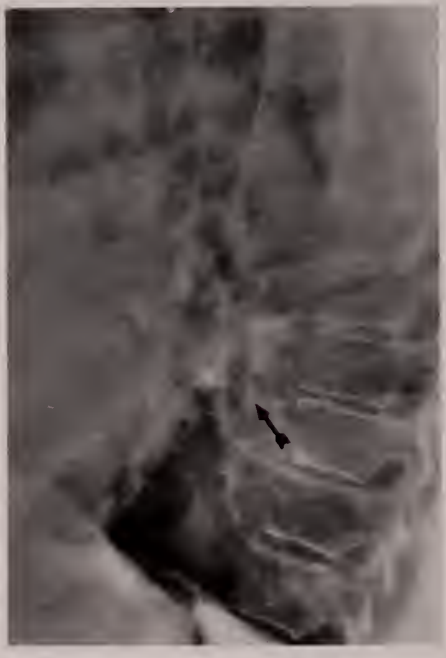


CASE 26, FIG. 2. Left anterior oblique projection of the chest with barium in the esophagus again shows the marked increase in the diameter of the descending aorta with a rather localized eccentric bulging occupying most of the left and posterior aspect of the thoracic aorta. There is a slight abrupt angulation at the junction of this area with the arch of the aorta proximally and with the descending aorta distally (arrows). No calcification was noted in the aorta.

CASE NO. 27

The first admission of this patient to the hospital was on May 29, 1954. At that time she was a 60 year old female who complained of intermittent abdominal pain. G.I. series demonstrated a deformed duodenal bulb. However, five years before admission a "spot on the lung" had been discovered and repeat films of the chest had been taken at approximately yearly intervals. There was an occasional nonproductive cough in the winter time. Except for this, the patient had no symptoms attributable to the lungs. It is said that the last film of the chest had suggested that the "spot" was enlarging. On admission, the

Case 27, Fig. 1. Examination of the chest in the PA projection shows an ovoid density with its base apparently against the thoracic cage which appears sharply demarcated. Its medial aspect is slightly serrated.



Case 27, Fig. 2. Lateral projection at the same time as Fig. 1 shows the ovoid density to be sharply demarcated throughout. Its posterior margin is pointed while its anterior aspect appears rounded. In this and in the oblique projections, the most likely location appeared to be within the lateral mid-portion of the interlobar fissure.

temperature of the patient was 102°F. but this promptly dropped to normal in a day. The sedimentation time was 28 mm. in one hour on one occasion and 34 on another occasion. Roentgen examination of the chest (Figs. 1, 2) showed a well demarcated, somewhat ovoid homogeneous density about $1\frac{1}{2}$ inch in its maximum diameter apparently located in relationship to the greater fissure on the left side. The appearance suggested an encapsulated interlobar effusion or so-called "pseudo-tumor". In the absence of symptoms, the patient declined operative intervention.

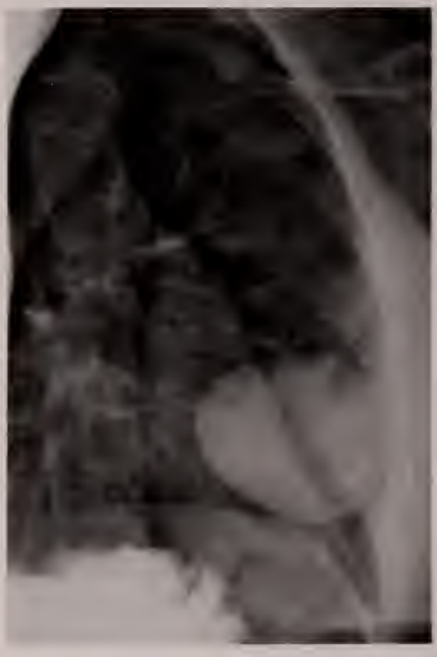
The patient was readmitted on April 16, 1957. There were no symptoms specifically attributable to the lungs but the patient complained of some weakness and occasional excess of perspiration at night. There was no history of any febrile course. Re-examination of the chest (Figs. 3, 4, 5) demonstrated that the shadow previously seen had more than doubled in size within the preceding three years.

The patient underwent thoracotomy and a freely mobile mass in the interlobar fissure in the left mid-axillary line was found which was attached to the lingular portion of the left upper lobe by a flat pedicle. The mass was about 6 cm. in diameter, smooth and firm. The pathological report was polypoid fibroma of the pleura.

Final Diagnosis: Polypoid fibroma of the visceral pleura in the interlobar fissure.

Case 27, Fig. 3. Re-examination three years after Fig. 1 again shows the homogeneous density which is sharply demarcated but has more than doubled in size. The superior aspect appears somewhat lobulated.

CASE 27, FIG. 4. Lateral projection at the same time as Fig. 3 shows similar findings. The growth of the mass apparently has occurred predominantly in a downward direction. The elongated pointed posterior margin has disappeared.

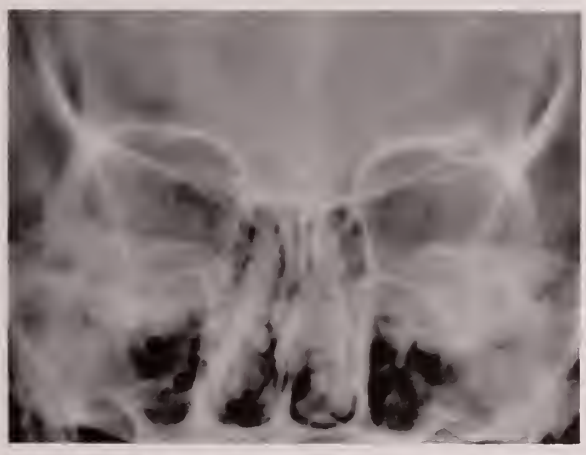


CASE 27, FIG. 5. Right anterior oblique projection shows exquisite sharp demarcation of the entire mass.

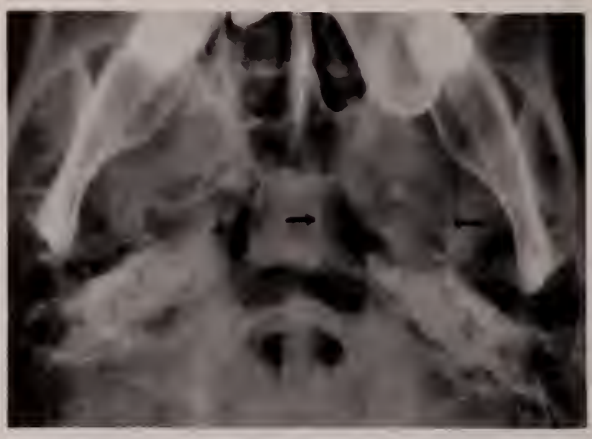
CASE NO. 28

This was the second admission of a 60 year old woman with the chief complaint of progressive difficulty in vision. Her first admission was three years previously. At that time she gave a history that nine years prior to her first admission there had been an episode during which she was unable to grasp objects with her left hand. Three years prior to this admission, she complained that the left side of her face did not appear to be straight, particularly when she smiled. A year after this, there was a sudden onset of diplopia and sticking pain in her left eye. Paralysis of the left inferior oblique and left superior rectus muscles were demonstrated at that time. Visual acuity, however, was 20/20 in each eye with correction. Neurological examination done shortly after this also revealed nystagmus and the impression at that time was that the patient had mid-brain disease presumably on a vascular basis. During the patient's first admission, there was also evidence of decreased corneal reflex in the left eye; the jaw was deviated to the left and there was weakness of the left masseter and temporal muscle with a slight left lid drop. Hypesthesia to pinprick was noted over the left side of the face. Roentgen examination of the skull and sinuses was not remarkable. Cerebral arteriography demonstrated an aneurysm about 1 cm. to 1.5 cm. in diameter in the parasellar region on the left.

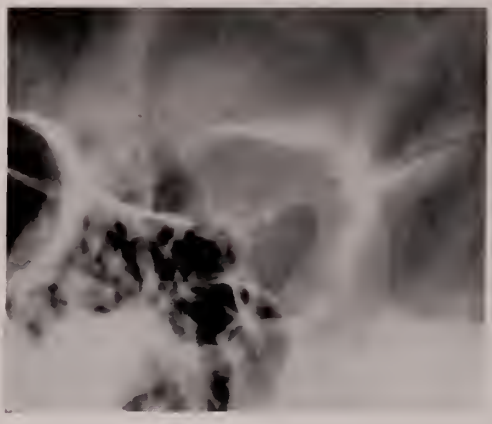
The second admission of the patient was in December 1956 because of progressive difficulty in vision. She had been relatively unchanged since the previous admission up to about six weeks prior to the current admission when she noted that vision in the left eye was becoming progressively poorer. Neurological examination showed the findings previously noted and in addition the left eye at this time was immobile. The left pupil was dilated and fixed. Hypesthesia over the left side of the face was more marked. The left corneal reflex was absent. There was atrophy of the temporalis and masseter muscles on the left. Visual acuity



CASE 28, FIG. 1. Postero-anterior view of the orbits shows a punched-out defect about 1.5 cm. in diameter in the medial portion of the greater wing of the sphenoid obliterating the superior orbital fissure. The superior margin of this defect involves the lesser wing as well which shows a sharply demarcated, arcuate contour, convex superiorly.



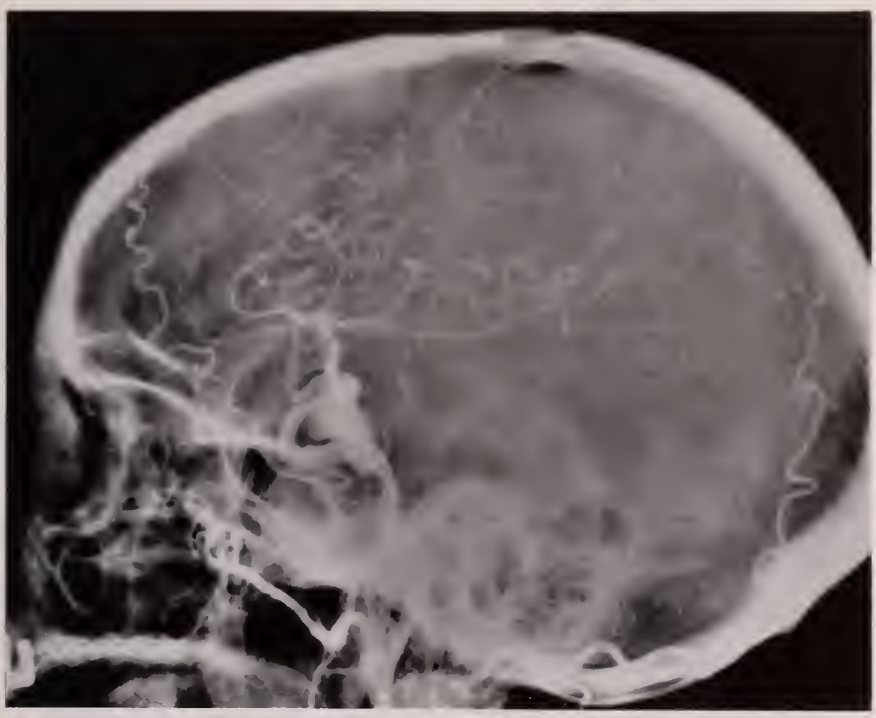
CASE 28, FIG. 2. Base view of the skull demonstrates that the bony defect in the greater wing of the sphenoid extends laterally to the foramen spinosum (lateral arrow) and posteriorly to involve the anterior aspect of the tip of the petrous pyramid. The foramen lacerum was also widened and the adjacent margin of the clivus is decalcified. There is another arcuate bony line about ½ cm. medial to the margin of the clivus (medial arrow) which presumably represents the medial extent of the bone erosion.



CASE 28, FIG. 3. Optic foramen view shows that the large defect includes the inferior margin of the optic foramen.

was markedly diminished on the left side especially in the temporal field. Lumbar puncture showed the protein content to be 75 mgm. per cent. On previous admission protein content of the lumbar fluid was 35 mgm. per cent.

Examination of the skull (Figs. 1, 2, 3) showed a sharply demarcated, punched-out bony defect in the greater wing of the sphenoid involving the optic foramen and extending laterally and posteriorly to involve also the foramen ovale. The anterior aspect of the apex of the left petrous pyramid also appeared to be eroded Cerebral angiogram (Fig. 4) was repeated and demonstrated that the opacified portion of the aneurysm had become about twice as large as on the previous



CASE 28, FIG. 4. Left carotid angiogram shows filling of a large aneurysm in the parasellar region. The elongated vertical course of the suprasellar portion of the carotid artery and the high take-off of the anterior middle cerebral vessels demonstrate that the nonvisualized or clotted portion of this aneurysm is considerably larger than the portion opacified. The actual origin of the aneurysm is somewhat uncertain. In the AP projection (not shown), it appeared to rise from the parasellar portion of the carotid, that is, the inferior portion of the siphon.

examination. The distal portion of the siphon was also elongated vertically. It is of interest to note that the portion of the aneurysm associated with the bony defect apparently was not opacified and contained clotted blood.

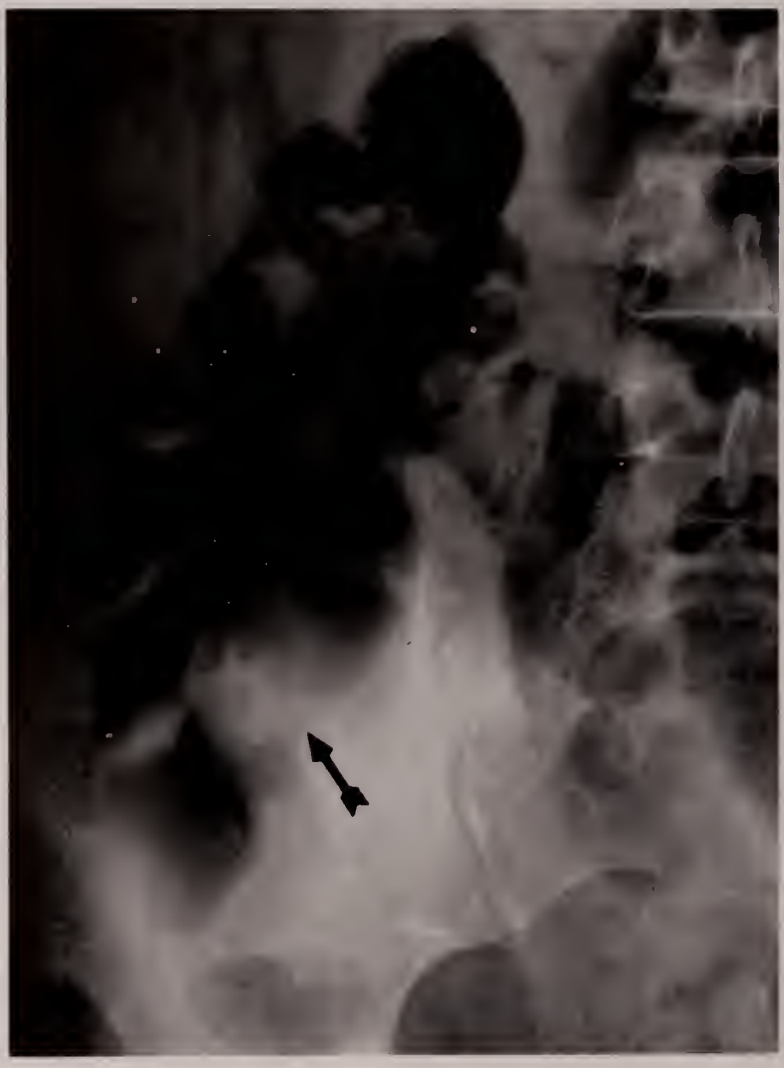
Operative intervention was declined by the patient. She was discharged without evidence of any change as a result of the hospital stay.

Final Diagosis: ANEURYSM OF INTERNAL CAROTID ARTERY WITH EROSION OF THE SPHENOID BONE.

CASE NO. 29

This was the sixth admission of a 41 year old postal clerk with known hemophilia due to AHG deficiency. Previous admissions were for recurrent hemathroses of the elbows and knees and hematuria on several occasions. The patient always responded well to fresh frozen plasma. Two days prior to this admission patient had a heavy, greasy meal with five or six ounces of alcohol. Twenty-four hours prior to admission, he complained of periumbilical pain followed in about four hours by nausea and vomiting. The vomitus contained food but apparently no

blood. A small, loose bowel movement also occurred at the same time without evidence of gross blood within it. The pain became progressive and radiated to the lower abdomen particularly the right lower quadrant. On examination, the patient was in moderate distress. The abdomen was somewhat distended and there was moderate rigidity with voluntary and involuntary guarding, deep and rebound tenderness on the right side. Tenderness was maximal at McBurney's point. One observer was suspicious of a mass in the right lower quadrant. Rectal



Case 29, Fig. 1. Film of the abdomen taken on admission shows a hemispherical soft tissue density projecting into the cecum from its medial wall (arrow) interpreted as marked thickening of the ileocecal valve. Multiple, air containing, loops of small bowel in the abdomen suggest a mild paralytic ileus.

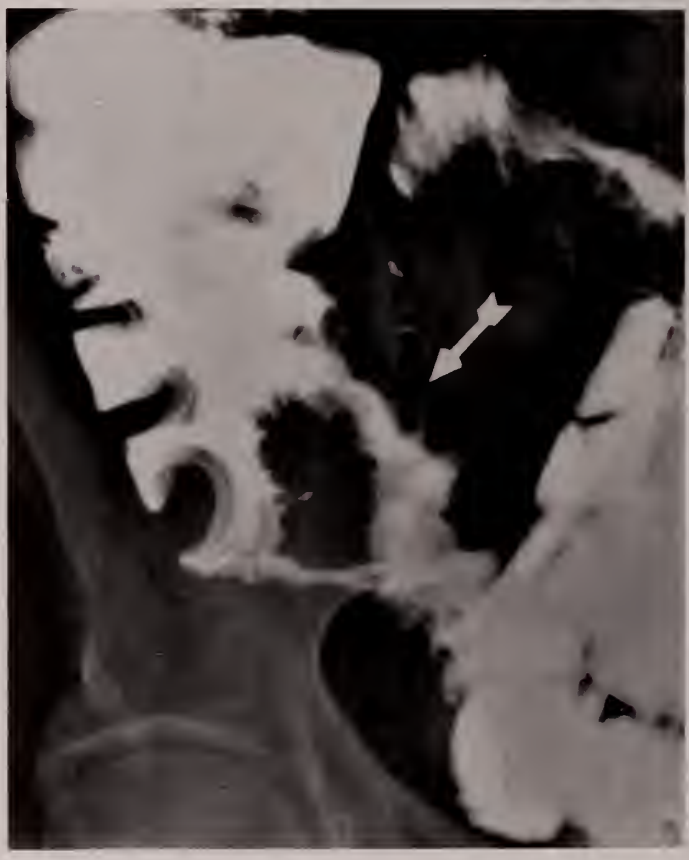
CASE 29, FIG. 2. Barium enema examination four days after admission. There was marked delay in barium entering the terminal ileum which appears markedly narrowed (arrow) and irregularly filled. The appendix was visualized in its normal position.

examination was negative. Stool guaiac on admission was negative. Clotting time was more than 90 minutes. Bleeding time was two minutes. Rumpel-Leede test was negative. Clot retraction appeared to be normal. Hemoglobin was 16 grams per cent, WBC 10,000 per cu. mm. with a normal differential count. Erythrocyte sedimentation time was 40 mm. in one hour.

The patient was afebrile and in the absence of leucocytosis, it was felt that the abdominal symptoms presumably were on the basis of intraabdominal bleeding. Six hours after infusion of two units of fresh frozen plasma, the clotting time was 25 minutes and the patient improved rapidly. He ceased to complain of pain and his abdomen became softer with little or no tenderness. Within three days, the patient was completely asymptomatic. A stool examination three days after

admission was reported four plus guaiac and three days later was guaiac negative.

Barium enema and barium meal examinations were done on this patient during his hospital stay and after discharge (Figs. 1, 2, 3, 4). On admission, a film of the abdomen showed moderately distended, air containing loops of small bowel in the mid-abdomen. A hemispherical soft tissue mass projecting into the lumen of the cecum on its medial aspect was also noted (Fig. 1). Barium enema examination four days after admission showed great difficulty in filling the terminal ileum despite considerable effort to do so. A small amount of barium finally passed the ileocecal valve and outlined a markedly narrowed, irregularly filled terminal ileum (Fig. 2). The appendix was demonstrated in its normal location. Two days after the barium enema examination, a small bowel series showed greater but still limited distensibility of the terminal ileum (Fig. 3A). The borders of the terminal ileum were grossly scalloped for a distance of about



Case 29, Fig. 3. Barium meal examination two days after the barium enema.

Fig. 3A. The terminal ileum (arrow) shows limited distensibility with irregularly scalloped contours.

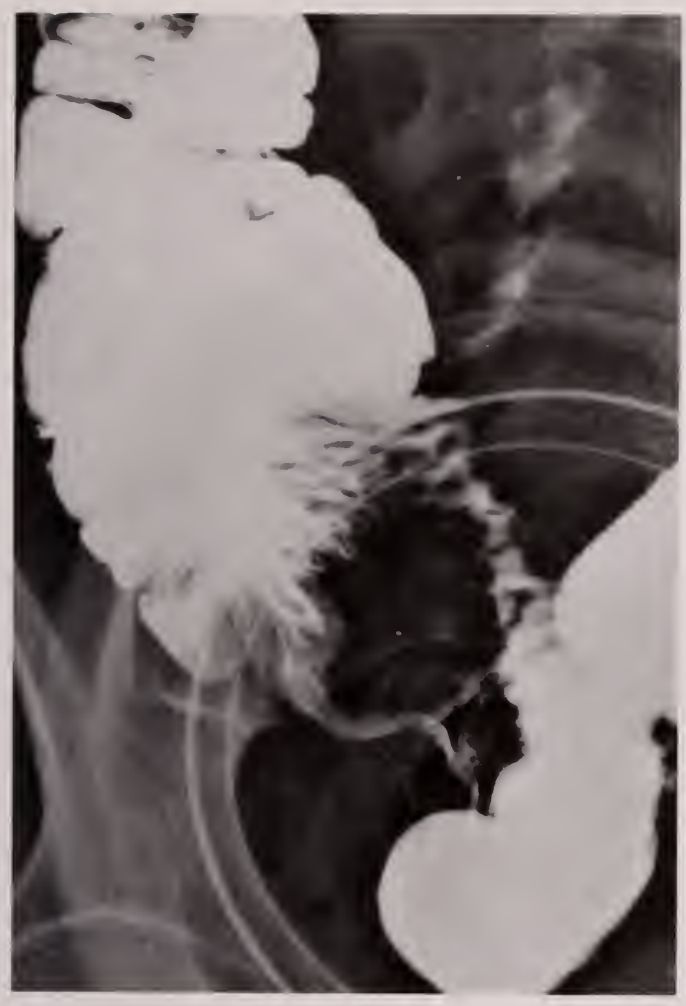


FIG. 3B. Pressure film of terminal ileum shows thick but apparently intact mucosal pattern. There is a suggestion of a mass or mesenteric thickening in the angle between the ileum and medial wall of the cecum. The appendix is well seen and is normally located.

3½ inches from the ileocecal valve. Pressure films of the terminal ileum indicated that the mucosal pattern, while thickened, was nevertheless intact (Fig. 3B). There was a suggestion of a mass or mesenteric thickening between the ileum and cecum. Barium enema five weeks after admission showed an essentially normal terminal ileum (Fig. 4).

The changes in the terminal ileum and ileocecal valve were interpreted as due to intramural and mesenteric bleeding and hematoma formation. The course of events confirmed this opinion.

Final Diagnosis: INTRAMURAL HEMATOMA OF TERMINAL ILEUM AND ILEOCECAL VALVE DUE TO HEMOPHILIA.

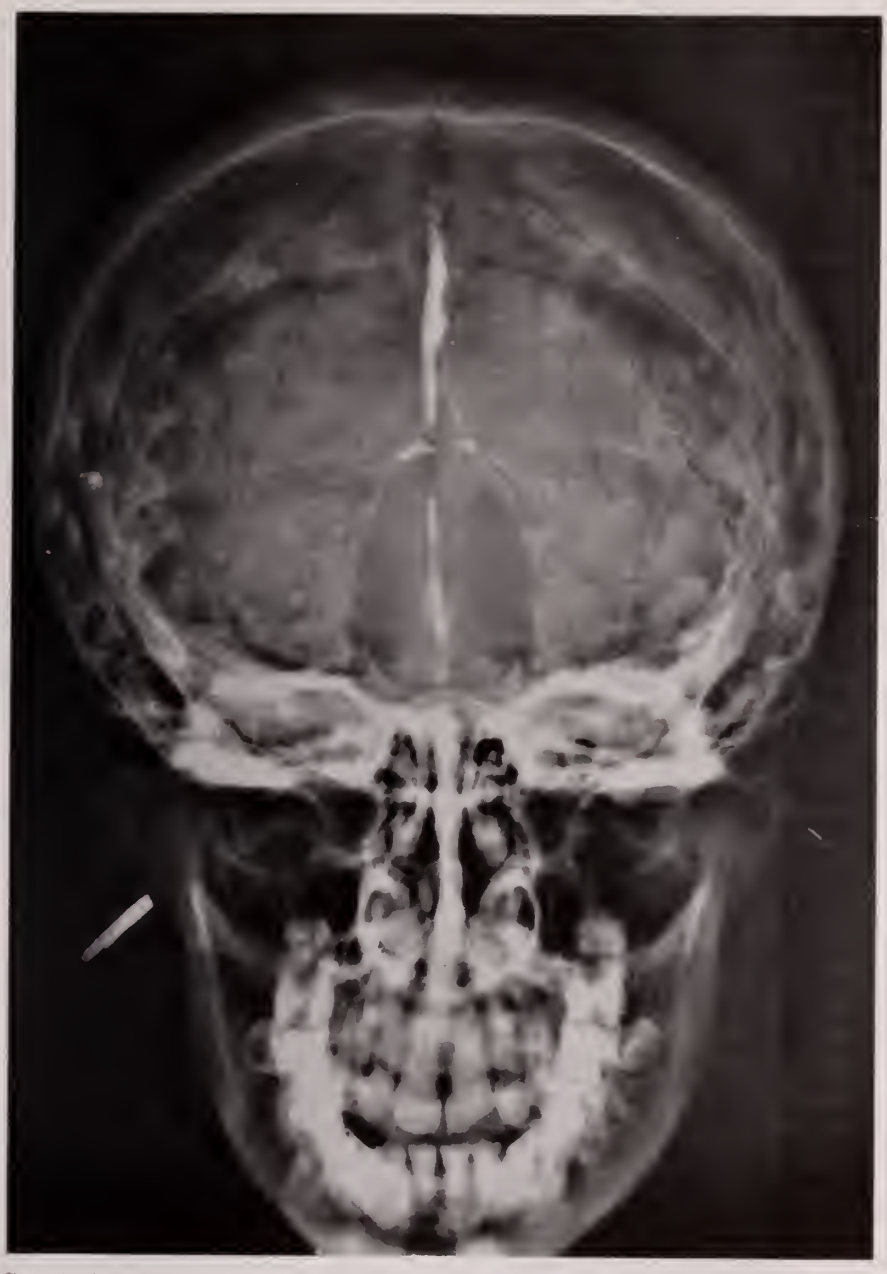
Case 29, Fig. 4. Barium enema examination one month after Fig. 3 shows normally distensible terminal ileum. Apparent filling defects are due to fecal content.

CASE NO. 30

(Submitted by Donald Gribetz, M.D.)

G. K., a ten year old white male child was admitted to The Mount Sinai Hospital in May 1953 with the chief complaints of short stature, anorexia with poor weight gain and urinary findings indicative of diminished renal function. The poor appetite of this child had been noted as an infant although obvious retardation in growth and weight was not remarkable until the age of four years. A urinalysis was not performed until the age of 9½ years and revealed a trace of albumin, pyuria and a low specific gravity.

Physical examination showed the child below the mean in both height and weight by four standard deviations. His head appeared to be relatively enlarged. An apical systolic murmur was present; blood pressure was 120/85. The child was alert and appeared quite bright. Urinalysis confirmed the presence of albuminuria and pyuria. Blood urea nitrogen was 46 mgm. %; serum calcium, 15.8 mgm. %; serum phosphorus, 4.4 mgm. %; and serum alkaline phosphatase,

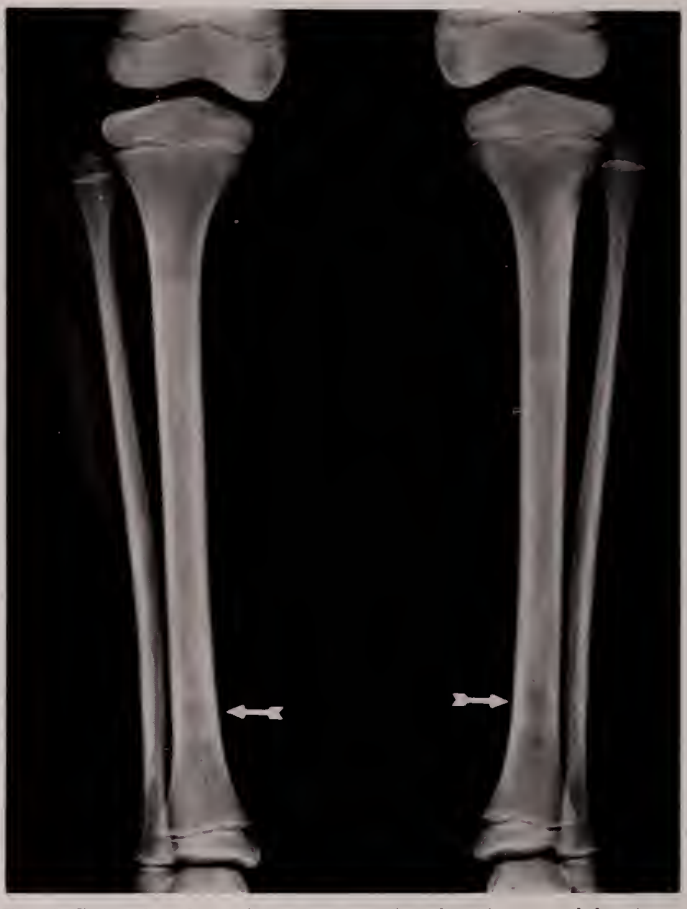


CASE 30. FIG. 1. Postero-anterior projection of the skull shows innumerable dural plaques in the tentorium, the falx and over both hemispheres. This is so extensive that the opening in the tentorium is completely outlined. The calvarium is somewhat thickened.

8 K.A. units %. The roentgen findings will be detailed below but included nephrocalcinosis.

The possibility of hyperparathyroidism was considered despite the fact that the 24 hour urinary excretion of calcium on a Bauer-Aub diet was normal. In June 1954, on exploration, three normal parathyroids were exposed and two of these were removed. The fourth parathyroid gland was not demonstrated.

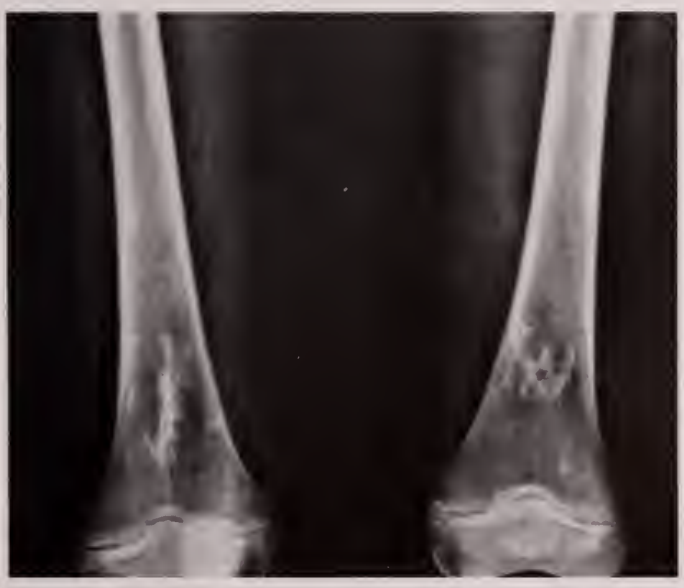
Since discharge from the hospital, this child has been followed over a period of 4½ years. Clinically, there have been no remarkable complaints and in fact the child showed an adolescent growth spurt during which he achieved normal height and weight. The serum calcium level has gradually fallen almost to normal limits despite no specific therapy but his blood urea nitrogen has remained ele-



Case 30. Fig. 2. Several rather faint transverse bands of increased density are seen in the distal portions of the shafts of both tibiae. These are rather poorly demarcated and located at some distance above the epiphyseal plates. The epiphyseal plates appear to be somewhat irregular in outline but the adjacent bone density must be considered to be within normal limits. There is a question of minimal cortical thickening of the shafts, particularly of the lateral aspects of the fibulae. A short distance below the superior epiphyseal plate of the left tibia on its lateral aspect there is a small lucent zone with sharply sclerotic somewhat scalloped periphery which has the appearance of a cortical or Caffey defect.

vated. Band keratopathy and corneal calcifications were demonstrated during this period.

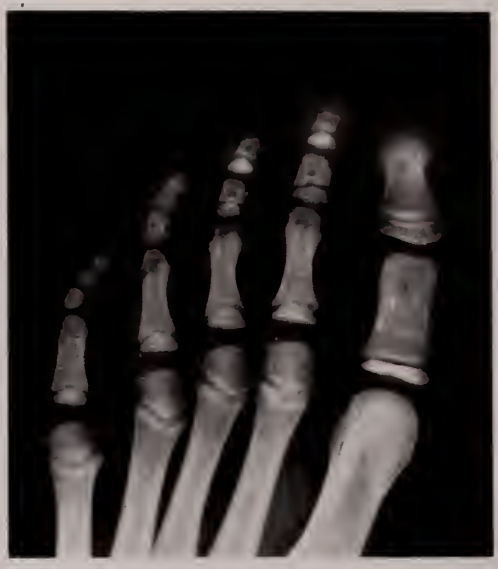
Roentgen examination during hospitalization in 1953 showed several unusual features. Throughout the dura of the brain (Fig. 1), there were innumerable calcific plaques. The bones of the calvarium appeared to be moderately thickened although the base of the skull did not appear unusual. The development of the teeth and the lamina dura did not appear remarkable. The sella turcica was within normal limits. The heart and lungs were normal. Examination of the abdomen showed innumerable punctate calcific deposits in the parenchyma of both kidneys. The renal outlines were within normal limits in regard to size. In the distal portions of the shafts of both tibiae (Fig. 2) there were several transverse bands of increased density. In the upper end of the shaft of the left tibia, a short distance below the epiphyseal plate, there was a small area of rarefaction with a sharply sclerotic scalloped contour. There was a question of minimal cortical thickening in both tibiae and fibulae. The epiphyseal plates were somewhat irregular in outline. In the lower portions of the shafts of the femora moderately extensive areas of irregular calcification within the medullary cavity were noted (Fig. 3). A similar small area was seen in the distal portion of the shaft of the right ulna. The laminae of the sacrum were absent and no centers of ossification for the coccyx were noted. The development of the carpal centers was distinctly retarded. This was most evident in the navicular and the greater and lesser multangular bones and in the distal ulnar epiphyses, whereas the other carpal bones were only moderately retarded. Similar retardation in the growth of the epiphyseal centers was present at both elbow joints but no retardation in



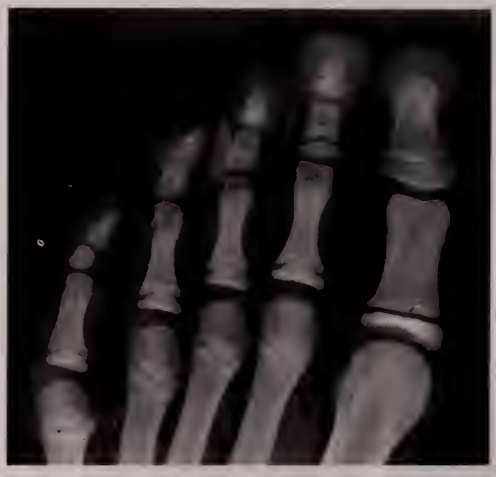
Case 30. Fig. 3. The lower ends of the femora show irregular intramedullary calcification characteristic of bone infarcts. The appearance of the epiphyseal plates is similar to those of the ankles.

epiphyseal development was evident at the shoulders, knees or ankle joints. It should be emphasized that there was no evidence of any diffuse demineralization or of generalized excessive bone density.

Re-examination of the abdomen 1½ years after discharge from the hospital showed no change in the nephrocalcinosis. Re-examination of the skeleton showed



Case 30. Fig. 4. Examination of the toes of the right foot 1½ years after admission to the hospital shows marked increase in bone density of the epiphyses of the distal phalanges of the 2nd and 3rd digits. Identical findings were present on the opposite side and also in the similarly located epiphyses of the 2nd and 5th digits of the right hand and the 3rd, 4th and 5th digits of the left hand.



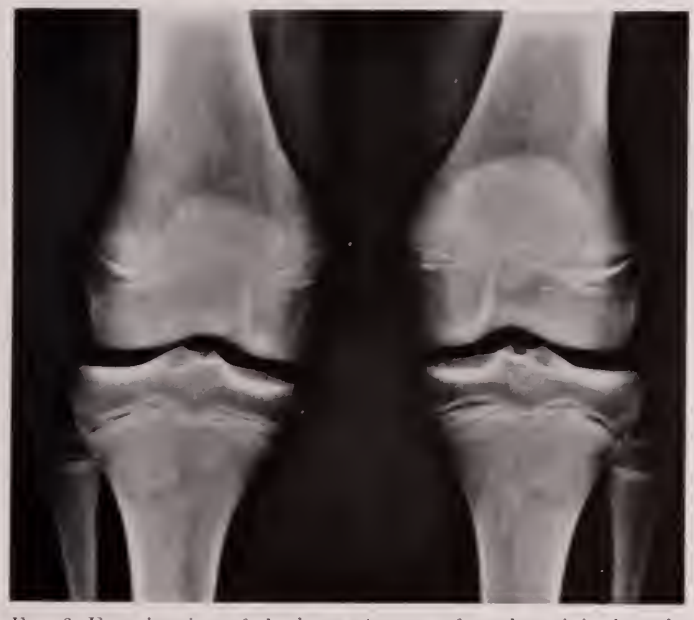
Case 30. Fig. 5. Re-examination of the toes of the right foot 14 months after the previous examination shows that the increased density of the epiphyseal plates of the terminal phalanges has diminished and is now confined to the central portions of these discs.

diminution in size of the bone infarcts in the femora. The cortical defect in the upper portion of the left tibia had disappeared. The development of the bony centers at the elbows and the wrists was still delayed but to a lesser degree. On this examination, the toes and fingers were included and it was evident that several of the epiphyses of the distal phalanges in both the hands and the feet were extremely dense (Fig. 4).

Re-examination eight months after the second roentgen examination showed a rather remarkable spurt in the bone age at the wrists and elbows which now appeared to be within normal limits. The excessive density of the epiphyses of the distal phalanges in the fingers and hands was diminished (Fig. 5). The transverse bands of increased density in the distal portions of the tibia had been only faintly seen on the second examination and were absent at this time. Only a faint indication of the bone infarct in the left femur remained.

A fourth examination of the skeleton was performed about four years after the original examination. The excessive calcification of the epiphyses of the terminal phalanges in the fingers and hands had disappeared completely and there was no evidence of the previous bone infarcts. The nephrocalcinosis and the dural calcification were unchanged. A new finding at this time was the presence of fairly well demarcated, symmetrical, somewhat circular areas of increased density in the superior metaphyses of the tibiae (Fig. 6).

The correct diagnosis in this case was not realized until about four years after the original work-up. It was then evident that the findings corresponded to the



Case 30. Fig. 6. Examination of the knees 4 years after the original work-up shows for the first time symmetrical, moderately well demarcated ovoid areas of increased bone density in the metaphyses of the upper ends of both tibiae. This is a surprising finding in view of the fact that the changes previously noted in the bones had disappeared and in view of the diminution in the hypercalcemia. Its significance is not clear at the present time.

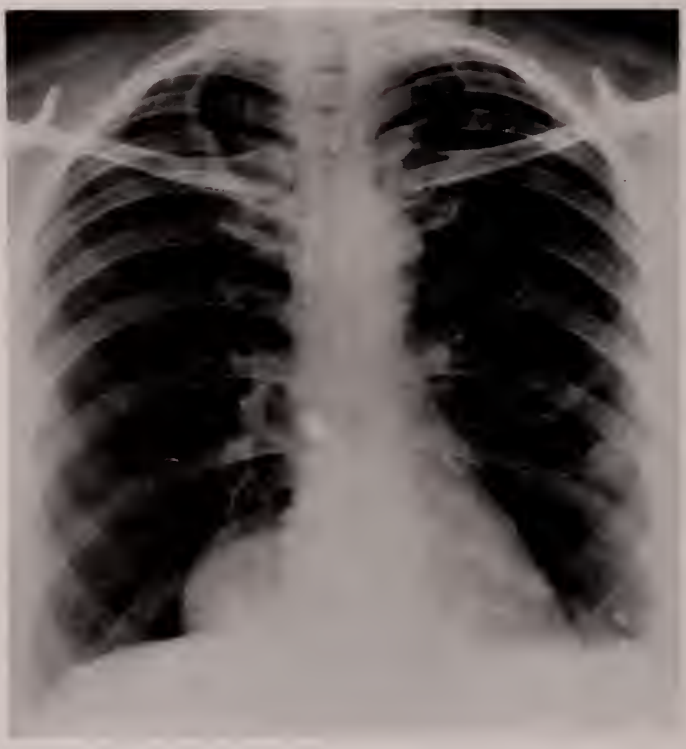
condition now being designated as "Idiopathic Hypercalcemia". This child must be considered to suffer from the chronic form, in contrast to the transitory variety. Despite this, however, he has done extremely well with reversal of bone changes and correction of retarded growth as well as improvement in the hypercalcemia. He also fails to show the mental retardation previously considered characteristic. However, in view of the persistent nephrocalcinosis, the prognosis remains guarded.

Final Diagnosis: Idiopathic hypercalcemia, chronic type.

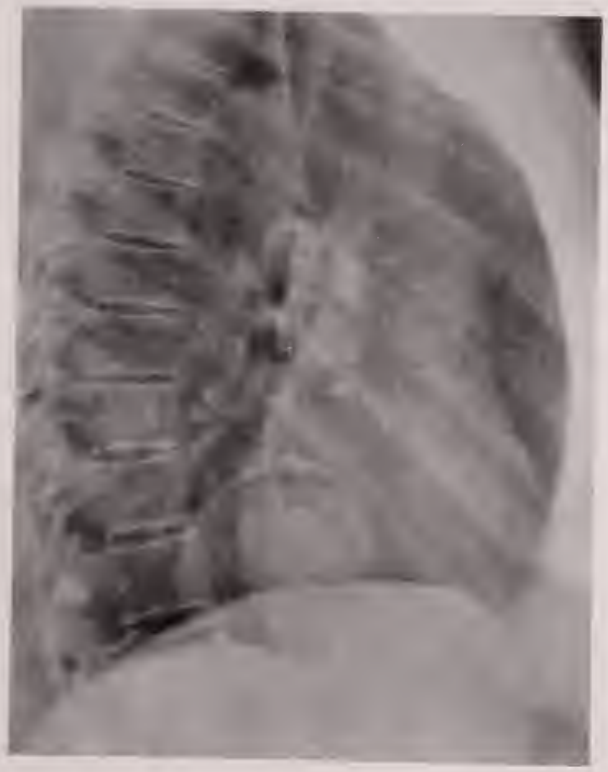
CASE NO. 31

(Submitted by John E. Moseley, M.D.)

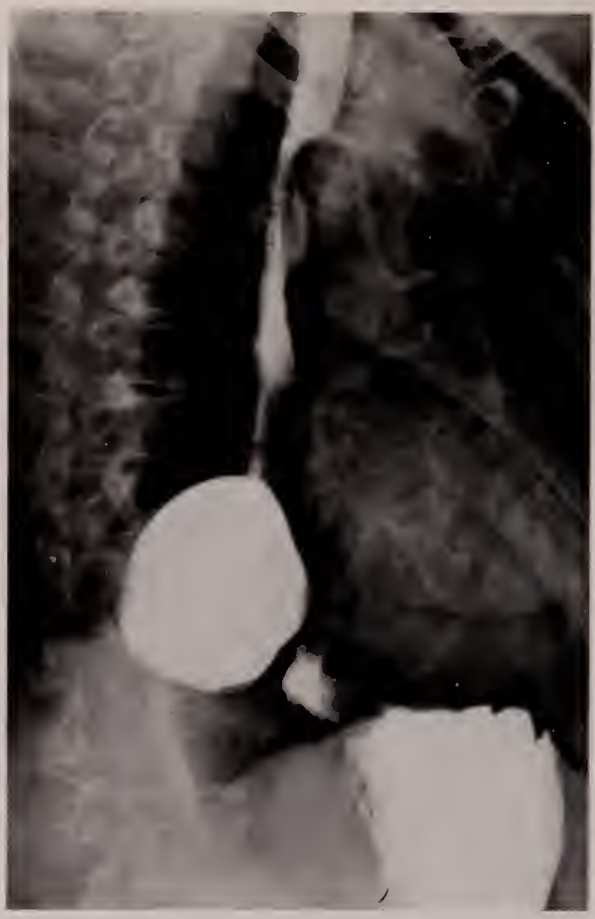
G.H. a 55 year old colored female was admitted to the hospital because of neurological complaints which were later demonstrated to be due to a Guillain-Barré syndrome. The routine photoroentgen film of the chest taken on admission revealed a rounded mass in the right cardiophrenic angle. Re-examination of the chest in the PA and lateral projections (Figs. 1, 2) confirmed this finding and demonstrated that the density was very sharply demarcated on all sides except on its mediastinal aspect and contained in its upper portion a lucent zone, pre-



Case 31. Fig. 1. PA projection of the chest shows a sharply demarcated spherical density in the right cardiophrenic angle with a lucent area in its upper portion. The right border of the heart can be seen through this density.



CASE 31. FIG. 2. Lateral projection of the chest shows the sharp margin of this shadow with the lucent zone in its upper portion. It is located adjacent to the posterior aspect of the heart in front of the spine.



CASE 31. FIG. 3. Barium swallow shows a large epiphrenic diverticulum extending to the right and posteriorly.

sumably gas. The location of this shadow and the presence of gas within it raised the possibility that this was a hiatus hernia extending to the right side. The patient had no symptoms referable to the esophagus or to the stomach. Barium swallow (Fig. 3) demonstrated that the density in the right cardiophrenic angle was due to a large epiphrenic diverticulum of the esophagus. There was no hiatus hernia.

Final Diagnosis: EPIPHRENIC DIVERTICULUM

PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION

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New York, N. Y.

The syndrome of uncomplicated patent ductus arteriosus has been well described and is generally considered to be one of the more easily diagnosed of congenital cardiac malformations. With the demonstration that obliteration of the ductus could be achieved with very low mortality and morbidity rates, early elective surgery has become an accepted and satisfactory mode of treatment for the usual case of patent ductus arteriosus.

However, during the past few years there has been delineated a type of patent ductus arteriosus differing considerably clinically, pathologically, physiologically and in its therapeutic implications from the usual, uncomplicated ductus. At present there have been a sufficient number of definitely established cases described (1–6) to warrant inclusion within a broad entity the syndrome of patent ductus arteriosus with pulmonary hypertension.

CLINICAL CHARACTERISTICS

Whereas the usual, uncomplicated patent ductus arteriosus is generally asymptomatic, symptoms of substernal pain, fatigue and dyspnea occur in about 75 per cent of those patients with pulmonary hypertension and signs of diminished growth may be present. Although similar symptoms may occur in association with patent ductus arteriosus with normal pulmonary artery pressure, they are present more frequently and are usually more severe when pulmonary hypertension exists. Hemoptysis has been described in about 15 per cent and congestive heart failure, usually right-sided failure, in one-third of the cases (Table I). About one quarter of the patients with elevated pulmonary arterial pressure have pulmonary hypertension of sufficient magnitude to cause either intermittent or persistent reversal of the usual course of flow through the ductus with the entry of unoxygenated blood into the systemic circulation and the production of cyanosis of the lower extremities or of the left upper extremity, a sign never observed in uncomplicated patent ductus. These cases of patent ductus with reversal of flow represent a distinct clinical and physiological entity (7–12).

The electrocardiogram in uncomplicated patent ductus arteriosus may be normal or may, in cases with large left-to-right shunts, show left ventricular hypertrophy. When pulmonary hypertension accompanies the patent ductus, an electrocardiographic pattern or right ventricular hypertrophy may be seen in

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Presented as part of the American College of Physicians' course in Recent Advances in Cardiovascular Disease, New York City, Oct. 8–12, 1956.

TABLE I

A comparison of the clinical characteristics in patent ductus arteriosus with pulmonary hypertension and in uncomplicated patent ductus arteriosus

	Uncomplicated patent ductus	Patent ductus with pulmonary hypertension
Symptoms and Signs	Usually none Occasional substernal pain, fatigue and dyspnea May have retarded growth May have left heart failure	Substernal pain, Dyspnea, Fatigue } >75% Right heart failure—33% Hemoptysis—15% Reversal of flow—25% (cyanosis greater in lower extremities or in left upper extremity)
ECG	Normal or LVH	RVH—⅔ Combined VH—⅓ Rarely normal
Murmurs	Continuous systolic and diastolic	Continuous systolic and diastolic Systolic only Diastolic only No murmur
X-Ray	LVH Prominent pulmonary artery and and peripheral pulmonary vasculature	RVH Prominent pulmonary artery Peripheral pulmonary vasculature reduced
Estimated operative mortality	About 2%	Left-to-right shunt—18% Right-to-left shunt—56%

about two-thirds of the cases and evidence of combined hypertrophy in about one-third. Only rarely is the electrocardiogram within normal limits.

The classical systolic and diastolic continuous "machinery" murmur, heard maximally at the pulmonic area is a well recognized diagnostic sign of uncomplicated patent ductus arteriosus. Auscultatory findings are variable in those cases with pulmonary hypertension. Either the usual pulmonic systolic and diastolic continuous murmur, a systolic murmur alone, a diastolic murmur alone, or no murmur may be heard, depending upon the pressure relationships between the aorta and the pulmonary artery (13). Figures 2–4, illustrating pressures obtained directly from the aorta and pulmonary artery during ductal surgery, demonstrate how the pressure differential between the aorta and the pulmonary artery may influence the auscultatory findings. In Figure 1, in which a gradient between aorta and pulmonary artery exists in both systole and diastole, a typical "machinery" murmur was heard. In Figure 2, direct pressures illustrate a pressure gradient across the ductus only in systole and in this case no diastolic murmur was noted, whereas in Figure 3, there is a gradient only in diastole and no systolic murmur attributable to the ductus was heard. In addition, an apical presystolic

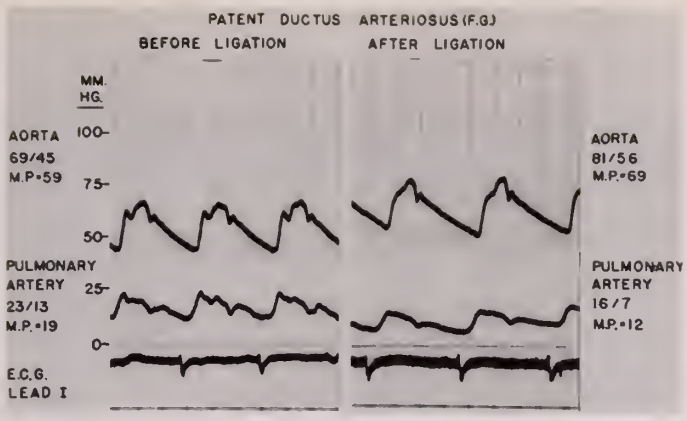

FIG. 1. Direct aortic and pulmonary artery pressures obtained during surgery and recorded from a single baseline at equal sensitivities in a case of patent ductus arteriosus with typical systolic and diastolic "machinery" murmurs. There is an aortic-pulmonary artery pressure gradient in both phases of the cardiac cycle to account for the continuous murmur. (Reproduced through courtesy of J. of Applied Physiology, 11: 161, 1957).

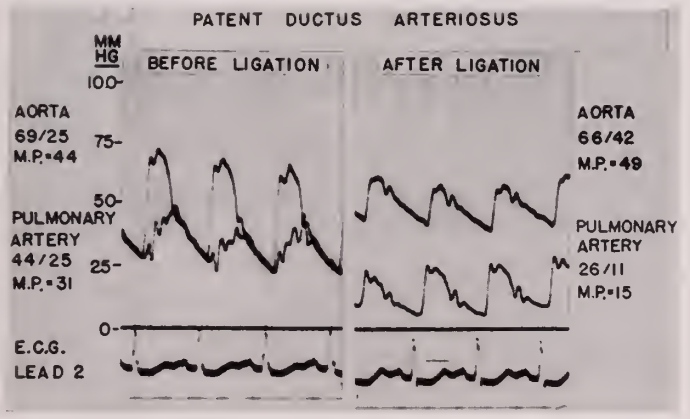

FIG. 2. Direct aortic and pulmonary artery pressures in a case of patent ductus arteriosus with a systolic, but no diastolic murmur. There is an aortic-pulmonary artery pressure gradient in systole but none in diastole. (Reproduced through courtesy of J. of Applied Physiology, 11: 161, 1957).

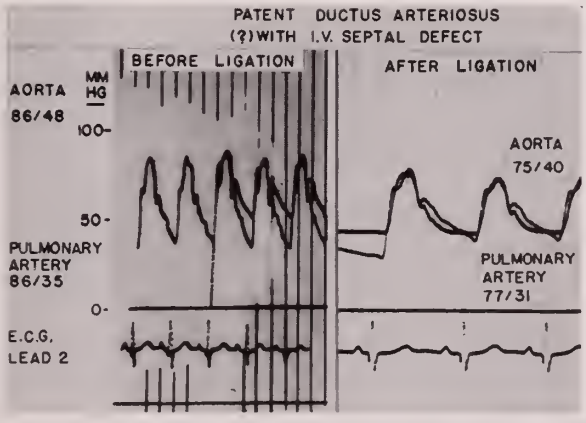

FIG. 3. Direct aortic and pulmonary artery pressures in a case of patent ductus arteriosus with no systolic murmur attributable to the ductus. Note the absence of a pressure gradient in systole, which accounts for this auscultatory finding. (Reproduced through courtesy of J. of Applied Physiology, 11: 161, 1957).

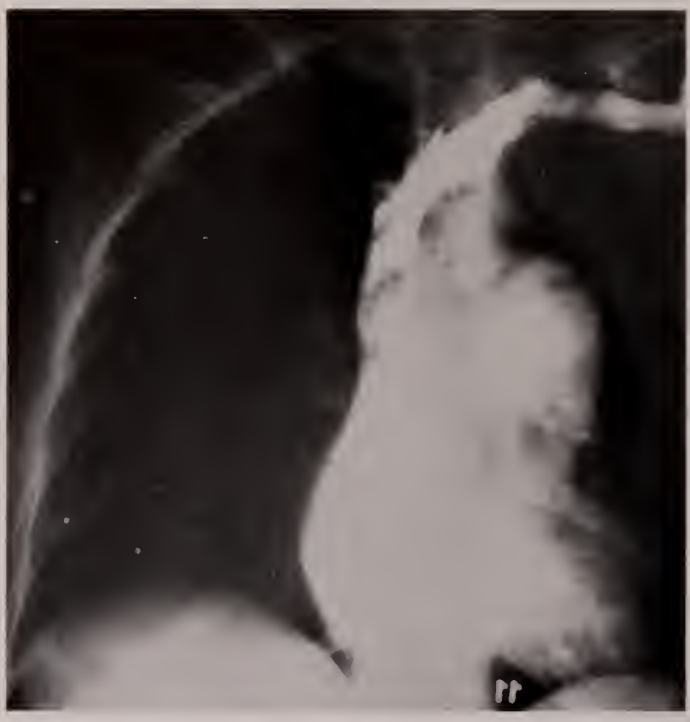

FIG. 4. An angiocardiogram taken 1½ seconds after intravenous injection in a case of patent ductus arteriosus with reversal of flow. The descending aorta is opacified and there is dye in the aortic arch, but the ascending aorta, left ventricle and left atrium are not seen, evidence that the ductus is filling from the right heart. The ductus itself is visible above the left pulmonary artery. (Reproduced through courtesy of New England J. of Medicine, 251: 923, 1954).

murmur, thought to be a manifestation of increased blood flow across the mitral valve, may be heard in some cases of patent ductus with either normal or elevated pulmonary artery pressure, provided that the shunt is from left to right.

ETIOLOGY

The pathogenesis of patent ductus with pulmonary hypertension is not well known. In fetal circulation, the ductus arteriosus is thought to play an important role in delivering oxygenated blood from the pulmonary artery to the aorta of the fetus. With the onset of pulmonary ventilation, it is supposed that the pressure relationships between the aorta and the pulmonary artery are altered; the pulmonary artery pressure normally declining in relation to aortic pressure.

After respiration commences, the patent ductus is no longer functionally necessary and obliteration normally occurs within two months, although rarely spontaneous closure may occur after several years. What initiates the events normally seen is not known, but persistent patency of the ductus, at least in this country, shows a striking relationship to maternal rubella contracted in the first trimester of pregnancy (14). There is also a definite familial tendency. Anderson (15) reported the risk figure for recurrence in later-born siblings at about one in fifty.

The genesis of the pulmonary hypertension is obscure and several explanations have been proposed. Before accepting a unitary explanation, it should be realized that the cases with reversal of flow may present two distinct clinical patterns—one in which the patient is cyanotic from birth and the other in which the patient is originally acyanotic, with a left-to-right shunt and then gradually develops a right-to-left shunt and cyanosis. Whereas in the first instance, changes are probably present since birth, in the second situation it is obvious that the circulatory dynamics are undergoing progressive alteration.

Pathological examination of the pulmonary vascular tree reveals widespread organic lesions, the most common findings being marked intimal proliferation and muscular hypertrophy of the small and medium sized arteries and, in several of the cases, organized thrombi. Edwards (16) believes that pulmonary hypertension occurs in many of these cases because of persistence of the fetal type of pulmonary arterioles with thick walls and narrow lumens. Others have proposed as explanations for pulmonary hypertension the occurrence of multiple pulmonary emboli, antecedent pulmonary arteritis (2) or functional spasm of the pulmonary arterioles (17). Finally, it has been suggested that gradual increase in pulmonary vascular resistance results from prolonged exposure to an increase in pulmonary artery flow and may represent a late complication of an ordinary patent ductus arteriosus (2) even though there may be no direct correlation between the size of the ductus and the degree of pulmonary hypertension. Although the normal pulmonary circulation may tolerate large flows (up to three times the systemic flow) with no pressure elevation (18), it may be that when there is pre-existing organic restriction of the pulmonary vessels, relatively small increases in blood flow are accompanied by increases in pressure. It has been postulated that a rise in pulmonary artery pressure may itself cause further constriction of the musculature of the vessels (19) (perhaps due to nervous impulses) which, in turn, causes further muscle hypertrophy and increased vascular resistance, thus establishing a cycle, the end result of which is reversal of blood flow through the shunt. The element of functional spasm is an important one from the standpoint of reversibility of the process. It is well known, for example, that shunts through the ductus may be intermittently reversed through crying, exertion or, particularly, hypoxia, which may increase the pulmonary artery pressure (20). A transient fall in aortic pressure will also produce intermittent reversal of the shunt.

DIAGNOSIS

As previously indicated, symptoms and physical findings may be extremely variable in patent ductus with pulmonary hypertension and, although the classical murmur may be produced, it may be considerably altered or absent. An accentuated pulmonic second sound, whether or not a murmur is present, is generally audible as a manifestation of the increased pulmonary artery pressure. In addition, there may be failure to elicit a normal, split pulmonic second sound on inspiration, a sign described by Gray (21). Normally, pulmonic valve closure occurs after aortic valve closure, thus producing a split pulmonic second sound, heard best in inspiration. In cases of patent ductus, the duration of contraction

of the two ventricles may be altered, causing valve closure to occur simultaneously and producing only a single sound in the pulmonic area (13).

Since the history and physical findings in patent ductus arteriosus with pulmonary hypertension may not adequately distinguish it from other lesions, it is usually necessary to resort to more complicated diagnostic procedures. If cyanosis does occur in patent ductus, it may have a distinct, pathognomonic distribution. Should the pulmonary arterial pressure rise sufficiently to be greater than the aortic, unoxygenated blood will enter the descending aorta and cyanosis and/or clubbing of the feet will occur to a considerably greater extent than occurs in the upper extremities. Simultaneous measurement of the arterial oxygen saturation in the femoral and radial or brachial arteries will, if the shunt is reversed, always show a lower oxygen content in the lower extremities and represents a most reliable diagnostic procedure for this condition. In doing this procedure, care should be taken to use the right arm vessels because unoxygenated blood from the pulmonary artery may find its way through reflux from the aorta to the left arm or left ear, rendering them cyanotic and at times producing a clue as to the diagnosis. It should be realized, however, that there may be a considerable difference in oxygen saturation without a difference in detectable cyanosis being evident and, therefore, failure to observe a difference in cyanosis between upper and lower extremities does not necessarily mean that the arterial oxygen contents are the same. Direct measurement of the arterial oxygen must be performed in these situations.

Certain diagnostic techniques have recently been employed to alter the pressure relationships on the two sides of the ductus in order to change the direction of flow from a bi-directional one either to left-to-right or right-to-left. Hypoxia, a well-known stimulus to increase pulmonary vascular resistance, has been used for this purpose. It has been observed that right-to-left shunts have been produced while low oxygen mixtures are breathed and left-to-right shunts produced when 100% oxygen is inhaled (20). This may be a useful procedure in doubtful cases but the dangers of further hypoxemia in a cyanotic patient render careful consideration necessary. It is also possible to alter the direction or degree of shunting by causing a diminution in peripheral vascular resistance with nitrites and thus increase the right-to-left shunt.

Roentgenographic findings in the uncomplicated patent ductus arteriosus have been well described. There are usually slight to moderate pulmonary arterial, left atrial and left ventricular enlargement and increased amplitude of pulsations in the aorta, pulmonary artery and left ventricle. In about one-half the cases, localized dilatation of the aortic arch, due to funnel-shaped widening of the aorta at the opening of the ductus, may occur (22). Other, less common, findings in the conventional x-ray film include ring-like aortic calcification at the ductus, elevation of the left main branch of the pulmonary artery and, occasionally, an associated aneurysm of the pulmonary artery (23), although the relationship of these x-ray findings to the level of pulmonary artery pressure has not been well defined. When pulmonary hypertension is associated with the patent ductus, there is usually evidence of right ventricular hypertrophy. The pulmonary artery may be more prominent than in the usual case of patent ductus. When

the shunt is reversed, there may be evidence of reduced vascularity in the periphery of the lung (24).

Angiocardiography may be a useful diagnostic technique. The conventional, right-sided intravenous angiocardiogram seldom demonstrates the ductus directly if the shunt is from left to right, but may produce indirect findings, namely reopacification of the pulmonary artery related to filling from the aorta and a transient defect in opacification of the pulmonary artery due to the entry of non-opaque blood from the aorta. Right-sided angiocardiography is much more revealing and may be exceedingly valuable when the shunt is reversed. Figure 4 demonstrates the filled ductus visible above the left pulmonary artery $1\frac{1}{2}$ seconds after venous injection. The descending aorta is densely opacified and there is a small amount of dye in the aortic arch, but the ascending aorta, left atrium and left ventricle are not visualized, evidence that the ductus is filling from the right side of the heart, a pathognomonic sign of reversal of flow through the ductus. More recently, dye has been injected selectively into the right ventricle and pulmonary artery in such cases with clearer visualization of the ductus and the surrounding structures (24). The preferred technique for visualizing a patent ductus with a left-to-right shunt is thoracic aortography with injection into the ascending aorta, reached through retrograde arterial catheterization, as worked out by Jonsson and his associates in Sweden (25).

Cardiac catheterization may definitely establish the diagnosis of patent ductus if the ductus is entered, an event which occurs more commonly when there is associated pulmonary hypertension, possibly because the ductus is usually wider in these cases. If the ductus is not entered at catheterization, the diagnosis rests on gas analysis which, if the shunt is from left to right, will show a higher oxygen content in samples from the pulmonary artery than from the right ventricle and right atrium. This finding is not pathognomonic of patent ductus as similar results may be seen in high inter-ventricular septal defects as well as in aortic septal defects. The catheterization findings in patent ductus may also mimic those in ventricular septal defect if the ductus is associated with pulmonary incompetence, producing relatively high oxygen saturation in the right ventricle as well as in the pulmonary artery. Other findings which may be seen at catheterization in patent ductus arteriosus with left-to-right shunt include a localized slight elevation of the pulmonary artery pressure with an extra peak in systole (26), attributed to inflow from the aorta to the pulmonary artery and an elevated pulmonary "capillary" pressure, thought to be due to increased left-sided blood flow.

Electrokymographic studies have been performed in a small number of cases of patent ductus arteriosus with pulmonary hypertension (24, 25). Although there is some difference of opinion, in general, in cases with left-to-right shunt, the pulmonary artery curve is described as showing a prolonged systolic upstroke and a dicrotic wave placed high on the descending limb, the aortic curve showing a low-placed dicrotic notch, similar to that seen in aortic insufficiency. In right-to-left shunts, however, the aortic curve shows a high dicrotic notch and a delayed ascent.

The differential diagnosis of patent ductus arteriosus with pulmonary hyper-

tension may be quite difficult. In addition, the patent ductus may frequently coexist with another congenital cardiac lesion. The typical continuous systolic and diastolic murmur may be heard as well in aortic septal defects. An aortic septal defect will usually produce a more vigorous pulsation in the ascending aorta than in the arch, a finding not seen in patent ductus. In addition, the catheter, if it enters an aortic septal defect, may be seen to emerge in the ascending aorta and the tip may be directed inferiorly towards the aortic valve (28), whereas the catheter in patent ductus arteriosus enters either the descending aorta or the left carotid artery via the aortic arch. Dye dilution curves, inscribed by sampling blood from the pulmonary artery after injection of the dye into various parts of the aorta, should theoretically aid in the differential diagnosis of these conditions.

If the typical murmur is not present, the auscultatory signs of patent ductus with pulmonary hypertension may be simulated by other conditions associated with pulmonary hypertension, principally by inter-ventricular septal defect with pulmonary hypertension (Eisenmenger's complex), primary pulmonary hypertension or, less commonly, atrial septal defect with pulmonary hypertension. Cardiac catheterization is necessary in distinguishing among these conditions. If cyanosis is present, its regional distribution is seen only with patent ductus with reversal of flow and the difference in oxygen content between the arteries of the upper and lower extremities or between the right and left upper extremities is diagnostic. Improved techniques of visualizing the ductus angiocardiographically and the apparent increased frequency of entry into the ductus at catheterization are resulting in greater frequency of recognition of this syndrome.

TREATMENT

Surgical treatment, preferably by division of the ductus, has come to be accepted in uncomplicated patent ductus. The risk is low, with overall mortality at about 2 per cent (25, 26), and the incidence of death in untreated ductus from infection, rupture and cardiac failure is high, the average age of death in the untreated group living to adolescence being 35–38 years in Keys and Shapiro's data reported in 1943 (31). With the use of newer antibiotics, death from infection is probably less common at the present time. Although the exact prognosis in large series of untreated cases with pulmonary hypertension has not been accurately determined, it is undoubtedly considerably worse than in uncomplicated patent ductus.

There has been some difference of opinion concerning the advisability of surgery when there is associated pulmonary hypertension, particularly if the shunt is reversed. Since sharp delineation of the syndrome of patent ductus arteriosus with pulmonary hypertension has been relatively recently emphasized, there is not an overabundance of statistical data either from the standpoint of the surgical risk or the therapeutic result achieved. It is important to realize that even though the pulmonary artery pressure is elevated and that there may be associated organic pulmonary vascular lesions, obliteration of the ductus may

TABLE II

A summary of the reported operative mortality in cases with patent ductus arteriosus and pulmonary hypertension

(Compiled from data collected by Ellis, F. H. Jr., Kirklin, J. W., Callahan, J. A. and Wood, E. H.—Journal of Thoracic Surgery 31: 268, 1956)

	Cases	Deaths	Per cent mortality
Total	102	20	20
Right-to-left shunt	30	16	53

result in regression of the pulmonary artery hypertension and apparent cure of the patient (32, 33).

An extensive review of reported cases of surgically treated patent ductus arteriosus with pulmonary hypertension has been compiled by Ellis and his associates (34). Table II summarizes the data in this review and demonstrates the increased mortality rate associated with surgical intervention in these cases, particularly in the cases with right-to-left shunt. Generally similar conclusions were reached after a review of the literature by Sirak and Humphreys (6) and after a poll of surgical opinions compiled by Waterman and his associates (30). Fatal hemorrhage from the ductus or pulmonary artery or circulatory deterioration were the principal causes of death. In general, however, survivors of surgery exhibited a satisfactory fall in pulmonary artery pressure.

Many surgeons, in deciding on the correct mode of treatment of a patent ductus with pulmonary hypertension, separate sharply the cases of left-to-right from those of right-to-left shunt. Generally, when the shunt is left-to-right, early division is favored, despite the increased operative risk (30). When the shunt is from right to left, there is no unanimity of opinion although most experienced surgeons do not favor surgical intervention in such a situation. First, the operative risk is considerably higher. Second, there are those who feel that the ductus operates as a "safety valve" for the right ventricle and that obliteration would result in further elevation of right ventricular pressure with resultant right ventricular failure (6, 7). However, in some cases such events have not occurred and obliteration of the ductus has been successfully accomplished in the presence of a right-to-left shunt (34, 35). Long-term follow-up studies of the post-operative pulmonary artery pressure are necessary to evaluate fully the advisability of ductal obliteration in these patients. One such recently reported study, eighteen months following closure of the ductus, indicated failure of the pulmonary hypertension to diminish (36). For immediate survival, the critical problem appears to be adjustment of the circulation in the acute phase of ductal obliteration. It may be that sudden occlusion of the ductus places too great a stress on the right ventricle. It has therefore been suggested in these cases that the ductus be obliterated slowly with careful monitoring of the effects of gradual obliteration on the pulmonary arterial and aortic pressures, since it is now feasible to measure these pressures during surgery (6, 13). It has also been suggested that the effects of occlusion of the ductus by means of a balloon be determined during cardiac

catheterization in an effort to determine whether ligation will result in a further rise in pulmonary arterial pressure (37). In addition, the possible use of hypothermia to allow cross-clamping of the aorta and the use of high concentrations of oxygen (34), phlebotomy and hypotension (6) in an effort to reduce pulmonary vascular resistance will probably enable more successful operations to be performed in the future. Although the risks are at present great in these cases, there is a prospect that as knowledge increases as to the physiological alterations produced by a patent ductus arteriosus with pulmonary hypertension, further significant advances in surgical therapy will be achieved.

SUMMARY

There has recently been delineated a type of patent ductus which produces alterations differing clinically, physiologically, pathologically and in their therapeutic implications from those seen in the usual, uncomplicated patent ductus. These cases have been included within a broad entity—the syndrome of patent ductus arteriosus with pulmonary hypertension, characterized pathologically by intimal thickening and medial hypertrophy in the pulmonary arterioles.

Patients with this syndrome have a poor prognosis and may frequently experience substernal pain, fatigue, dyspnea, hemoptysis and diminished growth. Right-sided congestive heart failure may occur and an electrocardiographic pattern of right ventricular hypertrophy may be obtained. In about one-fourth of the cases the pulmonary hypertension may be of sufficient magnitude to cause either intermittent or persistent reversal of the usual course of flow through the ductus with the production of cyanosis, particularly in the lower extremities, the cyanosis developing either at birth or during the natural course of an apparently ordinary patent ductus. Because of the altered pressure relationships between the aorta and the pulmonary artery, the classical systolic and diastolic continuous murmur found in the usual case of patent ductus is generally not heard when there is advanced pulmonary hypertension; systolic, diastolic or no murmurs are present.

Particularly helpful in the diagnosis of reversed shunt is the demonstration of lower oxygen content in the femoral arterial blood than in a simultaneously obtained right radial or brachial arterial specimen, or selective cyanosis of the left upper extremity or left ear. Angiocardiography may demonstrate filling of the descending aorta from the pulmonary artery in these cases. Breathing gas mixtures low in oxygen may aid in the diagnosis by causing temporary pulmonary arterial hypertension and a right-to-left shunt through the ductus. Lowering the systemic pressure may cause a similar directional change in the shunt.

It has been demonstrated that even though there are organic changes in the lung vessels, obliteration of the ductus may result in a fall of pulmonary artery pressure to normal. The operative risk is higher, however, than in uncomplicated patent ductus and in cases with reversal of flow, the operative mortality has been greater than 50 per cent. Generally, surgical intervention is favored when the shunt is left-to-right but is not advisable when there is a right-to-left shunt because of the high surgical risk and the questionable benefit of ductal closure.

The use of controlled hypotension and high oxygen mixtures combined with careful monitoring of the effects of gradual obliteration of the ductus on pulmonary artery and aortic pressures may permit more cases of patent ductus with pulmonary hypertension to be successfully treated in the future.

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MALIGNANT HEMANGIOENDOTHELIOMA: REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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INTRODUCTION

The following two cases of primary hemangioendothelioma of the liver are recorded here because of the rarity of their occurrence and the diagnostic difficulties they offer to the clinician as well as to the pathologist. The cases reported came to autopsy within a relatively short interval. Beside one case of primary sarcoma of the liver previously published (1), these have been the only instances of primary malignant tumors of the liver of mesenchymal origin in more than 10,000 autopsies performed at The Mount Sinai Hospital since 1927.

CASE REPORTS

Case 1

Clinical. W.P. (M.S.H. #632127), a 48 year old Puerto Rican male was admitted to The Mount Sinai Hospital on October 13, 1951 complaining of abdominal swelling of two months duration. At the same time he noted the onset of shortness of breath on exertion, weakness and anorexia. Previously the patient had been in apparently good health. During this interval he lost 15 pounds and occasionally noted dark urine and light colored stools. Two weeks before admission, he complained of crampy mid-abdominal pain which subsided by the time of admission. The patient had a long history of heavy alcoholic intake.

Physical examination revealed a fairly well developed but chronically ill pale male in no distress. The vital signs were normal. There was faint scleral icterus. A few typical spider angiomata were noted on the neck. The lungs presented crackling rales at both bases and the diaphragm was elevated on both sides. The left breast was enlarged and tender. The abdomen was markedly distended and the liver was percussed three fingers-breadth below the right costal margin; the spleen was not palpable. Shifting dullness was demonstrable. Collateral venous channels were seen along the sides of the abdominal wall. The remainder of the physical examination was unremarkable.

Laboratory studies revealed: Hgb, 13.9 gms. %; WBC varying between 3800 and 8500 per cu. mm. with a normal differential count. The sedimentation rate was 60 mm/hr. Routine urinalysis was negative but the urine contained increased amounts of bile and urobilinogen. The Wassermann reaction was negative; BUN, 11 mg %; fasting blood sugar, 84 mg %; bilirubin, 1.6 mg %; total protein, 8.0 gm %; A/G ratio, 3.0/5.0; alkaline phosphatase, 23 KA units; cholesterol 220 mg % with esters of 135 mg %. Cephalin flocculation test, 3+; thymol turbidity, 17.5 units; bromsulfalein retention was 46% in 45 minutes. Stool guaiac tests were negative. Electrocardiogram was normal.

Abdominal paracentesis yielded 7.5 liters of turbid amber fluid of low specific gravity, negative for tumor cells. Chest x-ray showed a hemispherical soft tissue shadow along the lateral aspect of the left chest wall together with a lytic lesion of the adjacent sixth rib. Barium swallow showed extensive esophageal varices. Aspiration of the sixth rib lesion was attempted but no tumor cells were found. After the aspiration, a partial left pneumothorax developed. In spite of subsequent re-expansion of the left lung, the patient developed increasing tachypnea and cyanosis and died in the fourth week of hospitalization.

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Necropsy. The sclerae were slightly icteric. The left hemithorax contained 100 cc of serosanguinous fluid. The liver descended 1 cm below the right costal margin. It weighed 2100 grams. The capsule was thin and the surface showed diffuse granularity; it was made up of 1 to 3 mm nodules of firm consistency, varying in color from red-brown to yellow-gray and blue-gray. Strands of gray fibrous tissue separated these nodules from each other, and wider bands grouped them together. The liver cut with increased resistance. On cut section, the normal lobular architecture was completely replaced by multiple, ill-defined gray and reddish-tan, firm 1 to 3 mm nodules interspersed with numerous 2 to 4 mm cystic areas. These cysts contained fluid and clotted blood. In numerous areas the firm gray nodules coalesced and displayed a serpiginous infiltrating pattern, the largest measuring 5 mm in diameter. Scattered throughout the parenchyma were nodules of yellowish-tan tissue of normal consistency showing lobular pattern but measuring about three times the size of a normal liver lobule. The intrahepatic bile ducts were poorly identified but they were not obviously dilated. The major intrahepatic portal radicles showed invasion by tumor, causing granularity of the vessel lining and irregularity of its lumen. The spleen weighed 150 grams and was of normal size. It was firm in consistency and on cross section normal architecture easily could be made out. The splenic vessels were intact. There was a soft oval swelling on the posterior aspect of the 6th rib, 6 cm in diameter, also involving the 5th intercostal space in the posterior axillary line. On cut section, the tumor was reddish-brown and contained some yellow streaks. The bony trabeculae were completely destroyed in the region of the tumefaction and the cortex was paper thin.

Microscopic examination. **Liver:** The normal lobular architecture was obliterated. Varying sized islands of liver tissue were seen widely separated and invaded by a highly capillarized neoplastic connective tissue. These islands of liver cells, even those surpassing the size of a normal liver lobule, showed no characteristic central veins. The peripheral triads could occasionally be recognized and some of them were widened by dense connective tissue. From these portal fields radiate connective tissue strands which contain numerous bile duct sprouts and chronic inflammatory cells. Broad bands of this type of connective tissue also could be seen without any relation to the peripheral fields. The arrangement of the hepatic cells was irregular and the individual cells showed great variation in size with occasional giant cells and mitoses.

In certain areas of the remaining liver parenchyma, the blood sinusoids were very dilated

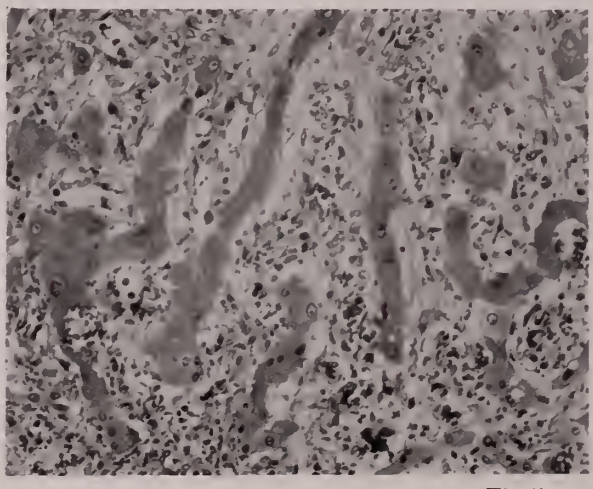

FIG. 1. Field showing liver tissue invaded by vascular tumor. The liver sinusoids are lined by numerous layers of malignant endothelial cells.

and the sinus lining cells were much enlarged, being thicker and longer than normal with a large flat hyperchromatic nucleus and a pink homogeneous indistinct cytoplasm. Other areas, often adjacent to the above, showed the liver sinusoids lined by similar tumor cells, but instead of remaining in a single layer these cells were piled up and filled the sinusoidal spaces (Fig. 1).

In other parts these piled up groups of cells were seen as nodules outside the remaining liver parenchyma. Most of the tumor area was composed of distinct capillary spaces lined by large irregular malignant cells as described above (Fig. 2). In a few alternating areas these capillary units were not distinct because of the proliferation of malignant endothelial cells forming small cords.

The stroma separating the capillaries was often scant and thin but in other places the capillaries were rare and the spindle cellular tumor tissue predominated. On closer examination of the highly vascularized neoplastic areas, one could see that they consisted of a matrix of fibrillar connective tissue within which were embedded spaces containing red blood cells; they were lined by elongated endothelial-like cells many of which showed great variation in size, shape and stainability.

In certain fields, the neoplastic tissue was seen surrounding, invading and progressively breaking up the remnants of liver parenchyma so that often cords of liver cells, in varying degrees of degeneration, were seen in the midst of the tumor tissue (Fig. 1). The tumor was also seen to invade the broad septa of mature connective tissue that separated the pseudolobules, i.e. the cirrhotic bands. In a section near the hilus of the liver, the angiosarcomatous tissue was seen invading the wall of the portal vein, the nerves and a large bile duct branch (Fig. 3). There were a few areas where the vascular tumor tissue, instead of appearing as typical angiosarcoma, was represented as dilated blood spaces appearing as cavernous angiomas; here the lining cells were regular and not primitive.

Rib lesion: There was a large area of similar angiosarcomatous tumor tissue replacing the normal bone marrow architecture. In a few places around these malignant capillary networks were found areas of cavernous blood spaces. There was cell atypism in and around some of the cavernomatous spaces.

In summary, this case is that of a 48 year old male with a diffuse nodular vascular tumor arising in a previously cirrhotic liver. Histologically, the tumor cells were seen to originate from the endothelial cells of the liver sinusoids. Varying stages of differentiation could be noted, the most highly differentiated being seen in some sections of the liver tumor itself

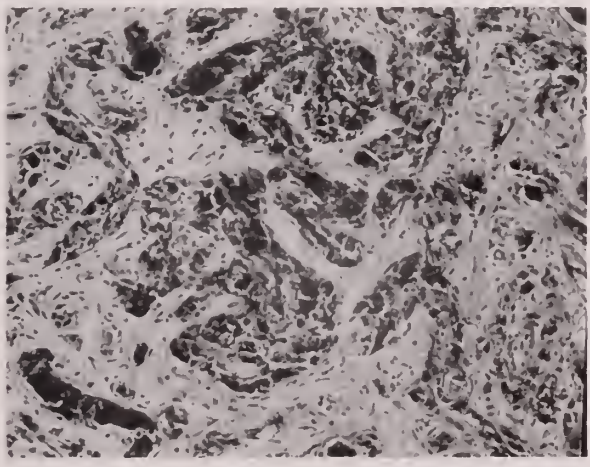

FIG. 2. Angiosarcomatous area in the liver showing distinct capillary spaces lined by large, irregular malignant endothelial cells.

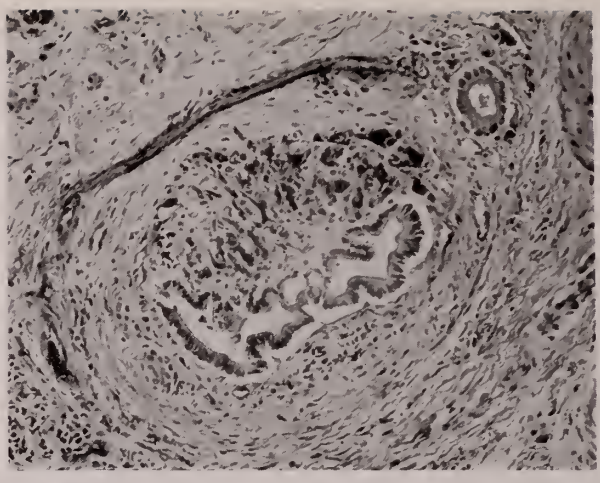

FIG. 3. Invasion of a large bile duct near the hilus of the liver by angiosarcomatous tumor.

and in the bone marrow lesion where cavernous hemangiomas develop. The angiosarcoma was limited to the liver and to one deposit in the 6th rib on the left.

Case 2

Clinical. F.C. (MSH #641131), a 39 year old white female, was admitted to The Mount Sinai Hospital on May 12, 1952 with complaints of increasing weakness and shortness of breath. The patient was in good health until two and a half months before admission when she noted the onset of weakness, palpitations, dizziness, dyspnea and occasional epistaxes. Because of these symptoms, the patient was admitted to another hospital where she was found to be pale and dyspneic. There were moist rales in the right lung and the liver edge was palpable four fingers breadth below the right costal margin. Chest x-rays showed infiltrations and congestive changes in both lungs. Hemogram revealed hemoglobin, 9.7 gms %; RBC, 3.26 millions per cu. mm.; WBC, 45,600 per cu. mm. with 36% segmented and 40% non-segmented neutrophiles, 12% lymphocytes, 6% monocytes, and 30,000 platelets per cu. mm. The icteric index war 22 unitg falling to 10 units; urine urobilinogen, 1:80; bleeding time, 7 min.; clotting time, 5.5 min.; LE preparation, negative. Bone marrow aspiration showed only erythroid hyperplasia. The patient was treated with multiple transfusions and ACTH. Petechiae were noted, epistaxis increased, thrombocytopenia worsened and the temperature remained elevated. After a month of similar treatment, the patient improved symptomatically; the hemoglobin and white blood cell count became normal. She developed abdominal swelling and a paracentesis was done with the removal of 1600 cc of straw colored fluid. No tumor cells were found. Biopsy of a mass in the left breast showed "benign adenomatosis." At home the patient experienced progressive difficulty in moving the left arm and leg. Because of increased weakness and dyspnea she was admitted to The Mount Sinai Hospital.

Physical examination revealed an acutely and chronically ill woman with normal vital signs. There was an irregular, firm, freely movable mass in the upper outer quadrant of the left breast, as well as a small hard left axillary node. Bilateral basilar rales were heated in the lungs. The abdomen was distended with fluid; the liver was firm, slightly nodular and descended to the level of the umbilicus. The spleen was not felt. There was edema of the lower extremities. A complete left sided hemiplegia was present. The remainder of the physical examination was unremarkable.

Laboratory studies revealed: hemoglobin, 9.1 gms. %; RBC, 1.27 million per cu. mm.; HCT 15%, WBC, 21,000 per cu. mm. with 80% segmented, 10% non-segmented neutrophiles,

7% lymphocytes, 3% monocytes and rare myeloblasts; platelets, 8,000 per cu. mm.; reticulocyte count, 11.2%; sedimentation rate, 2 to 15 mm/hr; BUN, 49 mg. %; total protein, 5.1 gm. %; A/G ratio 2.8/2.3; bilirubin, 2.3 mg % (indirect); alkaline phosphatase, 18 KA units; cephalin flocculation 2 plus; thymol turbidity, 7 units; stool guaiac tests, 3 to 4 plus; Coomb's test, negative; RBC fragility, normal.

The diagnosis was obscure; however, it was felt that she had a widespread malignancy with the primary site unknown. Her mental status deteriorated rapidly. The icterus increased and serum bilirubin levels rose to about 3.6 mgm%. The patient expired on the 9th hospital day.

Necropsy. Only the pertinent findings are included in the description. The sclerae and skin were slightly icteric. There was a freely movable, hard, irregular mass 4 cm. in diameter in the upper outer quadrant of the left breast. Discrete cervical and axillary lymph nodes were present. The lungs weighed 1700 grams. They were fleshy and red and show decreased crepitation. Their surface was smooth and showed numerous scattered circular lesions up to half a centimeter in diameter; these were composed of a white center surrounded by a hemorrhagic rim. The underlying lung tissue appeared normal. The liver was enlarged and weighed 2360 grams. The surface was coarsely granular with prominent depressed scars; the color was brownish and it was firm in consistency. The nodules on the surface measured up to half a centimeter in diameter. On cross section the lobular architecture was seen to be completely replaced by these nodules which were yellow and brown in color; their centers often appeared hemorrhagic. The major ducts and blood vessels were unremarkable. The spleen was small, weighing 70 grams. It was firm and smooth. On section, numerous prominent, firm, white areas were seen replacing the usual architecture. Only a small amount of pale red splenic tissue was noted between these nodular areas. The splenic vessels were unremarkable. The small intestinal mucosa showed small, slightly elevated, widely separated lesions always appearing on the antimesenteric side of the bowel. These lesions consisted of a soft brownish pinpoint center surrounded by a firm white area which in turn was bordered by a hemorrhagic halo.

Microscopic examination. **Liver:** The normal lobular architecture in places could be recognized with central veins retaining their normal relationship to the portal spaces. However, most lobules were distorted by strands of fibrous tissue containing numerous bile duct sprouts, chronic inflammatory cells and capillary spaces most of which were collapsed.

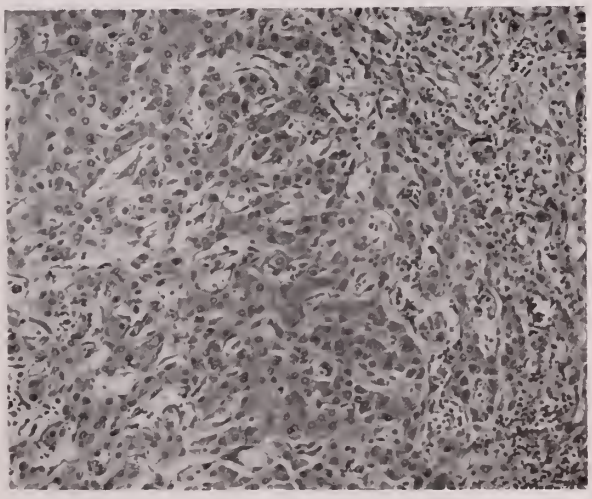

FIG. 4. Section of the liver showing hepatic sinusoids lined by a single layer of large flat cells with large hyperchromatic irregular nuclei and a thin rim of poorly demarcated cytoplasm.

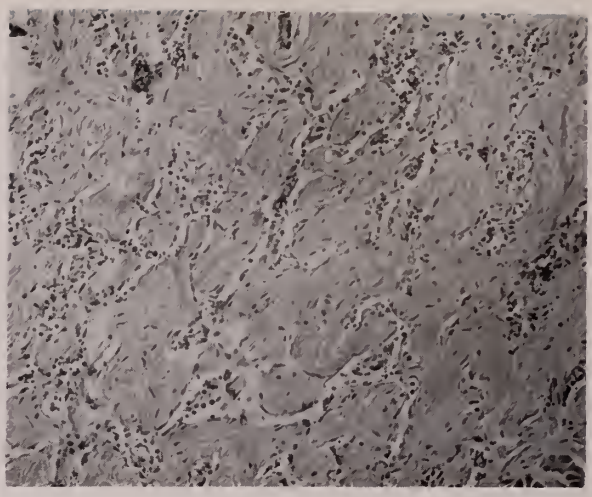

FIG. 5. Section of the liver showing a fibrosing angiomatous portion of the tumor where the knob-like connective tissue projections into capillary lumina are well demonstrated.

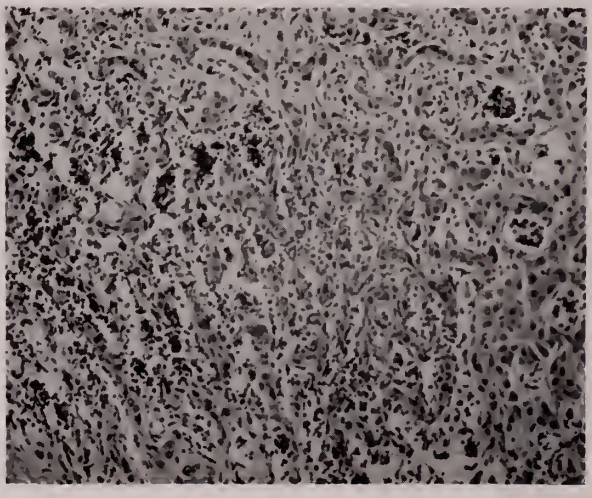

FIG. 6. Islands of hematopoesis located inside angiosarcomatous portions of the liver tumor.

The blood spaces were lined by endothelial-like cells which were large, irregular and had a hyperchromatic nucleus. The blood sinusoids inside the liver lobules were almost uniformly lined by a single layer of large flat cells with large hyperchromatic irregular nuclei and a thin rim of poorly demarcated cytoplasm (Fig. 4). In some areas there was piling up of these cells inside the sinusoidal space to the point of obliteration but without destroying the hepatic cells' lobular arrangement.

Portions of the tumor were formed by capillaries which were separated by loose connective tissue septa. In other areas, the capillaries were reduced in number; the intervening connective tissue was dense and knob-like projections were seen protruding into the lumina (Fig. 5). These fibrosarcomatous areas often could be seen to blend into more vascular parts of the tumor. Diffusely spread within the angiosarcomatous areas were small islands of new

blood formation comprising both erythroblastic and myeloblastic elements, with the former predominating (Fig. 6).

Spleen: The tumor within the spleen formed nodules of varying sizes destroying most of the normal parenchyma but leaving intact the trabeculae within them. The tumor cells seemed to originate from reticulum cells between the splenic sinuses (Fig. 7); the same developmental steps of neoplastic organization, including both angiosarcomatous (Fig. 7) and fibrosarcomatous (Fig. 8) elements were recognized. Similar areas were disseminated in almost every microscopic field. Foci of blood formation were also found inside the splenic tumor.

Lungs: In the lungs the tumor nodules were limited to the thickened pleura and septa; no tumor was seen in the parenchymal portions of the lungs. The angiosarcoma was noted

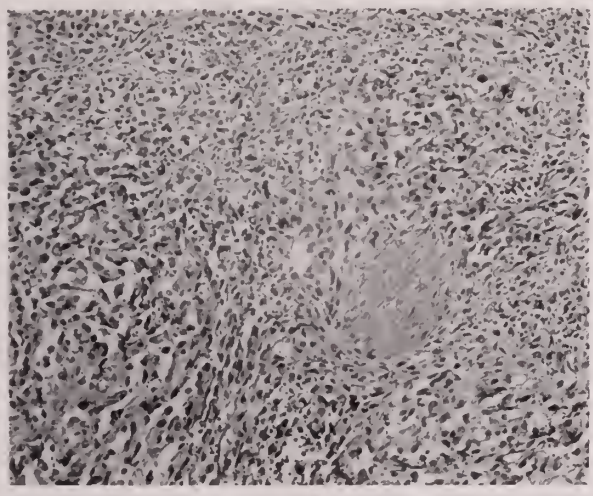

FIG. 7. Angiosarcomatous focus inside the splenic tissue showing splenic sinuses lined by malignant endothelial cells (lower left hand corner); relatively normal splenic pulp in the upper right corner.

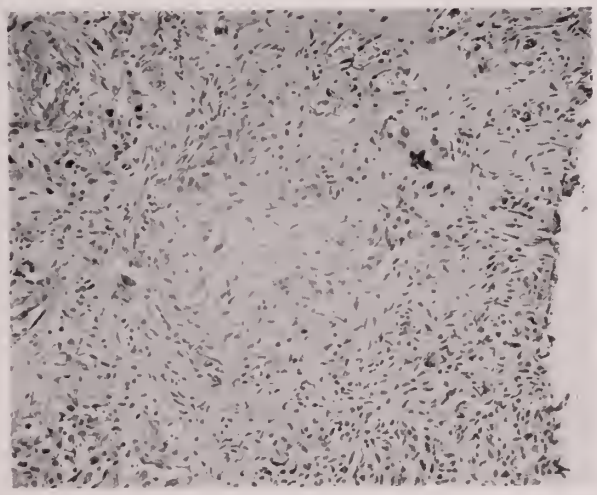

FIG. 8. Fibrosarcomatous portion of the tumor inside the spleen.

to be invading the wall of a medium sized pulmonary vessel. **Other tissues:** In the vertebra both typical angiosarcomatous and mature cavernomatous areas were seen replacing the normal bone marrow. Foci of hemangiosarcoma were also present in the fibrous stroma and fat tissue of the left breast. The left axillary lymph nodes were widely replaced by the same vascular tumor. There were numerous small well demarcated areas of angiosarcoma in the mucosa of the small intestine.

In summary, this is the case of a 39 year old female with diffuse angiosarcomatosis involving especially the liver and spleen but also present in the lungs, small intestine, vertebra, left breast and left axillary lymph nodes. In the liver and the spleen all stages of differentiation from a single layer of malignant sinusoidal endothelium to the fully developed angiosarcomatous tissue could be traced. The neoplastic deposits in the other organs were made up almost exclusively of angiosarcomatous tissue.

DISCUSSION

A number of similarities in the clinical aspects of these cases are found. Both patients' earliest symptoms occurred about two months before initial hospitalization. Their main complaints consisted of abdominal swelling, shortness of breath and weakness; all symptoms of a generalized disease. Case 1 had features pointing to liver involvement, including dark urine and light stools, abdominal pain and weight loss; he also gave a history of heavy alcoholic intake. The physical examinations were more helpful in focusing the attention on the liver. Both patients had definite hepatomegaly and ascites without splenomegaly. Case 1 also had icterus, spider angiomata and gynecomastia. Since this patient was found to have coincidental portal cirrhosis, these symptoms may be understood on this basis alone. Case 2 was complicated by a mass in the left breast with left axillary node enlargement and clinical signs of a right sided cerebrovascular accident.

Miller (2), reporting a case of endothelioma, mentions that, in the adult cases of primary vascular hepatic sarcomas described prior to 1939, the most frequent signs and symptoms were hepatomegaly and progressive loss of weight and strength. Ascites was present in about half the cases and dilated abdominal veins in one third of the cases. Other common findings were enlargement of the abdomen, constipation, hemorrhoids and jaundice. Hastings-James (3) describes a typical vascular hum heard on auscultation over the hepatic region with a respiratory accentuation as being helpful in the diagnosis.

The liver function tests in both our cases showed hyperbilirubinemia, positive cephalin flocculation and a slightly elevated alkaline phosphatase. In Case 1, these were accompanied by a reversal of the A/G ratio, increased bromsulfalein retention, high thymol turbidity and increased urinary urobilinogen. These are easily explained by the coexisting cirrhosis found at autopsy. In neither case did the cell block examination of the ascitic fluid reveal tumor cells. Case 2 had a severe anemia, a moderate leukocytosis with a shift to the left and an unexplained severe thrombocytopenia. A lytic lesion of the posterior aspect of the 6th rib on the left was demonstrated which was correctly interpreted clinically as a metastasis. In neither of our two cases was the diagnosis of hemangioendothelioma entertained clinically. Case 1 was thought to represent decompensated portal cirrhosis. The presence of the lytic rib lesion made the

clinicians suspect either a hepatoma or a coincidental neoplasm, primary site unknown. Case 2 was regarded as a far advanced malignancy with the primary site probably in the left breast.

Pathologically the two cases described conform closely to the criteria laid down by Herxheimer for the diagnosis of hemangioendothelioma of the liver. In 1930 he (4) reviewed 149 cases of primary liver sarcomas published in the world literature until then; of these he accepted only 67 as being genuine cases. More than half were excluded because of the incompleteness of the pathological investigation. Numerous others had neoplasms in sites other than the liver, all of which were more likely to be the locus of the primary malignancy. A third category was excluded because the author felt that the tumors which were primary in the liver were carcinomas and not sarcomas. The author further pointed out that any sarcoma, not necessarily angiosarcoma, can be vascular with malignant cells inside and surrounding blood vessels. Herxheimer stresses that the all important feature of hemangioendothelioma of the liver is the ability to find a continuum between the normal lining sinusoidal endothelial cells and the large atypical neoplastic endothelial-like cells lining the liver sinusoids. This very feature is clearly demonstrated in both our cases in which one can see numerous sinusoids lined by a single layer of large atypical endothelial cells (Fig. 4).

Finding a single layer of tumor cells lining the sinusoids is very strong evidence that these are the sites of origin of the hemangioendothelioma. If the vascular neoplasm were infiltrating into the sinusoids from the outside, such a single layer of tumor cells could not be found. Another supporting observation is the fact that the fully developed angiosarcomatous tissue is never found inside otherwise normal liver lobules.

As in Fischer-Wasels' case (5), a gradual progression from endothelial cells into tumor cells was found in the present cases. The endothelial cells either simultaneously or gradually develop into neoplastic cells destroying adjacent liver cells. This is described by Fischer-Wasels as "discontinuous growth". In our own cases one could observe areas where the tumor cells pile up, filling the sinusoids in which they proliferated and thereby formed nodules surrounded by hepatic cells. These tumor cell nodules, together with the great dilatation of the liver sinusoids by blood, cause the destruction of the adjacent liver cells by compression thus allowing the tumor nodules to "escape" from the liver parenchyma per se. Tumor nodules are thus found either completely devoid of liver tissue or else are still containing remnants of hepatic cells and bile duct sprouts.

As these cells further proliferate they may differentiate into blood cells. Numerous such areas were found in Case 2 both in the liver and the spleen (Fig. 6). Herxheimer (4) mentions that most malignant endotheliomas of the liver present such areas of extramedullary hematopoiesis. This was corroborated by Fischer-Wasels (5), Ogilvie and Mackenzie (6), Hastings-James (3) and Rabson (7).

In Case 2 parts of the tumor assumed an angiofibromatous appearance with knob-like projections invaginating the lumina of the neoplastic blood spaces and separating these from each other (Fig. 5). These areas are similar to those described by Livingston and Klemperer (8) in their case of malignant angioma.

They regarded these as being areas of mesenchymal tissue which had reached the highest degree of differentiation.

In both cases, a large portion of the tumor was made up of typical angiosarcomatous tissue; this is interpreted as being one of the end stages of differentiation of the proliferating sinusoidal endothelial cells (Fig. 2). There were no remaining liver cells in the midst of these tumor areas. The angiosarcoma was seen to behave as a very invasive and malignant tumor. In Case 1, it was seen infiltrating a larger bile duct (Fig. 3).

In each of our cases, but more especially in Case 2, large areas of the tumor were predominantly fibrosarcomatous in nature. This is another end stage of differentiation of the malignant sinusoidal endothelial cell. Another possible interpretation of these fibrosarcomatous areas is that they represent cicatrization of previously angiosarcomatous tissue.

It is important to understand that the mere presence of fibrosarcomatous areas does not preclude the histological diagnosis of a malignant endothelioma. The evidence that one or both of the above interpretations is correct is that angiosarcomatous and fibrosarcomatous areas are often found side by side blending into each other; also both contain cells resembling the single layer of malignant sinusoidal endothelial cells. This same coexistence of tissue type is described by Gray (9) and Kothny (10) who present a similar explanation.

In a few portions of the liver tumor of Case 1 and in the bone marrow lesions of both cases, typical cavernomatous tissue is present. These angiomatous areas represent fully differentiated vascular tissue derived from the malignant sinusoidal endothelial cell. The cavernomas are often lined by endothelial cells which are somewhat atypical, closely resembling the malignant cells seen in other portions of the vascular tumor. Klinge (11) also regards the formation of cavernous spaces inside a malignant endothelioma as "the highest level of differentiation having exhausted all the hematoblastic potential."

Stout (12) is of the opinion that no tumor should be considered a hemangioendothelioma unless it meets the following criteria: (a) the formation of atypical endothelial cells in greater numbers than are required to line the vessels with a single endothelial membrane and (b) the formation of vascular channels with a delicate reticulin fiber framework having a tendency to anastomose.

In Case 1 the primary site of the endothelioma is undoubtedly in the liver. It invades the liver diffusely and, as described above, the stages of differentiation from the malignant endothelial sinusoidal cell to the fully developed angiosarcoma can be traced. The rib lesion probably represents a tumor metastasis in that it is single, relatively well circumscribed and the surrounding tissue is normal. Case 2 however, presents a somewhat different picture. In the liver and the spleen, the tumor is diffusely invasive and in both these organs the same developmental steps can be found, from the single tumor cell layer, through the simple angiomatous formation, to the angiosarcomatous and fibrosarcomatous tissue. The diffuseness of the process is evidence of the malignant transformation of the sinusoidal endothelial cells in the liver as a whole. In the spleen, it is

probably the reticulum cell between the sinusoids that is undergoing neoplastic change. Both in the liver and spleen, but in none of the other organs involved by the tumor, areas of hematopoiesis are found inside tumor tissue. This is so because blood cells can only arise from undifferentiated neoplastic cell types. Once the tumor has developed into angiosarcoma or fibrosarcoma it has lost the potential for hematopoiesis. All these factors strongly favor the view that in Case 2 the tumor is arising primarily in both the liver and spleen. In other words it is multicentric in origin. The tumor found in the lungs, breast, small intestine and bone marrow all represent metastases. In these organs the surrounding tissues including all the endothelial cells are otherwise unremarkable.

The origin and significance of these multiple tumors have been the object of much speculation and discussion in the literature. Herxheimer (4) tries to differentiate between "circumscribed" and a "diffuse" forms of endotheliomata. The former refers to angiosarcomas probably arising from previous cavernomas and the latter represents neoplastic transformation of the capillaries of the entire liver, spleen and reticuloendothelial system. Willis (13, 14) and others (15, 7) agree that the multicentricity of some angiosarcomas is evidence for a malignant change of the Reticuloendothelial System as a whole.

Various authors have recognized the possibility of blood borne metastases to distant organs from the primary endothelioma (16, 2, 7). This is our interpretation of the tumor lesions in the rib of Case 1 and some of the organs as described in Case 2.

Many of the hemangioendotheliomas of the liver described in the literature have occurred in infants and children. In 1933 Kunstadter (17) reviewed 13 cases and added two of his own. He agreed with Foote that these represent congenital rests which have retained their embryonic characteristics (18). Numerous more recent reports tend to confirm this notion (19–24).

In Case 1 there is definite gross and microscopic evidence of a coexisting cirrhosis. Microscopically, the normal lobular architecture is replaced by pseudolobules of hepatic cells separated from each other by broad fibrous bands containing bile duct sprouts; there are no recognizable central veins. Undoubtedly many of the wide connective tissue bands breaking up the liver cells are actually part of the endothelioma. In Case 2 there is no evidence of cirrhosis, the fibrous tissue interspersed among the hepatic cells being an integral part of the hemangioendothelioma.

There is a controversy in the literature as to the relationship, if any, between cirrhosis and hemangioendothelioma. Rolleston (25), reviewing the cases reported before 1911, collected six instances of primary angiosarcoma coincidental with portal cirrhosis. He was of the opinion that the coexistence was fortuitous. Other cases have been reported by Jaffe (26), Gray (9), Ogilvie (6) and Miller (2). All these reports mention the possibility that the angiosarcoma arose in a previously cirrhotic liver with a malignant transformation of the endothelial cells. Another hypothesis suggests that the regeneration of liver lobules and the fibrosis are secondary to the destruction of hepatic tissue by the tumor itself.

In Case 1 the long history of alcoholism and the histological characteristics found tend to support the former view.

SUMMARY

Two cases are described, both of which satisfy the requirements for the diagnosis of primary hemangioendothelioma of the liver. Their clinical histories are presented in some detail in order to point out their characteristic features and similarities. A detailed pathological description is given, followed by a discussion of the various aspects of the problem of pathological diagnosis and pathogenesis. The past literature on the subject is reviewed.

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EXPERIMENTAL PANCREATITIS—A CRITICAL REVIEW

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It is useful in the investigation of the pathophysiology of a disease and in the evaluation of prophylactic and therapeutic measures to produce the disease experimentally in animals. Such an approach not only allows for more freedom in method of research but also permits controlled study of various isolated pathogenetic or therapeutic factors. This ideal method of investigation is not often achieved because of anatomic and physiologic differences between man and the experimental animal employed and also because the disease state to be studied is of complex pathogenesis. The latter comments apply particularly to the problem of pancreatic inflammatory disease for the anatomy of human pancreatic duct system and its blood supply are greatly different from the corresponding structures in the experimental animal. Moreover, it has become apparent from the results of clinical and experimental investigations that acute pancreatitis must be viewed as a disease syndrome of complex and multiple pathogenesis (1).

PATHOGENESIS OF PANCREATITIS

Surgical, postmortem, and experimental evidence lead to the concept of acute pancreatitis as a local autolytic digestion and tissue disruption with the early pathologic features of edema, hemorrhage, and necrosis. Suppuration, fibrosis, calcification, and cyst formation within the pancreatic parenchyma are later processes. Chronic pancreatitis is assumed to be the summation of repeated attacks of acute pancreatitis and intervening attempts at histologic repair (2).

The localized autodigestion of the pancreas which manifests itself in necrosis and disintegration of acinar cells, hemorrhage from necrotic vessels, and fat necrosis are ascribed to the effects of activated proteolytic and lipolytic enzymes which have been liberated from the ductal system into the interstitial pancreatic tissues. Escape of the enzymes may result from factors which cause mechanical disruption of the duct system or from those which alter the permeability of the ductal and acinar epithelium (3–5). Activation of the pancreatic enzymes is an important factor in pathogenesis even though it is true that unactivated pancreatic juice is capable of producing hemorrhagic and fat necrosis when injected into the subcutaneous tissue (3).

Normally the proteolytic enzymes appear in pancreatic juice as inactive trypsinogen and chymotrypsinogen; the pancreatic lipase is secreted in active form. Pancreatic juice also contains protease enzyme inhibitors (6). The liberation of active proteolytic pancreatic enzymes is accomplished by neutralization of these inhibitors. In the intestines, this effect is due to enterokinase; in acute pancreatitis, activation is attributed to bile, inflammatory exudates, or normal tissue fluid (7). Kalser and Grossman in a study of ethionine pancreatitis noted an additional means of enzyme activation (6). They reported an increase in the

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activated enzyme associated with a diminution in enzyme inhibitor both in the secreted pancreatic juice and in the gland substance. This increase in activated enzyme is ascribed to an alteration in the proenzyme-inhibitor equilibrium, a change which has been observed in human pancreatitis (8).

The systemic effects in acute pancreatitis are the result of entry of the pancreatic enzymes and the products of pancreatic enzyme digestion into the bloodstream (9). Amylase, lipase, and trypsin normally enter the bloodstream in small quantity probably by true endocrine secretion as with other digestive enzymes rather than by reabsorption from the duct system (4). With obstruction to the outflow of pancreatic juice from the duct system or with increases in hydrostatic pressure within the system, the passage of enzymes into the blood is markedly accelerated (10). Hence, secretin which stimulates the secretion of bicarbonate and water but not enzymes will, in the presence of pancreatic duct obstruction, cause a rise in serum amylase and lipase (11). There is a similar mechanism which produces the elevations in these serum enzymes that occur in man during cholangiography (12). On the other hand, blood amylase and lipase elevations are observed with pancreatic enzyme secretogogues only in the presence of pancreatic duct obstruction (13), a factor which suggests that the rise in hydrostatic pressure within the ductal system is the immediate pathogenetic agent rather than the ductal obstruction (1).

It is not as easy to demonstrate the presence of pancreatic proteolytic enzymes in the bloodstream because of potent inhibitors in the serum and because these enzymes are not easily differentiated from substances with proteolytic activity which naturally occur in the blood (14). Yet experimental and clinical observations have led to the inescapable conclusion that the entry of these activated enzymes into the bloodstream is responsible in large measure for the shock (9, 15), the cardiac abnormalities (16), the hemorrhagic and blood coagulation defects (17), and ultimately the early demise in the hyperacute cases of acute pancreatitis (18).

ETIOLOGIC FACTORS

The factors recognized to be of significance in the production of pancreatitis (19) have become more numerous and diverse since the classical experiments of Archibald (20) and Rich and Duff (3). The possible etiologic factors may be summarized as follows:

1. Infectious
   - A. Direct Invasion from the Bloodstream—mumps, septicemia
   - B. Lymphatic Spread from an infected Gall Bladder or Common Duct
   - C. Retrogade Direct Spread from the Duodenum or Biliary Tract
2. Mechanical
   - A. Common Channel Theory with Biliary Reflux as in
     - 1) Sphincter Spasm
     - 2) Biliary and Pancreatic Calculi
     - 3) Fibrosis or Hypertophy of the Papilla of Vater
   - B. Pancreatic Ductal Hypertension as seen in

1) Pancreatic Duct Obstruction due to stone, edema, spasm or fibrosis of the sphincter or papilla, ductal metaplasia, tumor, and parasitic infestation
2) Vomiting, Straining, Coughing
3) Hypersecretion due to overeating or alcoholism

3. Vascular
   A. Venous Stasis due to local edema, shock
   B. Vascular Spasm
   C. Embolism, Infarction, and Arteriolosclerotic Rupture
   D. Allergic Reaction—Arteritis, Atopy
4. Metabolic
   A. Mucoviscidiosis
   B. Essential Hyperlipemia
   C. Dietary Deficiency
      1) Kwashiorkor
      2) Alcoholism
      3) Sprue, Ulcerative Colitis, Jejunoileitis
5. Noxious
   A. Methanol
   B. Ethionine
   C. Zinc
6. Traumatic
   A. Non-Operative
   B. Operative.

The experimental evidence indicates that though infection may be the occasional cause of pancreatitis and may be a contributing factor in the pathogenesis, it probably plays an insignificant role in the vast majority of cases. The clinical evidence for an infectious etiology includes the appearance of acute pancreatitis in mumps (21), scarlet fever, and typhoid (22), as well as the classical association between biliary tract disease and pancreatitis (23). The latter association, so common that it cannot be disregarded, probably derives from mechanical factors.

A mechanical etiology, though not proven, offers at present, the most cogent explanation of the pathogenesis of acute pancreatitis. The common channel theory, though based upon an anatomic configuration in association with the reflux of bile into the pancreatic duct system, implies pancreatic ductal obstruction. It is this obstruction whether produced by sphincter spasm, edema, fibrosis, tumor or stone which is the potential basis for the dynamic sequence—pancreatic secretion, ductal obstruction, ductal hypertension, ductal rupture, extravasation of pancreatic juice into the interstitial tissues—which probably occurs in the majority of cases of acute pancreatitis.

Vascular and metabolic etiologies have received little attention until recently, but these factors, though their role may be secondary and contributory, may undoubtedly be decisive agents in the production of pancreatitis. Trauma as an etiology is of importance to the surgeon, occurring most frequently as a result of

surgical error in procedures about the head of the pancreas. Pancreatic poisons appear to be of minor importance in the pathogenesis of pancreatitis.

METHODS OF PRODUCING PANCREATITIS

Pancreatitis may be produced experimentally by one of five methods:

1) obstruction of the ducts
2) impairment of the blood supply
3) mechanical or chemical trauma
4) metabolic derangment
5) local anaphylaxis

The degree and type of pathology which occurs in the pancreas after simple ductal ligation varies with the species of experimental animal and the level of secretory activity of the gland. In general, ligation in the presence of copious secretion gives a more severe pancreatitis than ligation of the ducts in the unstimulated gland. The presence of impaired blood supply also adds to the severity of the histologic change.

In rats, ductal obstruction produces edema, inflammation, disintegration of acinae, as well as fat necrosis in and about the pancreas. The severity of reaction does not appear to be altered by the presence or absence of bile in the pancreas nor by stimulation of the gland with food or drugs (24). Evidence that the bile factor in pancreatitis has been much exaggerated has been furnished by Whitrock et al (25) who found that in goats shunting the entire biliary flow through the pancreatic duct system into the duodenum did not result in pancreatic necrosis.

In cats, Lium and Maddock (26) showed that ductal ligation alone produced pancreatic edema. Stimulation of pancreatic flow superimposed on ductal obstruction resulted in acinar necrosis, fat digestion, and minimal hemorrhagic necrosis in 14 out of 17 animals. Only five of these showed all the histologic changes mentioned.

Wang et al found little pancreatic inflammatory reaction in rabbits following ligation of the pancreatic ducts but there was ductal dilatation, acinar atrophy, and interlobular fibrosis (27). Stimulation of the pancreatic secretion in these animals following ductal ligation did not induce other pathologic changes.

Popper and Necheles studied the effect of ductal ligation in dogs (28). Ligation of the ducts followed by intravenous secretin produced pancreatic edema without fat or hemorrhagic necrosis in four dogs. However, ductal ligation with stimulation of the pancreas by mecholyl or pilocarpine did not produce pancreatic edema in four other dogs. In another series, these observers reported the effects of the superimposition of vascular impairment on ductal ligation in dogs (29). Of four dogs treated with ductal ligation and secretin stimulation, three developed pancreatic edema. Two dogs, having ductal and arterial ligation did not develop edematous pancreatitis. In nine animals ductal ligation and vascular occlusion were followed by secretin stimulation. Eight of these showed hemorrhagic pancreatic necrosis. Popper and Necheles concluded that ductal ligation of the actively secreting pancreas resulted in edema; vascular occlusion, in addition, superimposed necrosis and hemorrhage.

In all animals, prolonged pancreatic duct obstruction leads to atrophy and fibrosis. Stimulation of the gland during obstruction results in varying degrees of pancreatitis. Wangensteen et al have demonstrated actual ductal rupture under these conditions (30). Parenchymal ischemia appears to accelerate the histologic alterations induced by hypersecretion against obstruction and results in necrosis and hemorrhage.

The forcible injection of fluids into the pancreatic duct system causes disruption of the ductules by mechanical and/or chemical trauma. This results in severe hemorrhagic necrosis. The mere passage of fluids under physiologic pressures into the pancreatic duct system causes little or no histologic change, but Rich and Duff showed that the entrance of chemical irritants such as bile will produce transient edema (3). Mann and Giordano demonstrated that physiologic saline when injected forcibly at pressures above 300 mm H_2O induces pancreatitis (31). They stressed that it was the high pressure which forcibly disrupted the ducts and produced the pathology and questioned, together with Rich and Duff, whether such pressures were likely to occur spontaneously in conjunction with an anatomic common channel. Even the increase in intra-abdominal pressure which occurs with vomiting was not sufficient in the studies of Mann and Giordano to produce pancreatic ductal pressures required for the forcible rupture of the ducts.

Clinically there is some evidence that ductal rupture due to increased hydrostatic pressures initiates pancreatitis. Howell and Bergh reported elevations of the serum amylase in 52 patients in whom the pancreatic duct filled by reflux from the common duct during cholangiography (32). In all but four, the pressure of injection was below 300 mm H_2O. In two of the four patients in whom the injection pressure rose above 300 mm H_2O, the clinical symptoms of pancreatitis were observed. The frequent history of a large meal preceding an attack of acute pancreatitis also suggests that increased ductal pressure and subsequent rupture occur in man at least as an etiologic factor in pancreatitis.

Metabolic factors have been observed clinically in deficiency states of children (33, 34) and have been employed experimentally to induce pancreatitis. Acinar atrophy and pancreatic fibrosis have been reported in rats fed on various diets, all essentially low in complete proteins (35). Lindsay noted cirrhosis and moderate fat necrosis in addition to pancreatic fibrosis in dogs fed a protein deficient diet (36).

Alcohol has not been used experimentally to induce pancreatitis because of the complexity of pathogenesis with this agent. Unlike methanol, ethyl alcohol is not a direct pancreatic poison (37). Alcoholism in man appears to incite pancreatitis through factors:

1. which cause pancreatic ductal obstruction
   a) duodenitis (38)
   b) papillary edema (39)
2. which increase pancreatic ductal pressure
   a) stimulation of secretion (40, 41)
   b) vomiting (42)
3. which cause a nutritional deficiency.

Dreiling and Richman demonstrated in man that alcohol did not directly stimulate pancreatic flow (40). Oral ingestion of this substance, however, could stimulate large volumes of pancreatic secretion indirectly via the acid-secretin mechanism. These findings were confirmed in the dog by Brooks and Thomas (41). Dreiling and Richman postulated that alcohol produced pancreatitis by simultaneously obstructing the pancreatic duct system (edema of the papilla) and inducing the copious flow of pancreatic juice within the obstructed ducts (acid-secretin mechanism). This caused ductal hypertension and ductal rupture.

Ethionine has been extensively used to produce experimental pancreatitis. This drug is an antagonist of the essential amino acid methionine. Intravenous injection of a large single dose into dogs causes a marked diminution of the enzyme content of the external pancreatic secretion without impairment of flow and without cellular change (43). However, the concentration of trypsin inhibitor falls and the content of active proteolytic enzyme rises in the juice secreted (44). Similar changes in the proenzyme-inhibitor ratio have been observed in patients with pancreatitis (45). Continued feeding or injection of ethionine results in progressive histologic alterations. With low dosage schedules, atrophy, acinar disruption, and fibrosis occur (46); with higher dosage there is severe fat and hemorrhagic necrosis (47). Ethionine pancreatitis has not been reported in man even though the drug has been used experimentally in patients with pancreatic cancer.

Impressed with the vascular factors in pancreatitis (48), Thal has produced pancreatitis experimentally by both the local Schwartzman (49) and the Arthus (50) phenomena. He is of the opinion that the bile factor in pancreatitis operates through a purely vascular effect (51). His experiments have shown that the interstitial injection of bile causes extensive and prolonged circulatory stasis within the pancreatic parenchyma both by direct action on the capillary wall and by spasm of the muscular coat of the arteriole. Yet extensive bile staining of the pancreatic parenchyma has not been demonstrated either in pancreatic edema or in pancreatic necrosis.

COMMENT

The production of pancreatitis experimentally in animals is beset with difficulties similar to the problem of reproducing peptic ulceration in the laboratory. The anatomic structure of the pancreatic ductal system within the gland and its relationship to the common duct are nowhere mimicked in the animal kingdom. For this reason any method employed to produce experimental pancreatitis must be regarded as a compromise measure in which the etiologic agent or agents probably do not have the same weight as the corresponding factors in spontaneous human pancreatitis. Therefore, it will always be impossible to evaluate the significance of the various etiologic factors operative in human pancreatitis from data obtained in experimental pancreatitis. Such conclusions can only be drawn from observations made in patients; the experimental results must be prejudiced by the experimental method. Likewise, a true estimation of the prophylactic and/or therapeutic efficacy of any measure cannot be established from studies in

experimental pancreatitis but requires direct investigation in human cases. The results in animal experiments will always be markedly influenced by the method of production of pancreatitis.

Most investigations have been performed utilizing procedures which mechanically obstruct the pancreatic duct, attesting to the widespread acceptance of a mechanistic etiology. Yet such an approach entirely neglects the vascular and metabolic factors which recent studies have shown to be of great significance in the pathophysiology of pancreatitis. Many of the mechanical methods must be criticized on two accounts. First, there has been practically no study in which the method employed and the results of investigation have been conducted according to statistical criteria. Second, the procedures themselves usually impose dynamic conditions which are far in exaggeration of what might possibly occur in the pathogenesis of human pancreatitis. This is particularly true of those methods depending upon the forcible injection of fluids, irritating or bland, into or about the pancreatic duct. The trend should be away from such overemphasis of mechanical factors and towards a preparation in which the pathogenesis appears to result from several etiologic agents such as obtained with ductal obstruction in an ischemic secreting gland.

Further study of vascular and metabolic factors is of great importance in the elucidation of pancreatic physiology and related physiologic phenomena. The sensitization methods of Thal are extremely interesting and may lead to an understanding of the explosive character of human pancreatitis but the weight of evidence would assign such an etiologic factor only to a secondary or minor role. Likewise, the production of pancreatitis with ethionine would not appear to be a satisfactory method for the study of the problems of acute pancreatitis in man. Interference with pancreatic protein metabolism by this amino acid will more likely clarify the pathogenesis of the rare fibroses and chronic inflammatory disorders associated with various nutritional deficiencies and congenital metabolic defects.

CONCLUSIONS

The etiology, pathogenesis, and experimental methods of producing pancreatitis have been critically reviewed. A completely satisfactory experimental preparation for the study of etiologic, prophylactic, and therapeutic factors in human pancreatitis appears to be unobtainable.

The majority of cases of acute pancreatitis in man seem to result from the summation of mechanical, secretory, and vascular factors. For this reason, the most useful experimental method should be one which employs these, namely, ductal obstruction, active secretion, and diminished blood flow. There is a need to study such a technique statistically before individual variables and therapeutic measures are evaluated.

Vascular techniques and those involving aberration of pancreatic metabolism, though less useful in the investigation of etiology and therapy of human pancreatic disease, are of great importance in the unravelling of the basic physiology of that organ.

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CLINICAL CONFERENCE

EARLY RECOGNITION AND MANAGEMENT OF PSYCHIATRIC DISORDERS IN GENERAL PRACTICE

THE MOUNT SINAI HOSPITAL

Monday, April 22, 1957

Chairman King:

Ladies and gentlemen, tonight we have made a departure from our conventional scheme of presentation. It has been our policy up to now to present subjects with cases which illustrate various phases of the subject, and then have discussion which is pertinent to the phases involved. In so doing, we try to have representation at these meetings from as many services as possible. But tonight we have the privilege of hearing from one department only; the department of psychiatry which has chosen to devote this meeting to a discussion of the early recognition and management of anxiety states, depression and schizophrenia.

Dr. Ralph Kaufman, Director of the Department of Psychiatry will conduct this meeting in which the members of his staff will participate.

INTRODUCTION

Dr. Ralph Kaufman:

Thank you, Dr. King. Dr. King informed me that I was to take twenty minutes for this, but since I know psychiatrists and since they like to talk, I'm going to take about five so that the people who are going to present the cases and the discussion will have at least an extra fifteen minutes.

The purpose of this evening's conference is to discuss, "The Early Recognition and Management of Psychiatric Disorders in General Practice," and in order to implement the discussion three illustrative situations have been selected for presentation.

Psychiatry in recent years, has moved out of the confines of the state and private mental hospitals. This shift has had many implications for the practice of medicine. It has broadened the base of clinical syndromes that are recognized as psychiatric or as having psychiatric implications. It has focused on various psychological and emotional aspects of all illness, and it has emphasized the

need for an evaluation of these factors in all diagnostic and therapeutic programs. An illustration of this is a study done at our own Consultation Service, which demonstrated that of an unselected group of a thousand patients who came to the Consultation Service at the request of their physicians, 814 or 81.4 per cent of the patients had a psychiatric condition which was either of primary or secondary significance in their illness. It is hoped that tonight's discussion will demonstrate the importance of the recognition of the psychiatric factors in relation to all patients and not only those who are commonly placed in the category labeled psychosomatic.

There has been a tendency to limit the illnesses labeled as psychosomatic to certain syndromes such as ulcerative colitis, asthma, peptic ulcer, etc. This is a misapprehension of a basic concept. We should like to emphasize that psychological and emotional factors are involved in all instances of illness without regard to the presence or absence of somatic pathology. With a more generalized knowledge of the basic psychiatric concepts permeating throughout the whole of medicine, the general physician who is not a specialist is now in a position to formulate more clearly the total clinical picture than he ever was before. At the psychological level, his knowledge of the role of the patient-physician relationship and various aspects of psychotherapy permit him to convert the art of the practice of medicine into the science of the practice of medicine. The recent advent of the so-called tranquilizing drugs have increased the responsibility of a physician for sharpening his diagnostic acumen and a pinpointing of his therapeutic endeavors. It has become increasingly clear that any medication that has a widespread utilization in medicine calls for a more accurate diagnosis since otherwise, as has been aptly demonstrated by the antibiotics, the use of such medication ends up in its abuse. Certainly a combination of psychotherapy appropriate to the role of the general physician in combination with the use of pharmacological agents selectively prescribed, enables the present-day physician to treat a greater number of patients for psychiatric syndromes than heretofore.

The essential of good medical practice is to utilize to the fullest extent the training and techniques available to a given physician and at the same time to have that physician capable of recognizing his own limitation in order that colleagues specializing in various other fields, should be called in for consultation and treatment appropriate to their knowledge and skills. The aim of modern psychiatry as a basic science in medicine, is not to transform the general practitioner into a specialist in psychiatry, but rather to give him the necessary knowledge and techniques which will enable him to carry out his role as a general practitioner to his fullest extent. It is hoped that tonight's presentation will be a step in that direction, and that the three topics for discussion are illustrative, in a sense, of the problems involved because obviously there are many more areas than are presented in the three subjects selected tonight.

The first topic, Anxiety Reaction, will be introduced by a clinical presentation by Dr. David Schulman.

ANXIETY REACTION

Case Report

Dr. David Schulman:

The patient is a 36 year old married Jewish housewife who lives in Brooklyn with her husband and two daughters, ages four-and-a-half and fourteen months.

When first seen she was agitated, anxious and fearful. Her speech was characterized by marked urgency and she described herself as being "doomed to die." She considered herself to be well until November of 1955, at which time her mother experienced an acute coronary occlusion and was hospitalized.

She was an only child and was constantly at her mother's bedside. On the third day of her mother's illness, she was told by the family physician that her mother would be all right, and at his insistence she left her mother's side and returned home. At home she received a call from the hospital informing her of her mother's sudden death. She immediately recalled numerous situations in which she had scolded, belittled and neglected her mother and she thought if she had been a better daughter, her mother might not have died. Her sense of guilt was extreme. That night she had a dream in which a friend was sick in a hospital. In the dream she saw herself talking to her friend's husband in the hospital corridor. He told her that his wife had had surgery for a breast tumor and that the surgeons had told him that the tumor was not malignant. On awakening, she considered the dream to be a prophetic one based on her expectation of punishment due to her guilt. She immediately felt her own breasts as if she were the woman in the dream. She was alarmed to find in her left breast a mass which was easily palpable. She visited her family physician who recommended immediate surgery. Her doctor indicated that, since she had just had her second child in July of 1955, more likely than not the mass represented a "milk gland".

She went to her mother's funeral and, three days later, entered the hospital for breast surgery. In regard to this she said, "The dream was true. I had a fibroid tumor. It was not malignant and I came home in two days."

During psychotherapy it became clear that she had had a peripheral awareness of the mass prior to her mother's death and that she was able to recognize this only when the emotional need required it. Two weeks prior to her mother's death she and her family, including the mother, had moved into a new apartment. The mother had lived with the patient ever since the father's death eight years before. The patient often had wished that she did not have to care for her mother because the mother had frequently interfered with the management of the house and children. Following the breast surgery, she returned to a new apartment without mother. The fulfillment of her wish to be free of her mother and her fears of being on her own were the source of marked anxiety and guilt. Throughout January she felt she could not do anything right. She complained of marked fatigue, chest pains, palpitations and shortness of breath. In February she passed black stools on four occasions and became panicky. She began to feel that she had cancer and started to visit every doctor in her neighborhood. She reported that one doctor told her that she had colitis and the other that she had ulcers. Eventually an upper gastrointestinal series and barium enema x-ray studies were done and reported as being within normal limits. She was told that she did not have any organic disease. Nevertheless, she continued to feel that she had cancer and said that the doctors were keeping the "bad news from her." During the next few months she began to experience a variety of somatic symptoms including pain in the eyes, recurrent headaches, dizziness, feeling of emptiness in the head, abdominal cramps, chest pain and palpitation. She began to feel that she could no longer meet the demands of her house, husband, children and mother-in-law and started to use alcohol to obtain some relief from the symptoms. She used a pint of whiskey every two days. She felt that her husband did not understand her illness and was unsympathetic towards it. She resented the fact that throughout her illness, her husband had begun to assume her duties in the household much the same as her mother had done before.

In September of 1956 her symptoms became overwhelming to her and she finally accepted the view that some of the symptoms might be on an emotional basis. On the advice of a physician she voluntarily entered the Kings County Hospital Psychiatric Division. After about a three hour stay she became terrified and, on her husband's insistence, was discharged in his custody.

She began to drink more heavily than before and became fearful that she might become an alcoholic. About two weeks prior to admission to The Mount Sinai Hospital she stopped drinking entirely and this was associated with an increase in her symptoms and her feeling that she might die suddenly. On September 26, 1956 she was admitted to the psychiatric service. On arrival, she experienced a remarkable spontaneous cessation of all symptoms and felt that being away from her home, husband and children was responsible for her immediate improvement. On the second hospital day she had a return of her entire symptom complex. It was at this time that she revealed that she had a dream in September 1955 which she felt was prophetic. In this dream she felt that she was sick and that the doctor told her husband that she had cancer and had only one year to live. After this dream she continued to harbor the feeling that she would die in September of 1956. Thus, the exacerbation of her illness seemed part of a postmourning reaction for her mother.

In the hospital she was seen daily in intensive psychotherapy. In discussing her relationship with her mother, she finally was able to reveal that they had argued frequently and that she resented her mother's suggestions about her management of the household and children. She was able to express and understand some of her anger towards her mother and this was accompanied by a reduction in her sense of guilt. Through the course of treatment it became clear to her that she had held herself responsible for her mother's death and that the development of her symptoms was an attempt to expiate her own guilt. In a way she unconsciously was responding to the Biblical concept of an eye for an eye in that she felt that as a result of her mother's death that she too must die.

In the stress-free environment of the hospital ward and through her relationship with the therapist, she was able to reorganize her defenses which resulted in complete cessation of all her symptoms. During the treatment period she recalled that she had taken some iron medication in February of 1956 which undoubtedly was responsible for her black stools, although she had completely repressed this material at the time. After five weeks of hospitalization, she was discharged to the After-Care-Clinic. During the week of Memorial Services, one year after her mother's death, she had a moderate recurrence of her symptoms. Following the termination of these services and a trying period throughout the last week of December, she felt better. In January of 1957 after she had been home for two and a half months, she "accidentally" became pregnant, and this was accompanied by a return of her feelings of guilt, anxiety and inability to perform her household duties. She did not have somatic symptoms but her anxiety was extreme and immobilizing. She was readmitted to The Mount Sinai Hospital during the first week of March and after a period of three weeks she felt much better and was discharged to the Clinic.

In summary, this was a woman in whom the death of her mother in the setting of a hostile mother-daughter relationship led to guilt feelings and expectancy of punishment. She unconsciously felt that she must die because her mother had died. When she was made aware of her resentment of her mother and given an opportunity to ventilate her feelings in a permissive setting, her guilt and anxiety subsided. As of June 1957, the patient continues to be free of symptoms and has made realistic plans for her unborn baby.

Chairman Kaufman:

Thank you, Dr. Schulman.

Dr. Louis Linn will discuss this aspect of the presentation.

Discussion

Dr. Louis Linn:

The most important point about anxiety is that it represents a danger signal for the human organism. It is experienced as a disagreeable sensation which has the effect of alerting the organism to the necessity of taking flight or fighting back. The danger which elicits the anxiety may take the form of a real threatening situation in the outer world, as when a soldier is about to go into battle, or a patient about to undergo major surgery. The threat may come from within the patient's body, as when he is confronted with pain or some other symptom of unknown origin which arouses feelings of dread. Thus the anxiety may be related to a danger which is objectively identifiable and the suffering, in addition, may not seem disproportionate quantitatively to the situation which elicits it. In such circumstances, we are apt to refer to the experience as realistic fear, rather than anxiety.

Anxiety as a term, is more frequently used or reserved for conditions in which the reaction of fear is not based on an objectively identifiable external reality, or seems disproportionate in its intensity in terms of the actual danger. Thus, the patient may have a fear of riding in subways, of being alone, or of being in crowds. He may, like the patient presented, have an unwarranted fear of cancer. He may have a fear of dirt which drives him to a handwashing compulsion. The actual form that these pathological fear states may take is almost limitless and, in its details, is distinctive for each patient. In some the anxiety state may not relate to a specific life situation but is part of a panphobic attitude in which the entire world, in all its aspects, has become fearful. The reactions to realistic danger and the pathological reactions both have sensations in common which are identifiable as fear and are associated with a variety of psychological and physiological changes calculated to alert the organism to flight or fight.

The next most important point about anxiety, as far as the clinician is concerned, is the task of identifying the danger to which the patient is responding. Not so long ago it was said in jest that if a patient had fever, you gave him a shot of penicillin, and 24 hours later if the temperature hadn't dropped to normal, then you took a history and did a physical examination. Well, something of the same sort of situation has occurred in the psychiatric field too. If a patient comes in with symptoms that are identifiable as anxiety, nowadays he is apt to get a tranquilizer drug of one kind or another from some people, and if within a day or two his anxiety has not subsided, then for the first time, he may get a fair hearing of his personal problem. In my own experience, meprobamate or, as it is more commonly known, Miltown® or Equanil®, has been most helpful in situations of realistic stress such as during the process of dissolving a marriage which cannot be salvaged, in the suffering of a person after a bereavement, in a patient unable to become reconciled post-operatively to a mutilating surgical procedure, in certain high tension states as in the case of a lawyer involved in preparing a complicated legal brief, or an overworked executive carrying a

tremendous burden of responsibility. Unfortunately, the pathological fear states which present the most challenging problem to the physician are the ones least likely to be benefited by these drugs. Not only are such patients least likely to be benefited but, paradoxically, they may even react with exacerbations of the pathological state. Such reactions are not likely to be regarded as paradoxical, however, if one attempts to understand the danger, as the patient sees it. For example, recently I treated a patient with unconscious homosexual impulses which were clinically expressed as a cancerphobia. I will not go into the details of why his homosexual impulses translated themselves into a fear of having cancer, however, the cancerphobia served the purpose of defending him against the wish to give in to his homosexual impulses. Meprobromate did free him from his anxiety, but in its place there appeared a more terrible dread. He said, "I felt that the fear-free-state was not me. I felt as if some vital part of me had been cut away. I couldn't stand it. It was uncanny." To this patient, giving up his cancerphobia was tantamount to laying himself open to homosexual attack. Against such a background it becomes understandable that he did not welcome the anxiety-allaying effect of meprobromate.

Another patient, a female, with frightening-fantasies of indulging in exhibitionistic sexual behavior in public, reacted to the pharmacologic liberation from anxiety which she got from meprobromate with dread rather than the anticipated joy. She compared the effect of the drug to the cutting of the wires to a fire alarm. "Sure the clamor of the fire alarm is silenced, but the fire goes on unabated and nobody is warning me to fight it."

Another patient, a young man 32 years old, suffered from the unconscious fantasy that the female genitalia represented a mysterious engine of destruction to be avoided at all costs. Along with this unconscious fear was a conscious understandable yearning for the normal adult sex life which this fantasy prevented. Dates with girls were always fraught with anxiety and, if there seemed any likelihood that there might be opportunity for sexual intercourse, his anxiety would assume the proportions of panic. A physician prescribed meprobromate to be taken before going out on a date. Like our previous patients, he experienced a great release from anxiety on his next date. As a result, he took his girl home earlier than ever and spent the rest of the night alone in his room masturbating, as though to save himself from the trap which his anxiety-free-state might set for him.

Another young man, whose great problem was the need to conceal his aggressive impulses, suffered intolerable anxiety at any evidence of breakthrough of his aggression. He took meprobromate and experienced striking relief. Following this, he was seized with the troubling thought, "This drug can put Dr. Linn out of business!" This idea was associated with so much anxiety that he decided not to take the pill again. As if to emphasize that his cure was not to be found this way, he masturbated several times the night of this experience.

All of the patients cited refused to take meprobromate after reactions which superficially would seem to have been helpful. These cases emphasize that the task of the physician is to discover the danger to which the patient is reacting and to help him deal with that danger more realistically.

The uncritical use of tranquilizing procedures is not only irrational therapy, but, in some instances, may result in lasting harm. A young colored woman, for example, was brought into our Emergency Room, at 10:00 p.m. in a terrified state, complaining of a painful adductor spasm of her thighs. As a result of this she could not walk. Physical examination revealed the absence of any organic basis for her paralysis. She was given intravenous sodium amytal with the strong suggestion that as a result of that injection she would be able to walk. A few minutes later she hopped from the table and demonstrated gleefully that she was indeed able to walk and to dance. She left the Emergency Room in high spirits chatting volubly with members of the family who had accompanied her. She continued to talk without interruption until four o'clock in the morning. When she stopped she did not open her mouth again. She lapsed into a mute stuporous state. When she was returned to the hospital the next day, it was quite clear that she was in a catatonic stupor. Further history brought out the fact that she had recently come from the South as a visitor in the home of her sister and brother-in-law. There was reason to believe that she was sexually attracted to her brother-in-law. Her anxiety and the hysterical symptom represented her attempt to ward off the forbidden impulses. In this instance, indiscriminate removal of her protective adductor spasm left her defenseless in the face of her intolerable sexual desires and the result was a more deeply regressed state in the form of a catatonic stupor.

When a protective symptom is rendered inoperable, as in the previous case, then a flood of anxiety is released which may, at times, be overwhelming in its quantity and intensity. The clinical picture which then emerges may be characterized variously as a delirium, a catatonic excitement, or a state of panic. Many factors may render previous defenses inoperable. An alcoholic who has maintained his psychological adaptation in an inebriated state may go into a delirium if alcohol is suddenly taken from him. Similar states of excitement may be encountered when the eliminated supporting agent is a barbiturate, an opiate, or any other potent sedative. A patient with organic brain disease may be placid and even outwardly cheerful as he confronts the world in a twilight state of semi-consciousness. When he improves, particularly if this occurs suddenly, as sometimes is seen after a sub-arachnoid hemorrhage, he may be left temporarily without adequate defenses. The result is a delirium. It is worth emphasizing that the reaction of delirium in such cases is often the first sign of improvement, in spite of the fearful clinical picture which it presents.

A young man who is able to keep unconscious homosexual tendencies under control in ordinary civilian circumstances, may lose control of these impulses in the enforced physical intimacies of barracks life as a soldier. The result may be an acute delirium which is sometimes referred to as homosexual panic.

The following is an instance in which a previous state of psychological balance was disrupted by a particular factor. This patient was a 48 year old woman who lived a socially restricted existence because of cardiac invalidism. She was catapulated into a new world after a successful commissurotomy for mitral stenosis. She had experienced no anxiety at all in her socially protected state of invalidism. In this new setting, however, she was overwhelmed with anxiety.

Sexual wishes and fears which she did not have to face heretofore, flooded into consciousness. She experienced difficulty in falling asleep and an increasing tendency to early waking; both common signs of mounting anxiety. When she was sent to Miami, under the common but erroneous impression that Miami is a good place for nervous people, she became floridly psychotic. The psychosis subsided only after months of treatment in this hospital. She was discharged improved but under continued outpatient supervision.

The tranquilizing drugs, particularly the promazines, achieve their most useful application in the treatment of acute excited states. The patient in a state of acute psychological defenselessness is, in a fundamental sense, at a crossroad. To the degree that the acute psychotic reaction becomes stabilized and chronic, this is a malignant solution to the problem. Many times, however, we are able to reduce the quantity of anxiety by tranquilizers to levels which the patient is able to tolerate better. In this setting of reduced anxiety, we have an opportunity to offer the patient psychotherapy through which he may reorganize his defenses under more favorable circumstances and the result may be a more benign solution to the psychiatric crisis.

To repeat then, anxiety is first and foremost a signal of danger and any rational program of treatment of anxiety depends on a search for the danger to which the patient actually is reacting. It must be apparent from the cases cited that it is often difficult to delineate the psychological origins of this anxiety. These are usually to be found in the misconceptions about the world learned in early childhood. It should come as no surprise therefore, that the patient's ideas often fly in the face of adult logic and are resistant to common sense. This last remark is not said to belittle the value of common sense in general practice in helping the anxious patient. On the contrary, a warm, genuine, human relationship implemented by adult intelligence is still a most powerful psychotherapeutic instrument. Too often, however, common sense alone is not enough. The specialized skills of the psychiatrist must then be called into play to formulate the nature of the psychological trauma. The psychiatrist in turn must often depend on the special skills of the clinical psychologist and the social worker to complete his own understanding of the clinical picture.

May I end with a quotation from a great Jewish physician-rabbi of the 12th century, Moses Maimonides? He said, "Emotions affect the body and produce great changes in the state of one's health. Physicians, therefore, are advised that the emotions be observed, regularly examined, and kept in balance. This is essential for the cure of every patient, especially for mental cases like hypochondriacs and patients afflicted with depression and melancholia, . . . or assailed by hallucinations, or by nervous anxiety in matters that should not cause distress, or by lack of cheer in situations that usually give joy. *The physician should apply no treatment before he removes the irritating causes.*"

And so, in psychiatry, as in all other branches of medicine, one should seek to replace therapy that is purely symptomatic with therapy that is rationally based on an understanding of etiology.

Chairman Kaufman:

Thank you very much, Dr. Linn.

The next area for discussion is again a very common one, Depression. Dr. Zucker will make the presentation.

DEPRESSION

Case Report

Dr. Howard D. Zucker:

Mrs. S., a 65 year old white Jewish housewife, was admitted to the Psychiatric Service of our hospital on August 14, 1956. Her presenting complaints were weakness, weight loss and a hopelessness about her physical condition. Some of her somatic preoccupations, in addition to weakness and weight loss, included diabetes mellitus, sleeplessness, anorexia and painful gums. The husband had also reported that his wife had been very fearful during the past week and that she was so disturbed and so disturbing at night, that neither of them could sleep. The onset of the present illness was extremely difficult to pinpoint in time. The patient herself did not admit to psychiatric illness. The husband and each of the patient's four children were questioned and none of them could give an accurate date of onset. We might, for convenience, use the patient's complaint of painful gums as a landmark, in which case her illness was two years in duration. Or we might use the suggestion of one of her daughters that change of residence and neighborhood about a year before marked a real change. In any case, the family showed considerable agreement in the description of the illness. The patient had become intensely preoccupied with her health. She had been to dozens of physicians, but was never satisfied with the advice or treatment which she got. In addition, she frequently accused her husband of infidelity, apparently groundlessly. Eventually the pressure of the patient's complaints led to her being hospitalized April of 1956 with a diagnosis of Involutional Melancholia. She received six shock treatment over a nine day period and improved only to relapse quite promptly. The patient was readmitted three weeks after discharge and underwent another series of ten shock treatments, and, in addition, four teeth were removed. She was discharged improved on June 9th but after a few weeks the patient again relapsed. In addition to the complaints already described, she now developed a fear that people in the neighborhood were looking at her unfavorably because she was thin and poorly dressed. She hated to go in the street. On repeated questioning, only a bare picture of the patient's past life was obtained. A few of the salient facts will be mentioned. The patient was born in Poland, the youngest of five children. She had little schooling. Her father died when she was 14 years old. She came to New York City with her mother and other family members at the age of 16 years following a pogrom. The patient met her husband, a dress operator, when she was 19 years old and married at the age of 21. While the children were growing up the patient seemed to have been the dominant figure in the house, raising the two sons and two daughters, being active in the local community, handling the money. She was an excellent shopper who haggled with relish and felt victorious when she got a bargain. The husband and wife always had economic difficulties and debates. He wanted to save money for business ventures and she wanted to spend it for clothes and for an active social life. Three years prior to entry this marital tension reached a point at which the couple had a temporary separation.

The patient's first known depression came in 1942 when she was 51 years old. The onset came about a year after the patient's mother died in an accident, at a time when one son went into the army and the other son became ill with tuberculosis. This was also about the time of the patient's menopause. During this illness the patient showed agitation and depression and expressed the delusion that she had been poisoned by toxins from her sick son. She was hospitalized at a sanitorium where she recieved a course of electroshock therapy and was discharged improved. It was at about this time that the patient developed the

idea of her husband's infidelity which has never since been relinquished. The patient remained reasonably well adjusted from 1942 until 1946. Aside from the fact that her son was discharged from the army that year, we have no data relating specifically to this period. We do know that the symptoms of agitation and depression recurred and that the patient received a course of ambulatory shock treatment in the office of a psychiatrist. Again remission was obtained and the patient maintained a fair adjustment from 1946 until the present illness, whenever we shoose to date that.

On admission we were presented with a fearful, agitated, somatically preoccupied 65 year old woman who was in good physical condition except for moderately severe diabetes mellitus. Her fasting blood sugar concentration was 172 milligrams per cent. There was atrophy of both thighs and early cataracts bilaterally of which the patient was unaware.

Possible factors in upsetting the patient's equilibrium are listed as follows: Her inereasing age, the departure of the last child from her household four years prior to admission, the previously mentioned brief separation from her husband three years before entry and the change of neighborhood about one year previously which required the separation from a family physician with whom the patient had had a good relationship and in whom she had had considerable confidence.

The patient's picture changed rapidly during her first 24 hours in the hospital. Her somatic preoccupations disappeared and were replaced by delusions that she was being poisoned and that her family was dead or dying. She received a course of nine shock treatments over a 30 day period and during this time a social worker carried out an active program with the family, since it was felt that a change in their attitude was essential if relapse were to be prevented.

The patient improved markedly and was discharged on September 24, 1956 to a convalesceent home and then to her own home. She had only mild somatic complaints. The importance of sustained contact with one and only one family physician was stressed to the patient and to her family. The patient chose one with whom the patient's program was discussed. The patient received two maintenance shock treatments at roughly one month intervals and she was seen in the Out-Patient Department at gradually lengthening intervals. At present she is being seen once a month. On this regime she has gained weight, is cheerful and is much less somatically preoccupied. She sleeps well and feels more relaxed with her neighbors. Social Service has continued to work actively with the husband, a factor which cannot be overemphasized. Both the patient and her family are satisfied with her condition although the patient is still complaining to a certain degree of painful gums.

Chairman Kaufman:

Thank you, Dr. Zucker.

The discussion of depression will be by Dr. Bernard C. Meyer. Dr. Linn always ends the discussion with a quotation, Dr. Meyer always begins with one.

Discussion

Dr. Bernard C. Meyer:

My quotation is not from Maimonides, although it involves a co-religionist. This is from *The Merchant of Venice*. "In sooth, I know not why I am so sad. It wearies me. You say it wearies you. But how I caught it, found it or came by it, what stuff t'is made of, whereof it is born, I am to learn. And such a want wit sadness makes of me that I have much ado to know myself."

In its full expression no human attitude of suffering engages more general recognition than does the state of depression. Yet this mood disturbance characterized by sadness, lack of interest, motor retardation, withdrawal of attention

and lack of appetite is not to be construed as a disease in itself, but as a manifestation of a variety of emotional disturbances which range in intensity from the mild "blues" to black and suicidal despair. Depression is a common feature in many neuroses. Seen in adolescents or young adults, it may betoken a developing schizophrenia. In others, it may constitute a phase of a manic-depressive illness. In late middle life, this symptom appears as the outstanding manifestation of involutional melancholia. In other instances, it may be an initial signal of developing organic brain disease. In its most understandable setting, it arises as a reaction to a loss of someone or something held dear. Thus the grief that we call "mourning" reflects the sense of emptiness that follows death. Despondency may also appear as a reaction to a grievous disappointment, to a withdrawal of someone's love, to sickness, to a loss of a part of the body or to the collapse of all that one has painstakingly built.

Less comprehensible are those states of melancholia accompanied by tormented expressions of unworthiness, self-depreciation, guilt, and not rarely terminated by self-destruction, which occur in individuals who seem to "have everything to live for," and whose suicide provokes an expression of incredulity and bewilderment. In this category are those depressions which follow the retirement from active affairs of a successful business man, develop in the mother of a recently married son, occur in a young wife at the conclusion of a pregnancy during which she appeared happier and more blooming than ever, accompany the ultimate achievement of success in a chronically unsuccessful individual, and appear in a habitually outwardly good-natured man following the successful lowering of his arterial hypertension by drugs. What has happened to these individuals to explain the unexpected appearance of the mood of melancholy? To gain an understanding of the genesis of such depressions, it is instructive to observe the typical depressive reactions that have been noted in infants during the first few months of life which are attributable to the withdrawal of maternal care, loving, holding and stimulation. The later development of many depressive reactions follows this model wherein the mood of sadness and despair can be correlated with a sense of loss which is closely akin to the pervasive sense of hunger for a missing someone or something. Whereas in the infant this hunger pertains especially to a mother's love and nourishment, in the older child or adult this same hunger may reflect a loss of inner satisfaction, a loss of self-respect, a loss of a sense of usefulness, or a loss of capacity for fruitful productivity. Depressive reactions of this type tend to occur characteristically in individuals who, lacking an adequate inner sense of worth, are especially dependent upon a continuous stream of supplies of love, popularity, success and esteem both from the world outside and from within. There is little tolerance amongst them for even minor failures, while an unquestioned triumph may bestow but a temporary satisfaction for those spirits which possess an insatiable need for inner and outer proofs of worth. Indeed this very need predisposes such individuals to easy hurt and recurrent disappointment, which lead in turn to deep resentment and intense anger at the frustrating environment. Such attitudes, however, are often concealed behind a facade of painful melancholy so that many

of the self-tormenting accusations of the depressed appear to apply more appropriately to someone else, who has, in fact, created the sense of frustration rather than to the subject himself. In many depressive states there lurks therefore a vast accumulation of hidden rage whose ultimate expression may lie in a desire to kill, a desire which may eventuate as self-murder or suicide.

Seen in this light, a number of puzzling depressive reactions assume greater clarity. The retired business man, unequipped with inner resources, falls a prey to depression because he has relinquished the one area of functioning which provided him with a sense of achievement and inner worth. Similarly, the involutional depression occurs typically in those women for whom biological creativity and attractiveness constitute an essential bulwark of both their self-esteem and their capacity to elicit love. The mother who, with the marriage of her son, becomes despondent is expressing both a sense of loss of a possession and rage at her deserting son and her "kidnaping" daughter-in-law. The young wife, being pregnant constituted a sense of inner fulfillment, a species of built-in richness to whom the act of delivery means a separation or a loss akin to those typical menstrual or premenstrual depressions of so many women who discern in their periodic emptying a recurrent reminder of their sense of unfulfillment. It is pertinent to observe, parenthetically, that most female suicides are said to occur in close temporal relationship to the menstrual period. Childbirth may give rise to depression in the father, as well as in the mother, serving as a repetition of an earlier sense of abandonment and rage when a baby sibling was born. Particularly impressive are those depressions which occur accompanying success or achievement or a sudden release from chronic suffering. Guilt over competitive strivings, for example, warded off characteristically by the pursuit of chronic failure, may prove overwhelming in the face of triumph. In this category are those depressions which follow the realization of some long-sought dream; the ideal home, for example, after years of unsatisfactory living accommodations. Here an inner sense of unworthiness may find expression in the idea, "This is too good for me." Similar reactions may follow promotions, advancement or graduation. Physicians should be on the alert for comparable consequences following the cure of chronic illness or subsequent to the removal of physical blemishes of long standing. Nowhere is this more striking than in the field of heart surgery where a significant improvement in cardiac function is suddenly thrust upon individuals who, over a period of many years, have learned to meet the world about them with the psychological defenses and reactions of the semi-invalid. Other examples will be mentioned below.

Characteristic of many basically depressed individuals is a tendency toward concealment of their distress, for people endeavor to avoid the pain of depression much as they strive to escape from physical pain. As a consequence many an underlying depression remains hidden beneath an assortment of defenses or substitute expressions. In an endeavor to guarantee an endless supply of love or reassurance, for example, such persons may indulge in a variety of addictions. These comprise not only drugs, tobacco and alcohol, but food, as in the compulsive eater, and people such as an addiction to people characterized by an insistent

need to collect an unending stream of acquaintances and even love partners. Others who combat the threat of depression by a constant activity and repeated productivity, are consequently unable to engage in passive relaxation. Such reactions may at times assume a picture of virtual hypomania. Despite these efforts, manifestations of the underlying depressive trends may emerge in a variety of guises, as for example, in multiple subjective complaints embracing anorexia, weakness, fatigue, insomnia, headache, diffuse pains and aches and a tendency towards hypochondriasis. Depression plus a concomitant self-destructive drive may also underlie the tendency of some individuals to submit to repeated surgical experiences. Somatic illness, notably gastrointestinal disease, asthma and hypertension, may likewise serve as substitutions for an underlying depression. It has been noted, for example, that cure or relief of such conditions may be followed by the appearance of depression, a consequence which has become repeatedly evident in the successful use of hypotensive drugs, as a result of which severe depressive reactions erroneously attributed to the drug itself, replaces a previously elevated blood pressure. Similar observations have been made in other psychosomatic afflictions. In an analogous manner the removal of other barriers to a depressive reaction may release a long pent-up melancholy. Thus the patient who wards off his despondency by compulsive eating, may experience an overwhelming depression after the successful undertaking of a reducing diet. Similarly the advent of coronary thrombosis depriving a habitually compulsively energetic man of his usual defense, namely action, may unleash a major depressive reaction. And finally, the warding off of a depression by an attitude of chronic optimism voicing the expression, "Things will be brighter tomorrow," may be brought to a rude and sudden halt by the realization furnished by signs of advancing age that there aren't too many tomorrows left.

Treatment. The picture of overt classical depression necessitates, as a rule, a psychiatric opinion concerning the underlying diagnosis, the risk of suicide and the proper selection of treatment. The diagnostic possibilities embrace not only the major psychoses, neurotic depressions and reactive depressions, but organic disease of the brain as well. These considerations as well as the therapeutic potentialities will determine whether hospitalization is indicated or not and whether treatment should proceed along psychotherapeutic or physical lines. The fact that a depression has arisen as a reaction to external events or situations in no wise diminishes the potential gravity of the problem. There are losses too overwhelming to be endured and death so painful that only a reunion with the deceased through suicide can bring peace. In all depressions, in fact, there is a potential risk of suicide; a risk which must be evaluated with extreme care. Suicidal threats or gestures should never be taken lightly nor should comfort be sought in the cliche that "people who talk about it don't do it." The ingestion of large amounts of relatively innocuous drugs, for example, aspirin, generally should be regarded as a suicidal gesture, and it should be remembered that some suicides are quasi-accidents occurring in an individual who consciously meant only to toy with self-destruction. The phrase "jumped or fell," epitomizes the narrow margin which may determine the opposing impulses besetting some sui-

cidal individuals. The first measure to be undertaken in the care of depressed patients, therefore, is to protect him from self-injury. Whether this requires hospitalization, round-the-clock nursing care, or a more casual surveillance must be carefully determined. The element of the danger of suicide may determine also the method of treatment, for although electro-shock yields spectacular results in many cases of depression, its indiscriminate use in all depressive reactions as a routine measure is lamentable, and when it is safe to do so, its use should be postponed pending a trial of psychotherapy, environmental manipulation and so forth. Despite advertising claims, the use of drugs in severe depression tends to be unimpressive. In fact, some of the so-called tranquilizers appear to aggravate or initiate depressions. Cases of fatality have been reported among patients receiving reserpine and electro-shock in close temporal proximity.

There are other reactive depressions, however, in which the passage of time and supportive role of other persons may succeed in bringing about a happier outcome. This is especially evident in the realm of physical disease wherein loss of function or loss of body part may carry a severe depressive potential, for example, in poliomyelitis, after breast amputation, or the institution of a colostomy. Similar reactions may follow the birth of a defective child. In this area the role of the attending physician assumes paramount importance, for the recovery from the deep hurts to self-esteem engendered by such occurrences may be considerably enhanced or retarded by the attitudes manifested by environmental figures, among whom the physician often plays a major part. Such misfortunes, often construed by the subject as a partial death, must be counteracted by expressions of continued interest and warmth by those upon whom the patient sets store. Nor do the needs of patients for such manifestations correspond necessarily to the severity of the mutilation or to the seriousness in the alteration of body function. There are post-hemorrhoidectomy patients, for example, whose need for signs of continued attention and concern may exceed those who have endured a disfiguring amputation. The entire process of convalescence is, in fact, strikingly influenced by an inner conviction of being loved. Most sick persons wish to get well, but there must be indications to them that it is worthwhile. To this end they may achieve a vast encouragement from the beckoning finger of a devoted physician and the warm smile of his affection.

The non-psychiatrist physician also plays a major role among those patients whom we have designated as concealed depressives. Such individuals, exceedingly common in all medical practice, often present inconsistent, recurrent and puzzling complaints which must be understood as depression substitutes. These are the chronically unhappy individuals whose distress is expressed in eating disturbances and in various physical complaints ranging in origin from hypochondriasis to true psychosomatic disease. The recognition of the underlying psychologic disturbance is an essential element in the treatment of those persons whose complaints, far from being dismissed as trivial, imaginary or "due to tension," must be recognized as disguised frantic cries for help. Often times these patients seek out in their medical visits a warm and trusting relationship with the one human being with whom they secretly long to share their woes. Here

the perceptive physician may bring considerable relief by a warm, friendly and understanding response, whereas a sign of impatience or irritability, may only serve to deepen the distress. The physician's recognition of the true nature of the patient's complaints may serve as encouragement for a frank uncovering of secret unhappiness leaving the patient to face openly for perhaps the first time, the problems and conflicts by which he is confronted.

Finally, it is urged that the physician treating somatic disease recognize the vast potential for depression which may be released as a consequence of alleviation or cure of the condition. For this reason it is imperative that doctors treating cases of chronic arthritis, peptic ulcer, asthma, obesity, hypertension and so forth, be in possession of a considerable knowledge of the personality and emotional organization of his subject.

In summary, whereas the management of major depressions often demand the services of the psychiatrist, the broad scope of the problem of depression touches upon all aspects of medical practice and demonstrates thereby, in renewed affirmation the concept, that the treatment of the sick must be directed not alone at the sickness but at the patient as a total human being.

Chairman Kaufman:

Thank you, Dr. Meyer.

The next category for discussion is the broad one of schizophrenia. Dr. Reiser will make the clinical presentation.

SCHIZOPHRENIA

Case Report

Dr. Albert I. Reiser:

This patient is a 21 year old unmarried girl who was working on her master's degree at the time of her admission to the hospital. The acute phase of her illness began one month prior to her admission when she became confused and disorganized in her behavior. Finally she was unable to find her way around the city, began to dress in a slovenly fashion, could not locate belongings in her own room, and ultimately was unable to dress herself. This acute phase was brought about by a number of interacting factors in her current life. These included her own decision to move away from her parents and live with a roommate in the city, a progressively close relationship with her psychotherapist, the pressures of working full-time during the day and attending school in the evening, and involvement in promiscuous sexual relationships.

Two-and-a-half years prior to admission the patient began seeing a psychiatrist once weekly. Her reasons for beginning psychotherapy at that time were a series of vague complaints. These included the feeling that she was drifting in her goal. She was a Junior in college and was uncertain as to where her true interests lay. Also she complained of fighting with her parents, unsatisfactory relationships with schoolmates, a feeling of apathy about her problems at that time as contrasted to earlier in her life when she took herself more seriously, and a feeling that she was frigid. During two years of treatment she was considered to be a neurotic girl with severe but relatively typical problems of late adolescence. However, early in the course of treatment two complaints appeared which hinted at the presence of a severe underlying mental illness. These were her feelings that sometimes people did not really exist when she was with them and an episode during which she thought the psychiatrist seemed to be melting into his chair. However, it was only when the acute

phase of the patient's illness began with feelings of confusion and unreality that it became obvious that a schizophrenic reaction was taking place.

At first glance the early life history of this patient presents a relatively normal picture. As an infant, the patient was the envy of her mother's friends. She was an exceptionally good child who rarely cried and who was content to sleep most of the time. The patient began to speak a few words when she was eight months old and walked when she was fourteen months old. She learned to care for herself earlier than most children do. The patient's father was a professional man and he demanded that high standards be met by the patient and her only sibling, a brother three years her junior. From the first grade on, only A grades were tolerated and rarely did the patient bring home anything less. By the time the patient was twelve years old she was talking about wanting to be independent and live away from her family. During her high school years the patient attended a private school where she did well academically. During this period the patient was considered to be bright and healthy by both family and friends. In college the patient attended three schools in four years. After a poor start in her first year, she did well and it seemed that her future was promising. A more careful examination of the patient's history revealed certain significant trends. As mentioned before, the patient slept almost 24 hours a day as an infant. She rarely cried and she was rarely picked up and held. At the age of four years she developed severe eczema and hay fever but generally she was in good health. From the very earliest time, the patient was considered to be a shy child. Although she would be friendly to a few of her relatives, most were avoided completely whenever they came to visit the family. In other words, she was withdrawn although she was never thought to be such by the family. As she got older it was noted that the patient seemed to live through others. She always knew what other people wanted, disliked, and she would take over attitudes of important people in her environment in toto. She never seemed to have feelings and attitudes that came from within herself, but rather she knew intellectually how other people felt about different things and so she made up for some inner lack by outer imitation. During her last two years of college, the patient entered into numerous unsatisfactory relationships with schoolmates whose own emotional development seemed far from ideal. It is seen then that when she became less withdrawn she was quite promiscuous.

This patient's parental attitudes were quite striking. Her father would refuse to talk to her for weeks on end when she was only twelve years old and then suddenly would be friendly and want to be pals. This would be followed by more weeks of silence and the pattern continued. The patient's mother also vacillated widely in her behavior towards her daughter. Frequently the patient's emotional and material needs would be completely ignored only to be followed by a deluge of attention and newly purchased clothing. As the patient said, "There's one thing I could always count on in my family. They would say one thing and do another."

On admission to the hospital, the patient was extremely confused and disorganized. She was unable to walk down the hall and find her way back to her own room. She could not keep track of the few articles of clothing she had with her. Her speech was so circumstantial that she could not complete a single sentence with the same thought with which she had begun. During her first month on the ward a florid paranoia developed which began with fellow patients and expanding to include the hospital and the city. Because of the development of jaundice, Thorazine® was discontinued after the first week of hospitalization, and the patient was given no other medication during the acute phase of her illness. She was seen in intensive psychotherapy. Gradually the patient began to accept her paranoid ideas as her own feelings. Ideas of reference were then dreamt about rather than expressed during the waking state. Then the patient began to withdraw and isolate herself and she said that she detached her feeling to the point where she felt dead and empty inside. Ultimately she accepted her feelings more as her own and again established gradual relationships with other patients and the ward personnel.

This is merely the first phase in a long treatment program. No cure is presently available. This patient, like the diabetic, will need life-long management. She will have periods of

decompensation and vigorous therapy will be required. Hopefully, her intellectual ability and artistic talent with which she is endowed, can be utilized during periods of remission with resultant gains to both the patient and the community.

Chairman Kaufman:

Thank you, Dr. Reiser.

The discussion of this area will be by Dr. Harry Weinstock.

Discussion

Dr. Harry I. Weinstock:

I should like to direct my discussion to these questions: What is our modern concept of schizophrenia? What are the symptoms of early schizophrenia? Why is it important to detect schizophrenia in its early stages? What are the broad principles of management of early schizophrenia?

Schizophrenia, like carcinoma, is a concept that includes a wide variety of similar and different conditions. So much so, in fact, that abroad the Germans speak instead of the "schizophrenias". Like carcinoma, when the disease is well advanced, diagnosis usually is obvious, but, also like carcinoma, diagnosis in the beginning or early stages often is difficult, uncertain and, sometimes, impossible to establish by any tests, even though it may be strongly suspected. Some cases, too, move inexorably to disaster; others are mild, sometimes completely cured; and yet others, though limiting, are still consistent with a long period of satisfactory functioning.

The cause, as with carcinoma, is still unknown. Hereditary, constitutional and environmental factors have been described. Yet, the exact influence of each is not certain. Not all pipe smokers get carcinoma of the lip and not all children who have unfavorable environments or schizophrenic heredity develop schizophrenia. Rudin and, later, Kallman have shown that when schizophrenia occurs in one of two identical twins, it is found in the other in 86 per cent of the cases and in only about 14 per cent with non-identical twins. The average expectancy of schizophrenia is 0.85 per cent whereas the expectancy in the children of one schizophrenic parent is 16.4 per cent. The organic etiology of schizophrenia is still widely held and most of the research in this field is along biological and biochemical lines. Among the most recent is Heath's suggestive findings of enzyme disturbances as the etiology of schizophrenia, although there is some question as to the validity of his findings. Only in recent years has there been much investigation of the sociological and psychological factors that may be involved.

The picture that we ordinarily think of as schizophrenia—progressive deterioration of total functioning, development of hallucinations, delusions and major thought and behavior disturbance—is the primary problem of psychiatry. About one-fourth of all psychiatric hospital beds are occupied by patients with this chronic and often lifetime disorder. But this number probably does not begin to reach the number of those who are not hospitalized. Many unquestionable schizophrenics are ambulatory and follow all kinds of relatively normal to extremely bizarre ways of life without the dubious benefit of diagnosis. Some

are recognized only when sudden, strange, explosive or destructive behavior has gotten them into the hands of the law. An increasing number are being cared for in clinics and in office psychiatric practice, and it is to this group that we will give special consideration this evening.

The general picture of schizophrenia, although not called such, was first described by John Conolly in 1849. In his Croonian Lecture he stated: "Young persons not infrequently fall into a state somewhat resembling melancholia, without any discoverable source of sorrow, and certainly without any specific grief; they become indolent or pursue their usual occupations or recreations mechanically and without interest; the intellect, the affections, the passions, all seem inactive or deadened, and the patients become utterly apathetic."

The term "dementia praecox" first was used by the Belgian psychiatrist Morel in 1860 in the case of a boy of fourteen who previously always had been "first in his examinations and that without effort and almost without study. Unconsciously he lost his cheerfulness and became sober, taciturn and showed a tendency to solitude." The boy showed a "state of melancholy, depression and a hatred of his father, even with the intent of killing him. He progressively forgot all that he had learned and his brilliant intellectual faculties entered into a very disturbing period of arrest."

Kraeplelin, the great codifier of psychiatry, in 1896 established the dictum "that all cases of dementia praecox deteriorate—or else it wasn't dementia praecox". But it remained for Bleuler in 1911 to show that the basic psychopathology, a "splitting of the mind" with the breakdown of association of thought, was a disorder that was sometimes progressive, sometimes episodic, sometimes mild, and sometimes apparently entirely curable. He gave this disorder the name of schizophrenia and saw this syndrome not as a progression to dementia, but as a particular condition of splitting of the basic functions of the personality, thinking, and feeling, and by a disorder of association. He thus enlarged the boundaries of what should be included under this syndrome, and classified the symptoms in two sets of groups.

For our purposes, it is necessary to state that those symptoms that we are accustomed to think of as psychoses (such as delusions, hallucinations, catatonic postures, etc.) are accessory symptoms. They occur in some cases but by no means in all. To wait for such symptoms or behavior to develop before making a diagnosis of schizophrenia is equivalent to waiting for obvious metastasis before diagnosing carcinoma.

This evening I should like to confine my discussion to the early and relatively mild cases we now speak of as ambulatory schizophrenia, latent schizophrenia, pseudoneurotic schizophrenia, borderline schizophrenia and sometimes schizoid personalities. We emphasize this group because there is reason to believe that results are quite satisfactory in a goodly percentage of the cases when they are recognized early and treated with an understanding of the problem.

Schizophrenia rarely begins overnight. To be sure, symptoms may sometimes start explosively and violently but nearly always there has been a history of some kind of subtle deterioration of adaptation or previously long impaired

adaptation. The tendency in most instances is to overlook these signs, hope for improvement, or find some ready explanation, and rarely to seek for advice until one is severely frightened into action. It is the family physician to whom the parents finally bring the young adult or adolescent for help. Often the continuing symptoms and the lack of effective treatment by drugs lead the family to doctor after doctor, and sometimes lead the doctor on a futile chase for organic disease, until the basis for the symptoms is recognized in the psychologic structure.

The findings that should make a physician think of early schizophrenia are the following:

1. Difficulty in communication with the patient, a feeling of talking at, rather than to, the patient.
2. A vagueness, confusion or lack of cohesion in description of the symptoms.
3. Difficulty in eliciting from the patient a clear reason for the visit.
4. A bizarre list of symptoms, far beyond what one or more organ systems could produce.
5. Complaints of severe fatigue, depression and suicidal-impulses.
6. Apathy, lack of interest or feeling in the patient, and complaints of blocking of thought.
7. The young patient who comes in with a stack of negative laboratory examinations.
8. The patient of 25 or so, brought in by the mother.
9. Behavior suggesting that the patient is withholding some thoughts or feelings through fear. Recognizing this and through sympathetic encouragement, one may often elicit significant symptoms, such as early ideas of persecution or ideas of reference or feelings of awareness of inner disorder.

It is most important to obtain a developmental history from the family, if the patient has any difficulty in giving it himself. A history of progressive difficulty in keeping up with usual functioning in school, study, social activity and family life, with evidence of apathy, confusion, sitting around alone, etc., should make one strongly suspect this disorder. The usual method of systematic history taking is generally not satisfactory. One must listen and let the patient talk, and by sympathetic interest, help the patient to talk more and more of his feelings, thoughts and impulses. In schizophrenia, physical examination fails to disclose organic disease. One finds tall thin and short stout patients; those who seem agitated, anxious and perspired, and others who are excessively calm and cold, even to the touch. None of the laboratory examinations disclose significant abnormalities. Of course, a routine physical examination should be made, and if a meaningful sign is discovered, further examinations should be carried out to determine its significance. Other conditions which one should rule out are brain tumor, previous encephalitis, mental deficiency, and severe psychoneuroses during adolescence.

Often the early history is that of a quiet, somewhat seclusive child, very interested in reading and day dreaming, but having less than average interest

in social, recreational and usual pleasure activities. Some are of superior intelligence, some are gifted or artistic, some brilliantly scientific, while others are of average or lesser talent or intelligence. It is a mistake to think of schizophrenia as related only to genius, for we see every type of gifted and ungifted personality develop this disorder. In addition to this group of schizoid types that often develop schizophrenia, there is another group, a group that might grossly be described as the "stormy" personality. This second major group includes the highly neurotic, maladjusted child, the child with severe behavior difficulties, and the child who shows psychopathic tendencies. In other words, children or young people who show severe recurrent disturbance of adaptation and who fail to respond to usual efforts at management, often develop schizophrenia or are schizophrenic. Sometimes the sudden development of behavior disorder in adolescence presents great difficulty in diagnosis. We see so many instances of strange behavior at this period, that some suggest that all adolescence is a kind of psychosis or severe neurosis. Some psychiatrists speak of "acute adolescence". Unquestionably, we find some symptoms in these disturbed adolescents that occur in schizophrenia—excessive suspicion, almost delusional behavior, and varying types of anti-social activities. Often we do not know for a time, sometimes months or longer, whether we are dealing with a very stormy adolescent or a form of schizophrenia, or both. The previous history, the capacity of the patient to maintain and develop relationships to people, and the kind of communicability of patient to physician may help in the diagnosis.

In the very early stages of the thought disorder (i.e., the loosening of associations which today is considered to be the basic psychopathologic lesion of schizophrenia), even a careful competent clinical history and examination may be insufficient to establish the diagnosis. Often verification can be obtained from competent psychological testing using various of the projective tests—the Rorschach, Word Association, Thematic Apperception Test, etc. Results of these tests, combined with other clinical data, will usually give not only information as to the nature of the difficulty, but often an estimate as to the severity. Just as in other areas of medicine, this kind of appraisal aids materially in intelligent planning of treatment and so may greatly improve the prognosis.

Our working concept of schizophrenia is that it is a disorder primarily dependent upon a faulty personality organization, perhaps of organic and/or environmental origin, which develops when it does, because of the increasing demand of society at that time for greater independence and more responsible functioning; demands with which the faulty organization cannot cope. Since the symptoms show up as a breakdown in adaptation, we may compare them with the symptoms of decompensation in a child with a congenital or acquired cardiac lesion. For years the cardiac child often functions well enough, the heart enlarges in compensation, and we see slight symptoms, or fail to see clear symptoms even under moderately severe stress, as in the case with the pre-schizophrenic. But when the stress increases, as it inevitably must, the symptoms become more prominent, major incapacitation becomes grossly evident, and the immediate necessity for restoration of compensation becomes clear.

Obviously, the first principle of treatment is to reduce the stress. Just as there is no point to urging the decompensated cardiac to walk or work with severe dyspnea, there is no point, in fact there is great danger, in urging the schizophrenic to maintain his school standing, his social standing, or even his simple day-to-day responsibilities of living. In each instance, the appraisal of the severity and limitations imposed by the symptoms will determine the degree to which the patient must temporarily be nurtured. He often has to be taken from school, regardless of the apparent social disaster, and be permitted minimal responsibilities. Much time and attention must be given by the physician to the parents at this time and frequently over a period of time, to accept the fact of major paralysis of function for a while. They must be guided to refrain from adding any stress on one who is unable to function, and tolerate nurturing a partial invalid for the time-being. Not only must the parents discontinue their pressure on the patient, but the patient must be helped by the physician to reduce the stress on himself at that time and the guilt often suffered by him. This is not an easy process. It requires much time and patience, and it is questionable whether the busy physician will give it the time it requires.

A further principle of treatment is the finding of ways of increasing the pleasure or satisfaction needs of the patient, according to his special interest and abilities. Nearly always there is some degree of depression and minimal gratifying activity. The doctor, while increasing his understanding of the patient, may well find with and for the patient an activity that, unreasonable as it may seem, may satisfy an important need, fulfill some unconscious drives, and be of great benefit. This serves to restore lost self-esteem of the patient and raise hope in him. For example, a young college student, son of a professional man, developed an unquestioned schizophrenic picture, verified by Rorschach. He failed in his studies, was busied writing a confused fragmentary thesis on a meaningless subject, and became unable to adapt himself to usual living at home or with others. Leaving college, he found himself interested in working with a neighborhood shoemaker and, in spite of his academic background and family status, he was permitted by the family to become the shoemaker's assistant and worked there for many months. He improved greatly, returned to college after a while, completed his scientific education, and now is working as a research physicist in a major scientific institute. No psychotherapy beyond the one consultation was carried out.

In another instance a first-year medical student developed bizarre symptoms. Known as "The Brain" at college, he had graduated in three years, made Phi Beta Kappa and had one friend at college; a dog. Supposedly returning to medical school in another city after the Thanksgiving holidays, he disappeared and was found living in a third-rate hotel in a small factory town, spending his days and nights sitting in the movies, not speaking to a soul. After being found by his family through the police, he returned to medical school, got on well apparently, but then repeated the same performance after the next holiday in another city. When seen, he presented the typical apathy and confusion, and spoke only of a new theory of science that mixed mathematics, metaphysics,

religious philosophy and a then-popular kind of pseudopsychology called "dianetics". He said he had learned three years before to "stop his thinking by using a mythical switch", that he could think or not, that he knew in advance just where an author wrote his important contribution in any book, but that when he would find it, he would be totally unable to concentrate on it. He noted, too, that whenever he spoke about a subject not to his liking, he developed a bad taste in his mouth, and so had to change the subject. Though brought in by his father, a surgeon, this young man saw no reason for psychiatric examination or treatment. In fact, it took some three weeks to convince him to come in for examination. The family was advised to diminish all pressure on him immediately and alter expectations and ambitions for him, and the boy (who came in for treatment only rarely, and then only at urging from his parents) soon found himself interested in traveling about and somehow drifted into becoming a Fuller brush salesman. He did this irregularly for a few months, then began to function better socially, to speak more and more with his family, and gave up the confused work on his thesis. A little later he found himself interested in forestry, was admitted to an excellent school, graduated in two years, became an instructor and got a master's degree, and now is employed in a government research laboratory. To be sure, he is isolated, has few relationships with people, and it remains to be seen what happens to him. He seems to be very contented with his way of life.

These instances are mentioned, not to suggest that shoemaking or selling brushes are cures for schizophrenia, but that one must permit the patient to adapt himself at the level at which he can function with satisfaction for the time that is needed for re-compensation and rehabilitation. By that time the family may come to alter its expectations, and an adaptation often can be worked out, not at the level of previous ambitions or expectations, but yet very often well above the catastrophic level present at the time of the breakdown. The basis for the possible success of these principles of treatment is the establishment of a positive relationship between the patient and the physician or psychiatrist. Without this relationship, little can be expected. The physician should be able to have a feeling of devoted interest and acceptance of the patient, and be free enough of conflicts within himself to be able to reach to the patient and communicate with him at the patient's own emotional level. The psychotherapeutic procedure itself is entirely individualistic, and the physician is guided by the patient's functioning and guides the patient in turn. Only in a few rare instances has the classical psychoanalytic method been employed, but too few results are so far reported to determine its lasting effectiveness.

It is the general experience of psychiatrists long in practice that there are many individuals who have shown varying degrees of schizophrenic breakdowns in adolescence and who have been able to rehabilitate themselves and live full and useful lives. Perhaps in some of these cases we were dealing with episodes of schizophrenia that were self-limited, but there is much clinical experience to suggest that proper early management frequently results in major and continued restoration. It should be mentioned that Thorazine® often is particularly ef-

fective in the acute severe schizophrenic outbreak. It often will calm down such a process and quickly make possible a psychotherapeutic approach. Should this fail, insulin and electroshock therapy may cut short the secondary symptoms and permit further psychotherapeutic intervention.

Most favorable results can be expected when these conditions exist:

1. The disorder begins in adolescence.
2. The patient seeks treatment.
3. The psychical symptoms (rather than physical symptoms) are more prominent.
4. The patient recognizes that his behavior and mental processes are abnormal and he wants to be helped.
5. The patient is sufficiently communicative and able to cooperate with the therapist.

In this group a large percentage ultimately can elevate their functioning appreciably above that prevailing before treatment. However, one must not expect to produce any radical change in the basic personality type. The schizophrenic is likely to remain somewhat introverted, but he may be enabled to develop his assets, skills, talents and have enough understanding of his limitations to live safely and comfortably within them.

To condense my remarks into a brief summary, I would recommend to the physician:

1. More frequent suspicion of schizophrenia under conditions described.
2. That he avoid fear of diagnosing it.
3. That he verify it by psychologic tests or psychiatric consultation.
4. That he avoid fixing a hypochondrical state by medication or by repeated physical or laboratory examinations.
5. That, if he is interested in doing so, he may be able to treat patients himself, with guidance by a phychiatrist.

And one final point of view. Perhaps the best we can do for this disorder is prophylactic in nature. If we can recognize it earlier by suspecting it earlier, perhaps the ambitions and expectations of the parents may be adjusted to the level of the patient's basic emotional capacity and by so doing perhaps prevent the later breakdown with its severe and unhappy consequences.

PERFORMANCE TESTING AND CALIBRATION OF THE BALLISTOCARDIOGRAPHIC APPARATUS

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In the evaluation of clinical ballistocardiography two types of problems may be differentiated: (a) Physiological mechanisms, converting cardiac events into mechanical response of the body, and (b) the performance of the instrument which records this mechanical response. While the first is highly complex, the second appears simple and might be solved by straightforward physical testing. In the following we present a method for such testing of a Dock type ballistocardiographic instrument, designed by one of us (1), since such a test has not been performed previously.

This ballistocardiograph records the displacement and velocity of a ruler which is attached to the shin of a patient in the clinical application. The observed phenomena are periodic and the testing should therefore be a dynamic one and indicate both calibration of the deflections in the final record in terms of displacement (cm) and velocity (cm/sec) and also the frequency response, that is, the fidelity with which the more or less rapid changes in the ruler motion (displacement and velocity) are reproduced in the record.

Testing procedures of this type are common in engineering. The ruler must be forced to move in a known fashion by a mechanical vibrator and the enforced motion compared with the indications of the instrument. The motion which is easiest to produce by a mechanical device is a harmonic oscillation. Such a motion, however, makes it necessary to take multiple records with varying frequencies. It also has the disadvantage that the velocity curve looks exactly like the displacement curve except for a phase shift, so that no preliminary information can be gained by inspection. For this reason, nonharmonic forced vibration is preferred and the most useful waveform is a so-called square wave with a steep rise of the wave-front (step function).

We have designed the mechanical test vibrator in such a way that the velocity curve approaches a square wave shape; to achieve this, the displacement had to be constructed in such a way that it follows a "triangular" zig-zag wave shape.

The instrument is illustrated in Figure 1. The motor on the left drives through a flexible shaft (to reduce vibrations) a worm reduction gear and a variable ratio set of gears (boxed in the raised platform). The gear box permits the selection of five frequencies: 1.67, 3, 5, 8.4 and 15 cycles per second. The output shaft of this gear box carries the excenter, which transmits the oscillatory motion to the ruler. The excenter is specially shaped to obtain the triangular displacement

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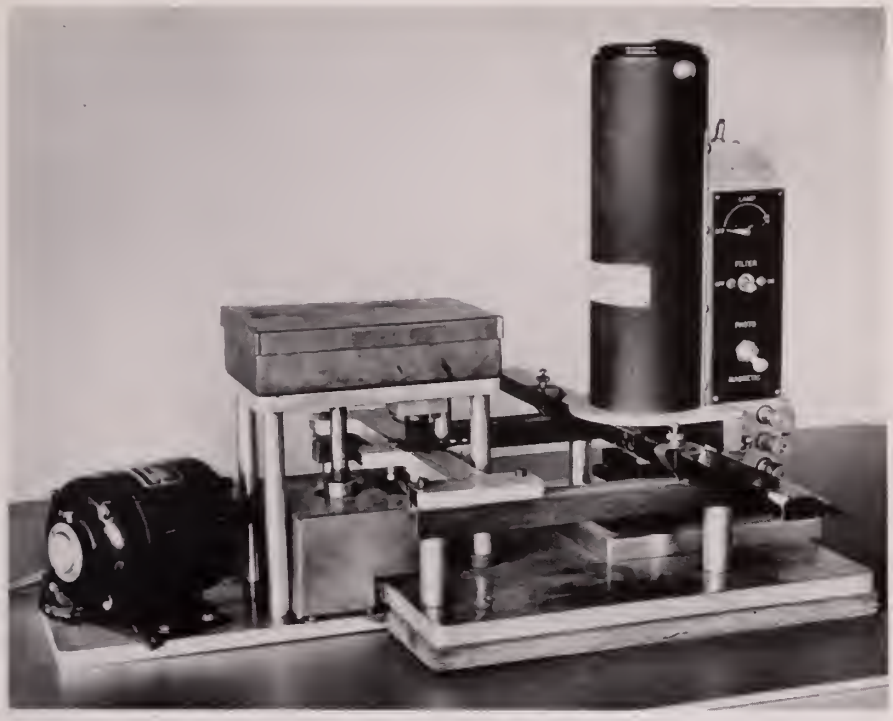

FIG. 1. Test vibrator with a ballistocardiograph in testing position.

motion. This is imparted to a rigid framework which can slide rectilinearly on supporting grooved bars. The framework has clamps for attaching the ruler of the ballistocardiograph on the right.

The actual motion is illustrated in Figure 2. This was determined by attaching a gonimeter head to the excenter shaft and a micrometer dial indicator to the ruler. The excenter shaft was rotated by hand, the angular rotation and the displacement noted and plotted (rotation was calculated in terms of seconds for a frequency of 1.67 cycles per second).

The displacement curve reveals two imperfections in the construction: (a) The rising and falling limbs of the curve are not straight lines, but slightly curved; the maximum deviation from linearity, however, is only 50 microns, an acceptable tolerance. (b) There is some backlash as indicated in a "standstill" of the ruler at every reversal of motion, lasting about 0.05 seconds. It should be pointed out that the transition from motion to standstill, and from standstill to motion, is indicated as a sharp kink in the curve of Figure 2; this does not occur in actual operation by motor drive, since such sharp kinks could be achieved only by applying an infinite force; it is actually somewhat rounded, but this rounding was too small to be measured and is negligible compared to the dimensions of the curve.

The graph indicates of course, in addition to showing the wave shape, the actual magnitudes of the displacement: the amplitude, peak to peak, is 0.89 mm.

The velocity curve in Figure 2 was obtained by differentiating the displace-

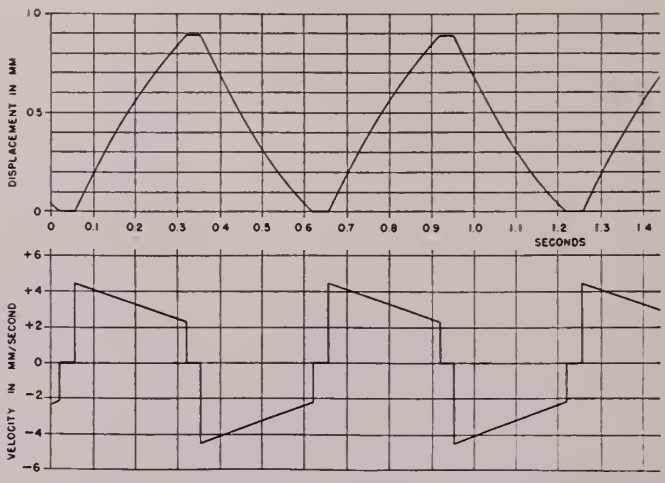

FIG. 2. Plot of motion characteristics of the test vibrator.

ment curve. It is zero for the short periods of standstill, rises sharply to a positive peak of 4.5 mm/sec., and declines to 2.5 mm/sec. (this decline is the reflection of non-linearity in the displacement curve). Then it drops to zero for the period of standstill and the process is repeated with the negative sign (indicating opposite direction of displacement motion).

In the actual tests a Sanborn direct-writing four-channel Poly-Viso machine was used as a recording instrument, with a suitable attenuation of sensitivity. Figure 3 shows a typical test record in which the deflection sensitivity is indicated.

Comparing this record with the plot of Figure 2, it appears by inspection that this record is a true reproduction of the actual ruler motion, both for displacement and velocity. The standstill is less pronounced; the reversal period is somewhat rounded as a whole. This is due to some elastic compliance of the instrument and was mentioned in discussing Figure 2. For the same reason there is clear evidence of vibration in the velocity record.

An examination of the vibrations in Figure 3 shows that there are marked superimposed velocity peaks at a frequency of 30 cycles per second, which cor-

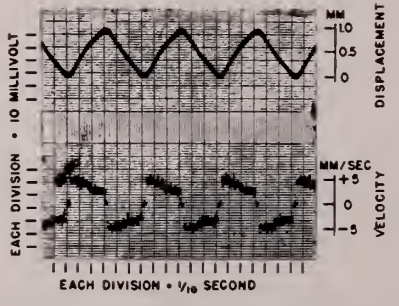

FIG. 3. Ballistocardiograph record with the test vibrator without bypass condensers. Tracing on a direct writing recorder.

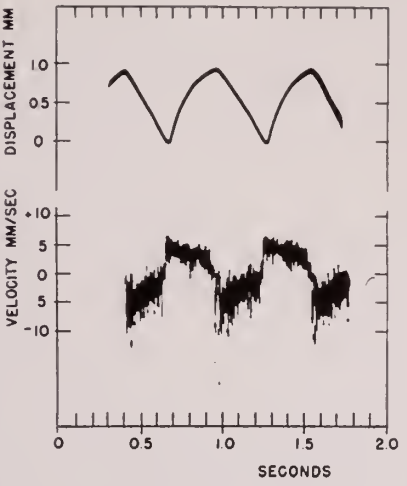

FIG. 4. Same as in Figure 3, but traced on a cathode ray oscillograph (negative of the original photograph, no retouching).

respond to the vibrations of the driving motor revolving at 1800 revolutions per minute. In addition, there seems to be an indistinct mechanical noise at a higher frequency. In order to inspect the output of the instrument free of the limitations of the direct writing recorder, a record was made by a cathode ray oscillograph (Figure 4) which shows a greater amplitude of the higher frequency vibrations with a random frequency of about 70 to 80 cycles per second. A simple inspection of Figures 3 and 4 gives therefore some semiquantitative information on the frequency response: this may be good at 30 cycles per second and it falls down very markedly at 70 to 80 c/s.

Since any vibration appears as a fast, superimposed, irregular ripple in velocity curves, it has been common practice to use bypass condensers in the velocity pickup system in order to smooth out such ripple. Figure 5 shows the effect of such bypass condensers on the recorded curves. It can be seen that while 1.8 microfarads offer some smoothing, there is no visible distortion of the velocity wave shape, but that 8 microfarads cause a marked distortion and that 32 and 60

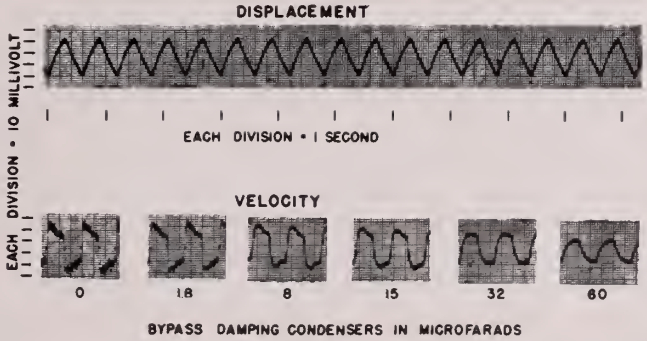

FIG. 5. Ballistocardiograph records with the test vibrator and different bypass condensers in the velocity pickup circuit.

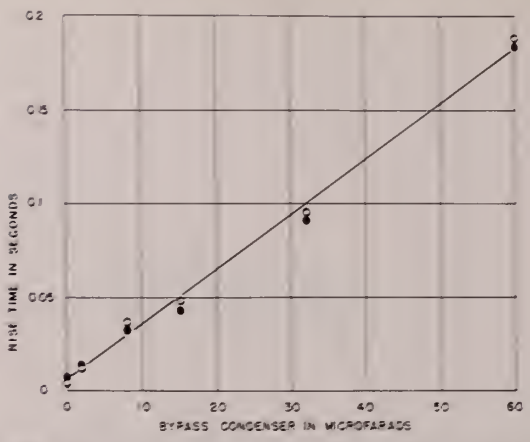

FIG. 6. Rise time as determined experimentally without and with different bypass condensers. White circles: measurements on the electrical circuit alone, on tracings obtained by applying an electrical step function (see text).

microfarads produce a curve which has no resemblance to the actual velocity wave.

The calibration of the ballistocardiograph in terms of displacement in mm and of velocity in mm/sec. for 1 millivolt deflection can be read off the graphs in Figure 3 directly. The testing instrument therefore serves also to calibrate a ballistocardiograph.

We can present the calibration result numerically. Velocity calibration: 1 mV = 2.5 mm per second (1 mm/s = 0.4 mV); displacement calibration: 1 mV = 0.21 mm (1 mm = 4.9 mV). Applying this calibration to a typical ballistocardiogram, we get an amplitude in the displacement tracing for the I-J stroke of 2 mV = 0.42 mm, and in the velocity tracing for the I-J stroke of 3.7 mV = 9.3 mm/second (recorded without any added bypass condensers).

The fidelity with which the actual wave shapes of displacement and velocity are reproduced cannot be read off the graphs by simple inspection. Since, however, the testing of "fidelity" of the response of electrical and electromechanical circuits in terms of frequency response by square wave testing is common in engineering, the mathematical treatment is readily available.

The measure of "fidelity" is frequency response which is for an instrument the highest frequency of a harmonic or sinusoidal motion which can be reproduced by a given system, reasonably well. By a common convention, this is agreed to be the case when the observed amplitude is equal to 70.7 % of the actual amplitude (attenuation of 3 db). For this permissible distortion the upper frequency limit can be calculated from the equation:

$$f = \frac{1}{2\pi T} \text{ cycles/second} \qquad (1)$$

In this equation, T is a time constant or rise time which has to be determined experimentally and can be found from records obtained by a square wave test as presented here and illustrated in Figure 5. The method is based on the definition

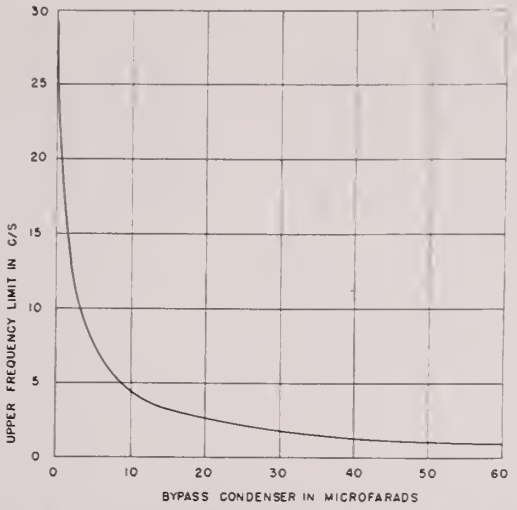

FIG. 7. Frequency response of the ballistocardiograph and recording system without and with different values of bypass condensers. Calculated from the experimental data in Figures 5 and 6.

of rise time: if a sudden impulse is imposed on a system (like the jump in velocity from zero to, say, 5 mm sec. the recording system will deflect with a certain delay; this delay is expressed as the time which it takes for the system to reach 63.2 % of the final and maximal deflection* and is called rise time or time constant T, used in the equation for frequency response.

Figure 6 (white circles) is the plot of this rise time in the ballistocardiograph as measured for different bypass condensers. It will be noted that the rise time is a linear function of the bypass condensers, which is in agreement with theory.

The black circles in Figure 6 represent values of the rise time of the electrical circuit alone, examined separately from the mechanical vibrator and the induction pickup coupling. This was done by applying to the electrical circuit a suitable voltage (opening and closing a mercury switch) with the vibrator standing still (care was taken not to change the electrical characteristics of the circuit in doing this). The close agreement in the rise time between the observation on vibrating mechanical motion and the electrical test eliminating the mechanical component indicates that there is no measurable distortion in the transducer mechanism as such, at the frequencies examined, and that all distortion appears in the electrical system (pickup circuit and recording apparatus).

The experimental data of Figure 6 and the equation (1) permit the calculation of the frequency response of the velocity recording of the ballistocardiograph. The result is presented in Figure 7. It can be seen that the frequency response without a bypass condenser is about 30 cycles per second. The recording instrument itself has a frequency response of about 100 cycles per second; the drop to an overall response of 30 cycles per second must be therefore ascribed to distributed capacitance in the ballistocardiograph circuit itself.

* For a convenient method to determine the time constant of a system from graphical records of "square wave" impulses, see page 42 f in Frank [2].

An added bypass condenser of two microfarads reduces the pickup of vibrational noise and lowers the overall frequency response to 15 cycles per second. If the assumption is valid that the physiologically relevant frequencies in ballistocardiography are below 10 cycles per second, a frequency response of 15 cycles per second offers acceptable fidelity.* Bypass condensers around 10 and more microfarads reduce the frequency response below 5 cycles per second and cause prohibitive distortion.

SUMMARY

1. A mechanical vibrator is described for calibrating and testing ballistocardiographs of the Dock type.

2. The test results of a modified Dock type ballistocardiograph are presented. They show an upper frequency response of 30 cycles per second in the velocity record without bypass condensers, and of 15 cycles per second when a two microfarad bypass condenser is used for moderate suppression of vibrational "noise", which is adequate for clinical applications.

3 In conventional use of this ballistocardiograph, bypass condensers of over two microfarads are used. *This increases the distortion to such levels that little resemblance is left between the ballistocardiographic record and the actual velocities imparted to the body by cardiac activity.*

4. It must be emphasized in conclusion, that the present investigation was concerned exclusively with the ballistocardiographic apparatus *per se*. The complex chain of physiological mechanisms involved in the transmission of mechanical cardiac events through the body to the recording transducer was not examined. Since each link contributes to the distortion in the representation of cardiac vibration on the record, these factors require separate critical evaluation before a ballistocardiographic technique can be accepted as a procedure of adequate fidelity in clinical medicine.

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2. Frank, E., Pulsed Linear Networks. First edition, New York, 1945. McGraw Hill Book Co.
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* Nickerson and Mathers (3) state that the frequency response of a ballistocardiograph should be linear to 11 cycles per second.

THE GASTROESOPHAGEAL VESTIBULE ON ROENTGEN EXAMINATION: DIFFERENTIATION FROM THE PHRENIC AMPULLA AND MINIMAL HIATAL HERNIATION

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Various authors have described localized dilatations or sacculations in the distal esophagus or esophagogastric region under many different names (1–3). Some of the terms used were the cardiac antrum, the epiphrenic bell, the Vormagen, the phrenic ampulla, Arnold's pouch and Luschka's pouch. In general, these structures were identified during the course of anatomical investigations carried out by different methods. Specific criteria for identifying these normal structures, particularly *in vivo*, were not included in the original descriptions. Moreover, it was realized that some, if not all, of these appearances represented transient phases of functional states. In the absence of clear-cut criteria for the identification of these presumably normal structures, it has been a difficult, if not impossible, task for the radiologist to recognize them and particularly to differentiate them from small, sliding, direct or concentric hiatus hernias (4, 5).

In 1950, Lerche (6) published an important monograph describing detailed anatomical dissections of the distal esophagus and proximal stomach on selected specimens. It was his belief that he could select examples which represented, in a fixed state, sequential functional changes, specifically during expulsion or regurgitation of gastric contents into the esophagus. As a result of these studies, Lerche described a segment two or three centimeters in length located between the tubular esophagus and the stomach which he believed possessed distinctive functional and anatomical characteristics and therefore deserved a special name. He designated this segment the gastroesophageal segment of expulsion or the gastroesophageal vestibule and pointed out that this segment could distend and elongate in rather remarkable fashion during regurgitation. The transformation of this segment into a ballooned-up discrete sac was made possible, according to Lerche, by the presence of sphincters at both its proximal and distal ends. The sphincter at its distal end consists of a double sling arrangement of special muscle fibers located at the cardia or cardiac incisura. These muscle bundles have been designated for many years as the cardiac sphincter or the constrictor cardii without, however, *in vivo* evidence of their sphincteric nature. At the proximal end of the vestibule, according to Lerche, there is a ring of specialized circular muscle fibers to which he applied the name "inferior esophageal sphinc-

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ter". Lerche believed that the inferior esophageal sphincter remained contracted until swallowing occurred.

The conclusions of Lerche as to functional phenomena were based on anatomical dissections. Correlation with roentgen or other *in vivo* findings was minimal. The question, therefore, remained unanswered as to whether the vestibule, the inferior esophageal sphincter, and the cardiac sphincter could be demonstrated *in vivo* and whether they played the rôles ascribed to them by Lerche. In contrast to previous authors, the description of Lerche is sufficiently detailed to make investigation of this question feasible.

Attempts to recognize the vestibule as a discrete distensible sac between sphincters during the course of conventional roentgen examinations of the esophagogastric region in normal individuals were not successful. In contrast, as is well known, patients suspected of having small sliding or direct hiatus hernias showed a variety of constrictions and dilatations immediately above the diaphragm to which Lerche's terms could be applied, but in quite arbitrary fashion. It was clear that elucidation of these bizarre configurations in this group of patients required motion picture roentgen studies in order to determine the sequence of events and to recognize the conversion of unfilled or contracted segments into saccular structures. For purposes of such a study, a group of patients without dysphagia were selected from the conventional gastrointestinal examinations because of the presence of a small sliding or direct hernia. The esophagogastric region was then studied in greater detail with the aid of x-ray motion pictures. An important advantage in studying patients with direct hernias was anticipated because of the fact that, in these individuals, the esophagogastric junction is located above the hiatus of the diaphragm. It was therefore hoped that the phenomena observed in the esophagogastric region could be attributed to intrinsic motor activity and that direct action of the hiatus of the diaphragm would be excluded.

Motion picture studies of the esophagogastric region were performed with a five inch image intensifier on 35 millimeter film. The factors used varied between 75 and 100 KVP and between five and ten milliamperes. Most sequences were done without a grid at rates no greater than eight frames per second in order to minimize radiation exposure to the patient. The optimal position for these studies was with the patient prone, left side elevated, although other positions and maneuvers were also utilized. For most purposes, a fluid-barium mixture was administered in order that maximum distensibility could be achieved. An attempt will be made in this report to summarize the conclusions which have been drawn from these studies as well as from ancillary investigations by more conventional methods. It must be noted, however, that reproductions of individual frames or of sequences in diagrammatic fashion are poor substitutes for viewing the original movies.

The findings in this group of patients with small direct hiatus hernias were not identical in every case but a basic pattern could be discerned with little difficulty. The events of greatest interest occurred during phases of filling and emptying rather than during continuous swallowing. Moreover, with inter-

FIG. 1A. W.W. Enlargement of 35 mm. frame from movie sequence showing barium filling the tubular esophagus and a hernial sac. A gap (arrow) between these two regions 2 to 3 cm. in length remained contracted and unfilled for 5 to 6 seconds.

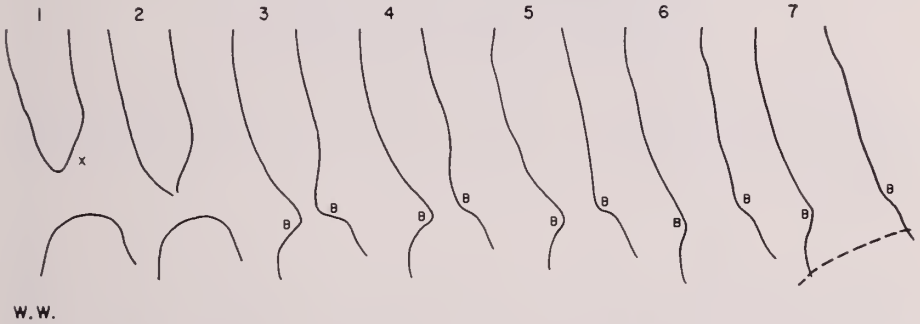

FIG. 1B. W.W. Tracings of selected frames from a movie sequence of this patient. All the structures outlined are above the level of the diaphragm which in frame 7 is indicated by a dashed line. Barium was retained in the hernial sac at the beginning of this sequence, as in Fig. 1A. The sequence shows the appearances during filling of the segment intervening between the tubular esophagus and the hernial sac. The letters BB indicate the proximal margin of the hernial sac. The letter X in the first frame indicates the site at which the barium column in the tubular esophagus was delayed for several seconds.

rupted or rapidly repeated swallowing, some barium was often retained in the distal esophagus and or a small hernial sac, making it possible to visualize both the proximal and the distal margins of an unfilled or contracted segment. It is often possible under these circumstances to recognize that a segment two or three centimeters in length is present between the tubular esophagus and a small hernial sac which may not relax for several seconds and then suddenly fills as a unit (Figs. 1, 2). From its location, its length and its appearance when distended (Figs. 3, 4), this segment appears to correspond with the vestibule as described by Lerche and will be so designated in this report. The esophagus proximal to the vestibule does not distend to the same degree and may be referred

FIG. 2A. D.W. Enlargement of 35 mm. frame from movie sequence showing barium filling the tubular esophagus and a hernial sac. A segment between these two regions, about 2 or 3 cm. in length, remained unfilled for several seconds. Preceding this frame, it was evident that the barium in the hernial sac originated from below the diaphragm by retrograde flow.

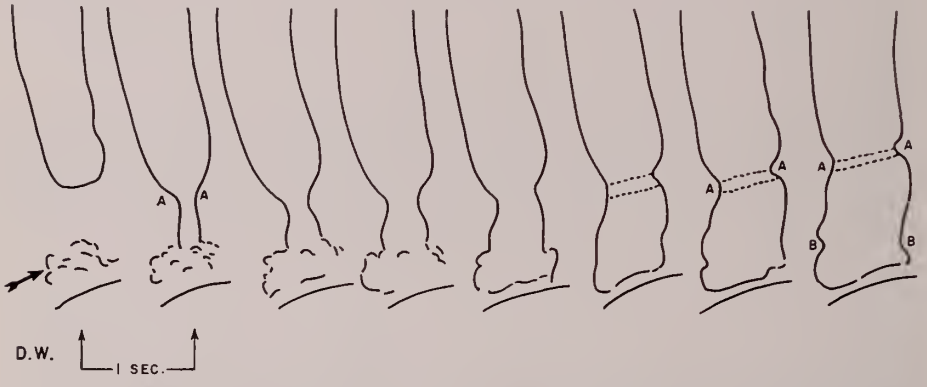

FIG. 2B. D.W. Tracings from a movie sequence. At the beginning of this sequence there was retained barium in the hernial sac, as indicated in the first frame (arrow). Barium entering the tubular esophagus was delayed for about a second at a point about 2 cm. proximal to the hernial sac. This level is indicated by the letters AA. Tracings after the first show phases of filling of the contracted segment intervening between the tubular esophagus and the hernial sac. In this patient, after filling, persistent notches and often a thin ring were seen at the AA level. Notches were also seen a short distance above the diaphragm, at the proximal margin of the hernial sac. This latter level is indicated in the last frame by the letters BB. A photograph of the last frame is shown in Fig. 3A. A spot radiograph of this same patient in a similar phase is shown in Fig. 7A.

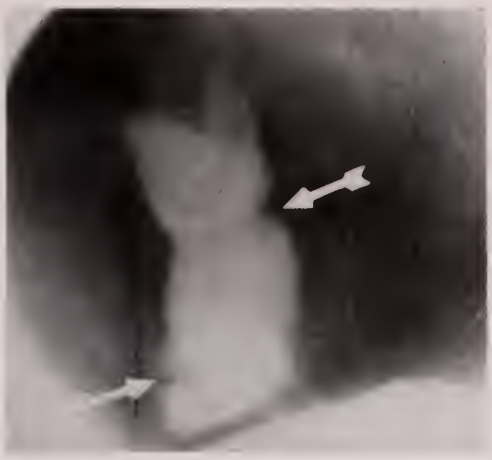

FIG. 3A. D.W. Enlarged 35 mm. frame showing persistent notches and a faint ring at the distal end of the tubular esophagus (upper arrow). 2 or 3 cm. distal to this level on the right aspect, a short distance above the diaphragm, another notch is evident (lower arrow).

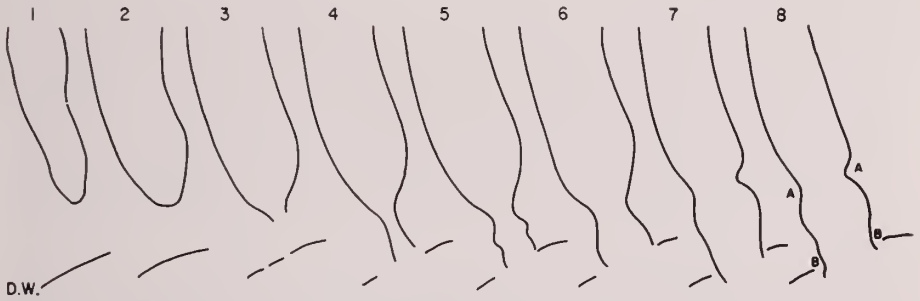

FIG. 3B. D.W. Tracings of sequence showing the entrance of barium into the tubular esophagus, delay in passage of the barium column several centimeters above the diaphragm, and the filling of an intermediate segment between the A and B levels. In contrast to the sequence shown in Fig. 2B, at the beginning of this sequence, the hernial sac was contracted and emptied.

to as the tubular esophagus. From the functional point of view, the contracted state of the vestibule (a phase not emphasized by Lerche) appeared to be of considerably greater significance than its relaxed state. The appearance of a sac with a complete constriction at both ends has not been seen. In fact, after the contracted vestibule relaxes, it may be completely obscured and unidentifiable. However, in some patients (Fig. 4A), notches or a complete circumferential ring may be seen during or after distention at both the proximal and the distal margins of the vestibule. When such landmarks are present, they serve to identify the margins of the vestibule during phases of relaxation and filling. These margins are of special functional interest since discrete sphincteric activity should be present at both ends of the vestibule if the description of Lerche is correct. A special effort was therefore made to determine whether localized sphincteric activity distinct from contraction and relaxation of the vestibule as

FIG. 4A. D. W. Enlargement of 35 mm. frame showing maximum distention as a result of deep inspiration. The upper arrow indicates the notches previously seen in Fig. 3A. At the site of the distal notch seen in Fig. 3A, however, bilateral, deep, rectangular, horizontal notches are seen with a connecting lucent line indicating a circumferential ring.

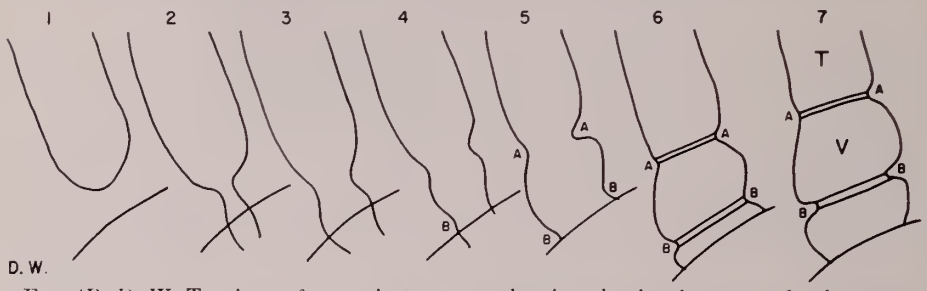

FIG. 4B. D. W. Tracings of a movie sequence showing the development of a deep transverse ring at the B level in association with deep inspiration and maximum distention. In frame 7, the letter T indicates the tubular esophagus and V indicates the segment between the A and B levels. This segment appears to correspond to the vestibule as described by Lerche.

a whole could be identified at the proximal and the distal margins of the vestibule.

The motor phenomena at the margins of the vestibule in patients with small sliding hernias may be summarized as follows:

1. The passage of the barium column from the tubular esophagus into the vestibule often shows transitory delay at the proximal margin of the vestibule (Figs. 1B, 2B, 3B, 4B, 5). This delay is manifest not only by the failure of barium to enter the vestibule, sometimes for several seconds, but by the fact that during this interval the barium column proximal to the vestibule widens and its distal end assumes a rounded or bullet-nosed configuration. Faint bilateral notches and sometimes a thin transverse ring may appear and persist at the proximal margin of the vestibule during distention, or notches visible during distention may disappear after complete distention (Fig. 5). As far as can be determined from the roentgen appearances, it is the failure of the vestibule as a whole to relax that is the cause of the delay to the passage of barium. This description

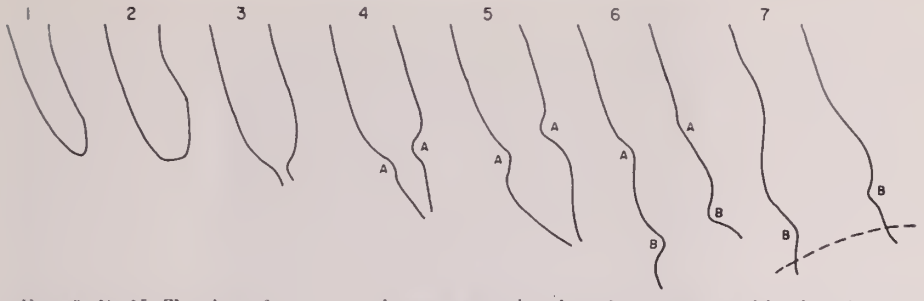

FIG. 5. R. K. Tracings from a movie sequence showing the entrance of barium into the distal esophagus and stages in filling of the vestibule in a patient with a small hernia. During filling of the vestibule, notches were seen at the A level which disappeared with complete distention (frame 7). The notches at the B level, however, persisted.

applies particularly to the first or a single swallow of barium or to orderly swallowing.

2. Additional information can be obtained during phases of repeated swallowing. The patient is directed to swallow the fluid-barium mixture, to stop and then to resume swallowing after a variable period of time. Under these circumstances, the vestibule and the hernial sac may remain distended with barium after the tubular esophagus has been emptied by a stripping peristaltic wave. With prompt resumption of swallowing, fresh barium may be observed to enter the tubular esophagus proximal to the vestibule while the vestibule itself remains filled from the previous swallow. In occasional instances of disorderly swallowing of this type (Fig. 6), a band or ring about three millimeters in length may be evident between the tubular esophagus and the vestibule. The sphincteric nature of this band is indicated by its localized character and because of the fact that its diameter may vary independently of its length. When such a ring is seen, it may abruptly relax and disappear, sometimes leaving residual profile notches or it may go on to complete contraction (Fig. 6D) which may be propagated both proximally and distally (Fig. 6B, 6D). In other words, during unusual episodes of rapidly repeated swallowing, roentgen appearances may be seen which furnish *in vivo* evidence for the existence of the inferior esophageal sphincter of Lerche. However, contraction in this region is rarely evident independently of the vestibule distal to it or of the tubular esophagus proximal to it. In fact, as fresh barium enters the distal portion of the tubular esophagus, it is common to note delay in distending of the tubular esophagus for a variable distance proximal to the vestibule (Fig. 6C). Under ordinary circumstances, the activity of the adjacent portions of the esophagus obscures, if it does not replace, the action of the inferior esophageal sphincter. At times, a ring-like contraction in this region seems to be only the most distal and most persistent of a whole series of tertiary contractions at various levels in the tubular esophagus.

3. A ring of variable diameter and constant length has not been seen at the distal margin of the vestibule. In contrast to the ring at the proximal margin of the vestibule which may disappear completely when distention occurs, a ring at the distal margin of the vestibule is seen clearly only after complete dis-

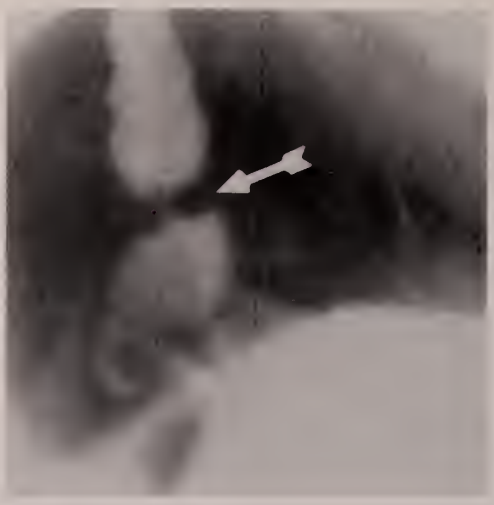

Fig. 6A. D. W. Enlarged frame showing a marked circular constriction several millimeters in length at the junction of the tubular esophagus and the vestibule. This constriction had a variable diameter while maintaining a constant length and suggests a circumferential sphincteric band. Several small tertiary waves are seen in the tubular esophagus proximal to the constriction.

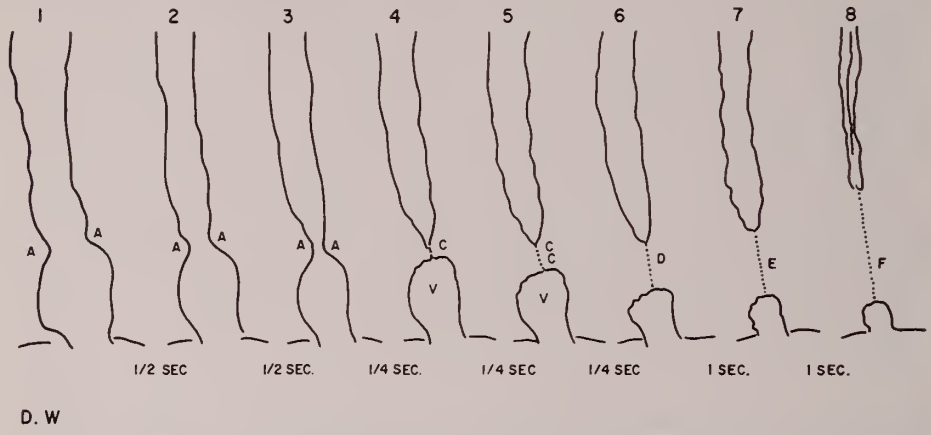

Fig. 6B. D. W. A rare sequence of this patient showing the appearance of a circular constriction at the junction of the tubular esophagus and the vestibule which became complete (frame 4). This contraction then proceeded proximally up the tubular esophagus which also appeared to contract in a diffuse fashion; at the same time, typical vestibular emptying was seen distally.

tention has been achieved. Under these circumstances, this distal ring is of reproducible or constant diameter which is considerably greater than the caliber of the tubular esophagus. The notches representing such a ring in profile are characteristically deep, sharply marked and rectangular. However, prior to complete distention, this ring and these notches are represented by more shallow, somewhat triangular or rounded indentations (Fig. 4B) which presumably have a similar origin and nature. These less well-defined but nevertheless distinct and definite notches are much more commonly seen than a complete ring. The

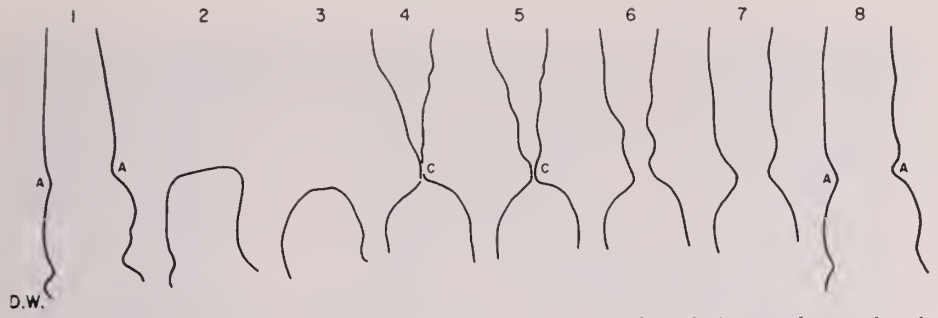

FIG. 6C. D. W. Sequence shows the reëntry of barium into the tubular esophagus shortly after the stripping peristaltic wave had emptied it; the vestibule remained filled with barium. Frame 4 shows the conical configuration of the distal part of the tubular esophagus often seen under these circumstances with a short complete constriction (C) at its distal end. Subsequent frames show progressive filling of the distal esophagus, disappearance of the marked constriction and the appearance of notches at the A level.

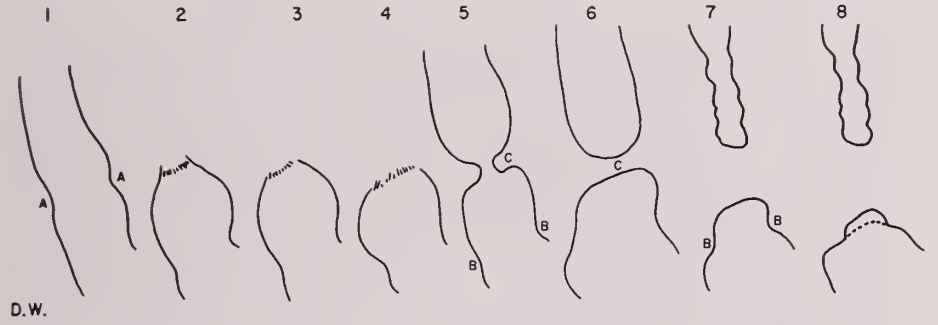

FIG. 6D. D. W. Selected frames from another unusual sequence in this patient showing barium reëntering the tubular esophagus while the vestibule remained filled. A short marked constriction is seen between the tubular esophagus and the vestibule. This went on to a complete contraction (frame 6) which appeared to progress both proximally and distally. The appearances in frames 5 and 6 suggest a localized sphincteric band.

demonstration of a complete ring usually requires some maneuver to increase intraabdominal pressure and produce over-distention of the vestibular region. There is no delay to the passage of the barium column at the distal margin of the vestibule. In other words, no evidence could be produced in these swallowing studies in patients with small hernias, or in ancillary studies of regurgitation, to substantiate the concept of a discrete sphincter with independent function at the distal margin of the vestibule.

The conclusions noted above indicate that the usual sphincteric mechanism in the esophagogastric region is a contraction of the vestibule as a whole. There is evidence to suggest that there may be a band of circular muscle about three millimeters in length at the junction of the tubular esophagus and vestibule which may function independently of the portions of the esophagus on each side of it. There was, however, no evidence of a cardiac sphincter. However, a discrete discontinuity of some type at the distal margin of the vestibule is indicated by the presence of the notches and the ring often seen in this area. It may be assumed that the discontinuity in question is related to the existence of the

FIG. 7A FIG. 7B

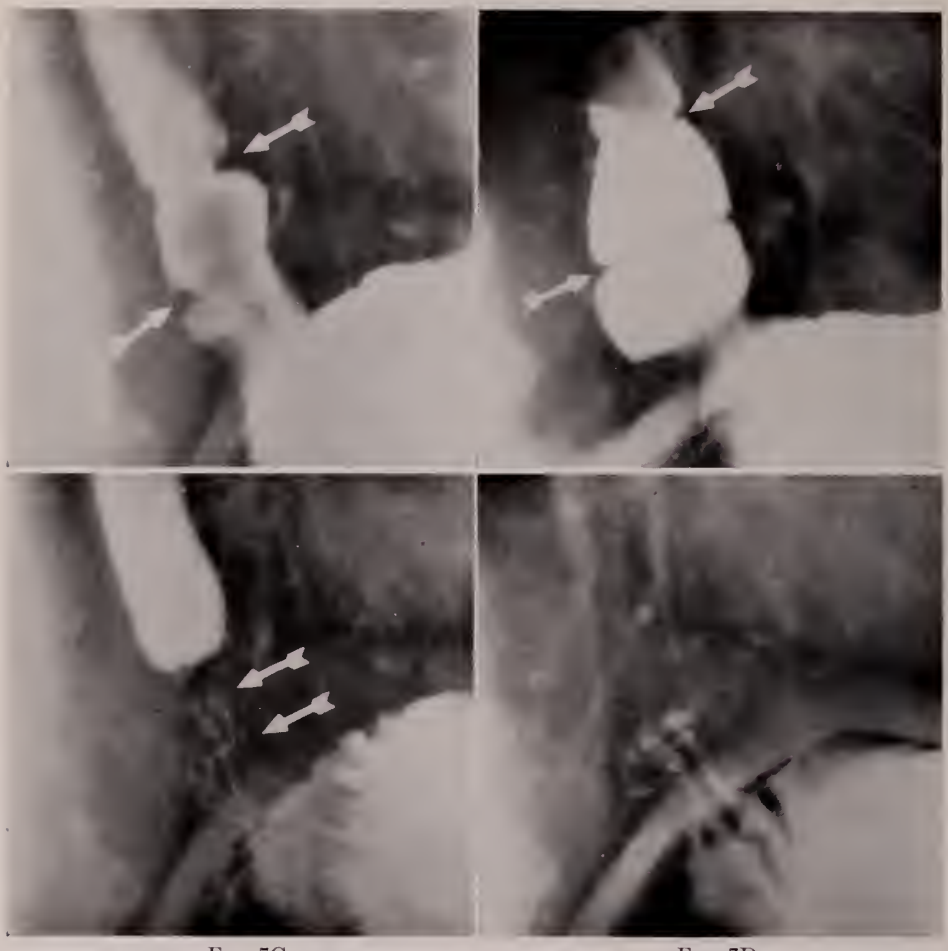

FIG. 7C FIG. 7D

FIG. 7. U. W. Spot radiographs showing phases also recorded in movie sequences. FIG. 7A. The vestibule is moderately distended and there are fairly deep notches at its proximal margin (upper arrow) and a single notch at its distal margin on its right aspect (lower arrow). FIG. 7B. In inspiration, the vestibule is distended to a greater degree than in 7A. The notches at its proximal margin are less marked (upper arrow) but a complete ring is evident at its distal margin (lower arrow). FIG. 7C. Traces of residual barium in the contracted vestibule (upper arrow) and in the hernial sac (lower arrow). Barium, filling the tubular esophagus, is delayed at the proximal margin of the markedly contracted and foreshortened vestibule. FIG. 7D. Residual traces of barium in the hernial sac only.

specialized muscle fibers to which the term cardiac sphincter has been applied for many years. However, the use of the term sphincter appears to be a misnomer. The terms distal ring and distal notches for these findings have been used in this report in order to remain non-committal about their nature and to distinguish them from the proximal notches and the proximal ring noted at the proximal margin of the vestibule. As additional assistance in differentiating the two types of rings (Fig. 7), it may be noted that the proximal ring is variable

in diameter, relatively infrequent and difficult to reproduce, does not exceed the caliber of the tubular esophagus, is quite thin and faint and the associated profile notches are small and shallow.

At this point, the question must arise whether the vestibule as demonstrated above should be considered part of the esophagus, part of the stomach or in accordance with Lerche a unit distinct from the esophagus and the stomach. It is true that, from a functional point of view, in these patients with small hernias, the vestibule might be considered as a separate unit. It is difficult, however, to transfer functional criteria to the anatomical findings of the surgeon or pathologist. Moreover, in a variety of conditions, the vestibule as a well-defined functional unit is not evident. It appears necessary therefore to associate the features of the vestibule as described above with more conventional anatomical designations. Attempts to do this are confused by the fact that the definition of the level at which the esophagus ends and the stomach begins is equivocal and depends on whether the criteria used are based on (a) mucosal, (b) mural or muscular, or (c) serosal observations. The mucosal criterion is the beginning of gastric mucosa and gastric rugae which both grossly and histologically is usually quite distinct although irregular or zigzag in appearance. The mural or muscular criterion is the location of the cardiac slings or the constrictor muscle bundles. These require detailed dissection for their demonstration. The serosal criterion is the level of reflection of the peritoneum, evident only at operation or necropsy. The "cardia" as the abrupt opening of the esophagus into the stomach is not a satisfactory criterion since, in many instances and in patients with small sliding hernias, it is not clearly demarcated. The relationship of these various landmarks to each other may not be constant from patient to patient. Moreover, in a particular patient, the relationship of the level of the constrictor muscle bundles to the mucosal junction must vary to a limited degree depending on the state of contraction or relaxation of this and adjacent regions (7). In the contracted state, the mucosal pattern of the vestibule often appears thickened (Fig. 7C). Changes in the relative positions of the mucosal junction and the constrictor slings were well demonstrated in the dissections of Lerche.

Since the most commonly used criterion for the junction of the esophagus and the stomach is the mucosal zigzag line, it is of interest to determine the relationship between the level of the distal ring or distal notches (constrictor slings?) to the mucosal junction. The mucosal junction can rarely be identified on roentgen examination with any certainty, particularly during phases of distention (8). Special procedures such as the application of clips or the injection of opaque material into the wall of the esophagus at the mucosal junction at the time of esophagoscopy are therefore required to determine this relationship. The evidence available from such studies (Figs. 8, 9) confirms the expectation that these two levels are approximately the same. Moreover, practical confirmation of this relationship is available by the observation at endoscopy of gastric rugae two or three centimeters higher than normal in any instance in which a distal ring or distal notches are demonstrated roentgenologically above the diaphragm.

On the basis that a distal ring or distal notches furnish a satisfactory demon-

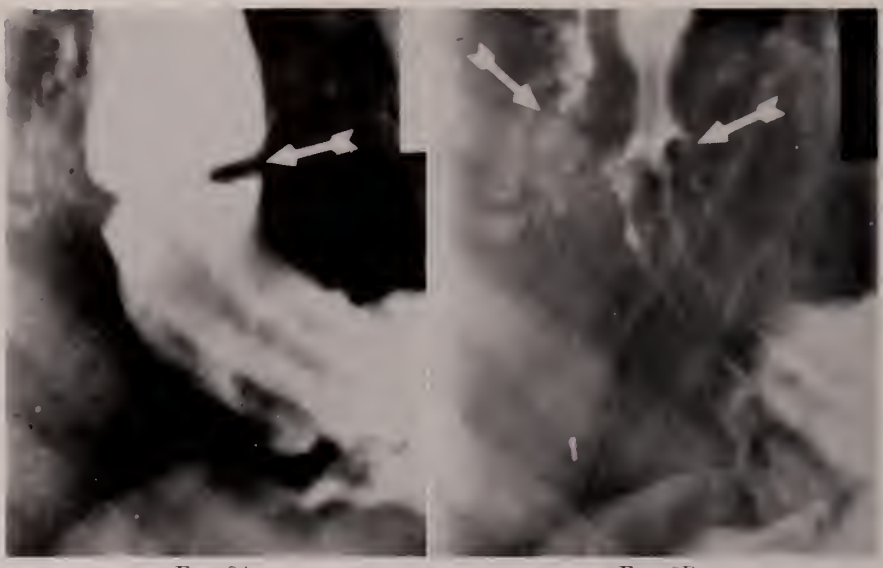

FIG. 8A FIG. 8B

FIG. 8. S. Z. This patient showed a constant, deep, distal or B ring as well as a small hernia. At esophagoscopy, opaque material was injected into the wall of the esophagus down to the beginning of the gastric rugae. Roentgen examination was performed 5 days later. FIG. 8A. The injected material seen as opaque droplets and short streaks in the right posterior wall of the esophagus extends distally to the level of the ring. This indicates that the distal ring and the esophagogastric mucosal junction are at the same level. FIG. 8B. Same examination. The esophagogastric region in a contracted state. The transverse ring (right arrow) can be faintly seen with thick folds beginning distal to it. The opaque material (left arrow) extends a millimeter or so beyond the ring.

stration of the junction of the esophagus and the stomach, several statements can now be made explicitly:

1. The vestibule may be considered as a specialized portion of the esophagus.

2. If a distal ring or distal notches are seen clearly above the hiatus of the diaphragm, some degree of hiatal herniation of the direct type must be present (Fig. 10). This conclusion of course is of considerable utility in the roentgen diagnosis of small direct hernias. It is recognized that the use of this criterion will multiply the number of instances in which the diagnosis of herniation is made. It seems pointless, however, to deny the high frequency of minimal herniation in the older age groups by adopting other terms such as "hiatal insufficiency". The radiologist must emphasize to his colleages, however, that this finding is a statement in regard to the anatomical status and does not imply that these patients are necessarily symptomatic or require operative intervention. The absence of reflux into the esophagus in the majority of these patients should serve as a deterrent to clinical overemphasis.

3. Under normal circumstances, the proximal portion of the vestibule is located above the diaphragm while its distal part is located in and below the hiatus of the diaphragm.

The reason why the vestibule as a single distensible segment is not demonstrable roentgenologically under normal conditions is now evident (Fig. 11).

FIG. 9A

FIG. 9B

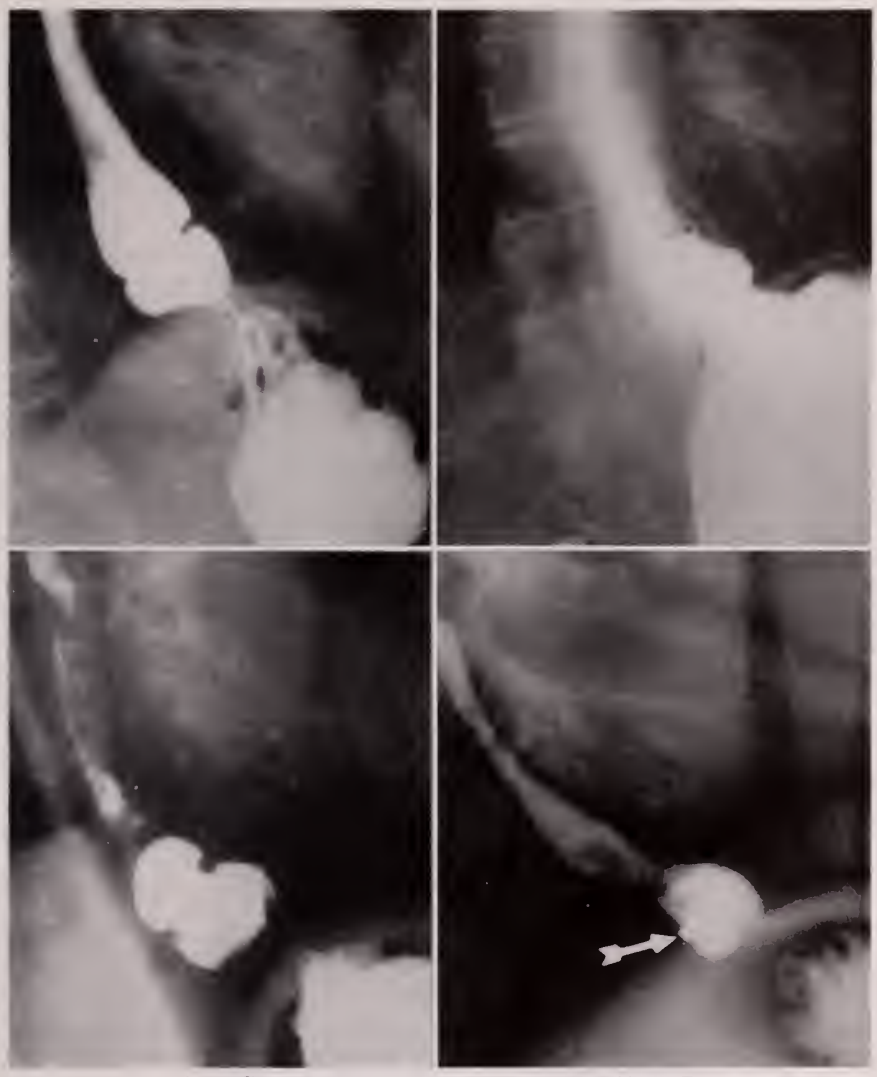

FIG. 9C

FIG. 9D

FIG. 9. L. L. FIG. 9A. A distal ring with a deep notch on its left aspect and a somewhat shallower notch on its right aspect was easily demonstrated in this patient. FIG. 9B. Patient in Trendelenburg position. Reflux of barium from the stomach into the esophagus occurred without delay. This is important evidence for the presence of a hiatus hernia. FIG. 9C. A film taken 2 hours after esophagoscopy shows marked distal notches. The tubular portion of the esophagus is quite spastic and there is a localized segment, 3 or 4 mm. in length, at the junction of the tubular esophagus and the vestibule which appears completely constricted. This is the site of the presumed inferior esophageal sphincter. FIG. 9D. A film taken 2 hours after the application of a clip (arrow) to the esophagogastric mucosal junction at esophagoscopy. Distal notches were not demonstrated during the course of this examination. There was no delay to the passage of barium at the site of the clip. Comparison with films from previous examinations suggests that the clip is approximately at the level of the notches.

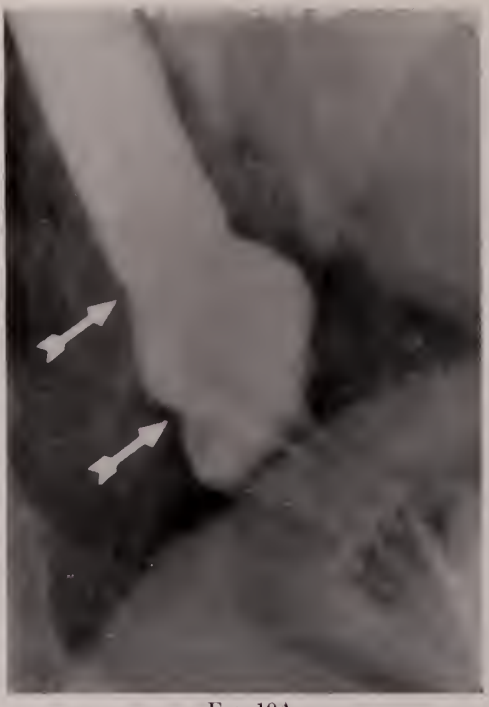

FIG. 10A

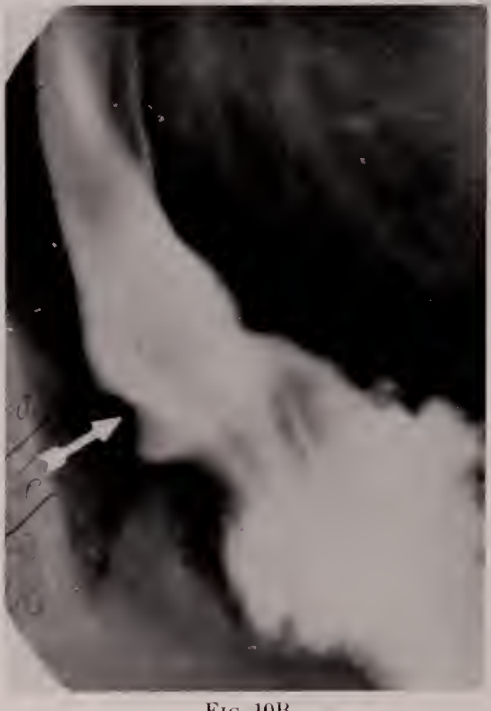

FIG. 10B

This is related to the fact that the distensibility of the distal part of the vestibule located in and below the diaphragm is artificially limited by extrinsic factors, i.e. the relatively greater intraabdominal pressure. For the same reason, a distal ring or distal notches are not evident when this area is normally located. Delay to the passage of the barium column may be seen normally (Figs. 11C, 12, 13) one or two centimeters above the hiatus of the diaphragm and this level presumably corresponds to the proximal margin of the vestibule in its normal location. A ring-like complete constriction at this level, however, is not seen normally thus confirming the previous conclusion that contraction of a sphincter in this location rarely occurs independently of contraction of the vestibule as a whole.

As noted above, the progress of a barium column may be delayed at the proximal margin of the vestibule but there is no evidence that there is any delay at the cardia *per se*. This is true in the presence of a small hernia as well as under normal circumstances. The passage of barium, however, is often delayed at the level of the hiatus of the diaphragm (Figs. 12, 13). This delay is markedly exaggerated when the patient takes a deep breath during the course of swallowing. In fact, if the patient is sufficiently coöperative and takes a deep inspiration, the barium column in the hiatus in the diaphragm is usually completely cut off thereby producing an appearance to which the term "pinchcock action" of the diaphragm has been applied. This pinchcock action is evident not only in patients with a normally located esophagogastric junction but also in those with hiatus hernias of the direct type, both large and small (Fig. 14). It must therefore be the result of extrinsic rather than intrinsic factors. When a patient takes a deep breath, not only is the barium column cut off at the level of the hiatus, but a stripping peristaltic wave is also initiated which empties the proximal esophagus in progressive fashion. As a result, residual barium becomes trapped above the diaphragm and assumes a sac-like configuration (Figs. 15, 16). The term "phrenic ampulla" was used by Templeton (2) to refer to this specific and quite characteristic roentgen appearance. This author also clearly described that the constriction at the apex of the phrenic ampulla configuration may continue to progress distally while some of the trapped barium is forced to go back in a retrograde fashion. As this occurs, the phrenic ampulla of course diminishes in height (Figs. 15, 16). In other words, there are multiple phrenic ampullae of continually diminishing size depending on the extent of progress of the peristaltic wave (Fig. 17). The phrenic ampulla is therefore not a unique structure. In patients with small sliding hernias, the hernia also contributes to the ampullary configuration (Fig. 17B) and forms a part of the phrenic ampulla. In a patient with

FIG. 10A. M. B. Example of a small direct hernia with notches (arrows) marking the limits of the vestibule. FIG. 10B. A small hernia with prominent notches (arrow) at the junction of the vestibule and the hernial sac on both sides. No evidence of notches or a constriction at the proximal margin of the vestibule. FIG. 10C. The proximal and distal margins of the vestibule are indicated by notches (arrows). FIG. 10D. Multiple tertiary contractions in the esophagus and a constriction (upper arrow) at the junction of the tubular esophagus and the vestibule which is suggestive of a short sphincteric band. The convex notch on the right posterior aspect of the saccular structure above the diaphragm (lower arrow) indicates the junction between the vestibule and the herniated portion of the stomach. A phase such as this suggests that the inferior esophageal sphincter may be an exaggeration of the multiple potential areas of circumferential contraction indicated by tertiary waves.

FIG. 10C

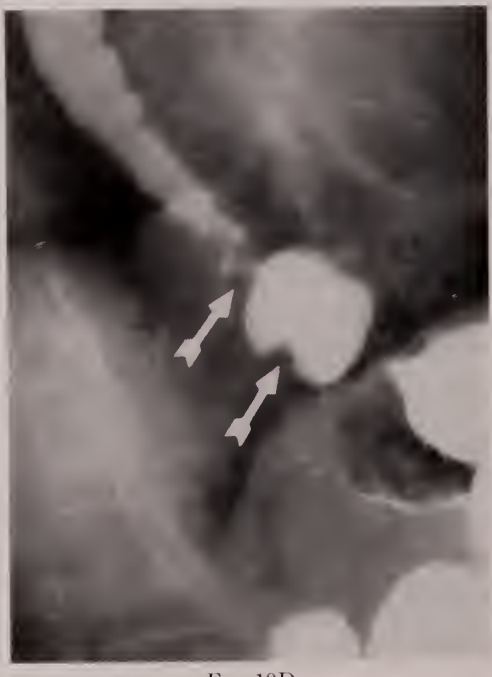

FIG. 10D

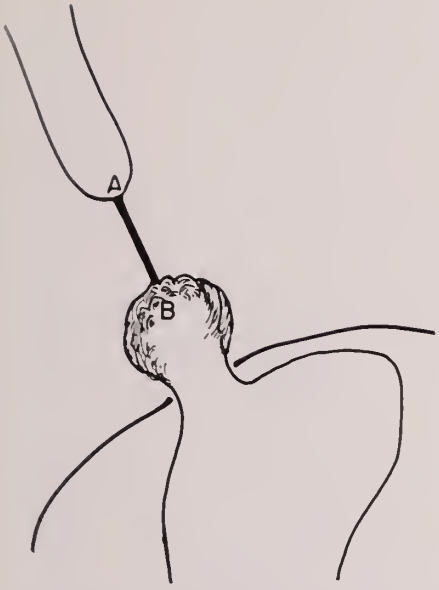

FIG. 11A

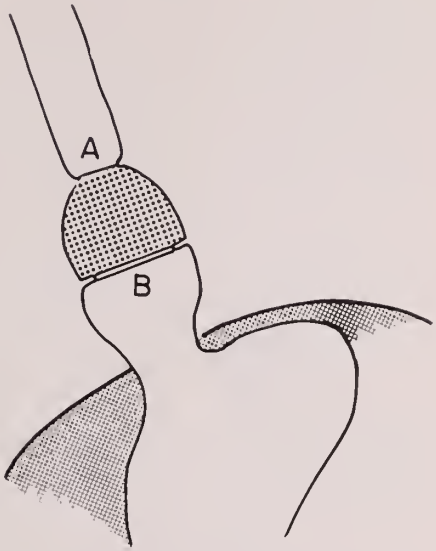

FIG. 11B

FIGS. 11A and 11B. Diagrammatic representation of the location and appearance of the vestibule in a patient with a small hernial sac of the direct type. FIG. 11A. The vestibule, which extends from A to B, is shown in its contracted state. In this phase the entire vestibule may be considered to act as a sphincter and the terms vestibular sphincter, gastroesophageal sphincter or internal sphincter are applicable. (For purposes of comparison with Fig. 11B, the longitudinal shortening of the vestibule usually present in its contracted state is not shown.) FIG. 11B. Demonstrates the remarkable distensibility of the vestibule, the faint notches which may be seen at its proximal margin, and the deep notches and sharply demarcated ring at its distal margin.

a hiatus hernia therefore, the phrenic ampulla is frequently of surprisingly large size. A distal ring is often best seen during this particular functional phase because of the marked distention associated with it. When a ring is seen in a phrenic ampulla, it may be noted that the ring is fixed in location and static in character and that the stripping peristaltic wave stops a short distance proximal to it. It may be assumed that the point about two centimeters or so proximal to such a distal ring at which a peristaltic wave stops represents the proximal margin of the vestibule.

Phrenic ampullae as described above in accordance with the original description of Templeton are very familiar to radiologists. Unfortunately, however, the term phrenic ampulla was previously used in the anatomical literature to describe a saccular dilatation above the diaphragm. When Templeton adopted this term to refer to his roentgen findings, it was in the belief that he was describing this particular anatomical structure. However, he clearly reserved the right to change his mind if this should turn out to be incorrect. It is not possible at this date to determine the precise meaning of the original anatomical description of the phrenic ampulla but, if specific at all, it appears more applicable to the structure currently termed the vestibule rather than to the roentgen appearances described by Templeton. The duality of the use of the term phrenic ampulla,

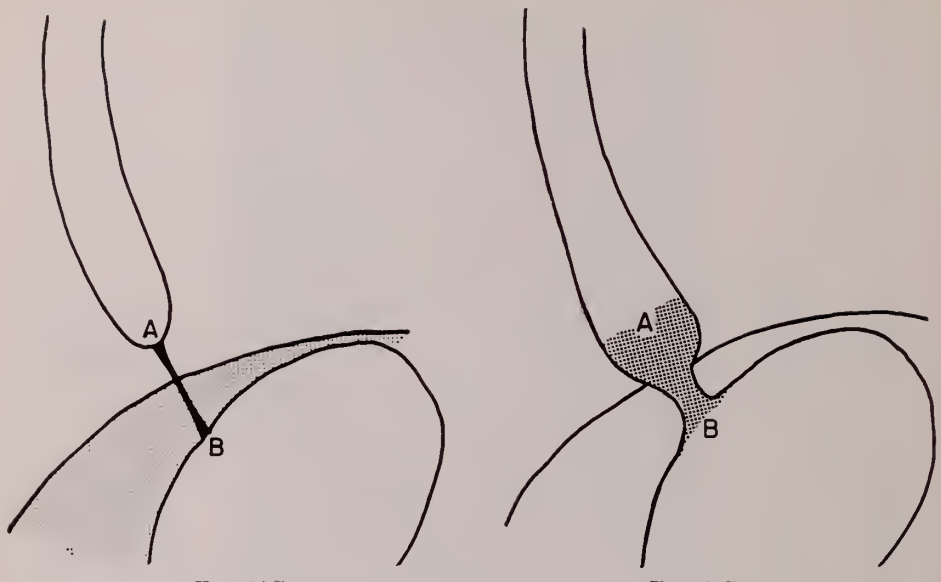

FIG. 11C FIG. 11D

FIGS. 11C and 11D. Diagrammatic representation of the location and appearance of the vestibule under normal circumstances, that is, in the absence of a hernia. FIG. 11C. The contracted vestibule traversing the hiatus of the diaphragm. The exact level of the hiatus of the diaphragm in relationship to the dome of the diaphragm cannot be determined under these circumstances. FIG. 11D. With the vestibule relaxed and filled, only the portion above the hiatus of the diaphragm distends to a caliber greater than the remainder of the esophagus. The portion of the vestibule in and below the hiatus of the diaphragm is limited in distending by the greater external intraabdominal pressure. The demonstration of the vestibule as a single distensible saccular structure with a distal ring is therefore not possible under normal circumstances. The narrow distal portion of the vestibule serves to identify the location of the hiatus or the hiatal canal.

originally in the anatomical literature and then in the roentgen literature, has created considerable confusion. It is therefore recommended that the anatomical connotation of this term be dropped completely, that its use be confined to the functional appearances described so well by Templeton and that phrenic ampullae be clearly distinguished from the vestibule (Figs. 11, 17).

The phrenic ampulla phenomenon has greater significance than the fact that it can be produced by requesting the patient to take a deep breath while swallowing barium. With patients in the recumbent position, phrenic ampullae of diminishing size can often be seen at the end of swallowing. This phenomenon appears to play a rôle in transferring the last bolus of fluid from above to below the diaphragm without permitting reflux. Normally, the stripping peristaltic wave does not completely empty the esophagus since it does not appear to enter the vestibule. A special mechanism, therefore, is required at the end of swallowing for final clearance just as a special mechanism is required at the beginning, in order to prevent the relatively greater intraabdominal pressure from producing reflux. Another feature of the phrenic ampulla phenomenon, particularly as seen during emptying, is the fact that the constriction which appears at the apex of the phrenic ampulla may persist for a variable period of time. This may be

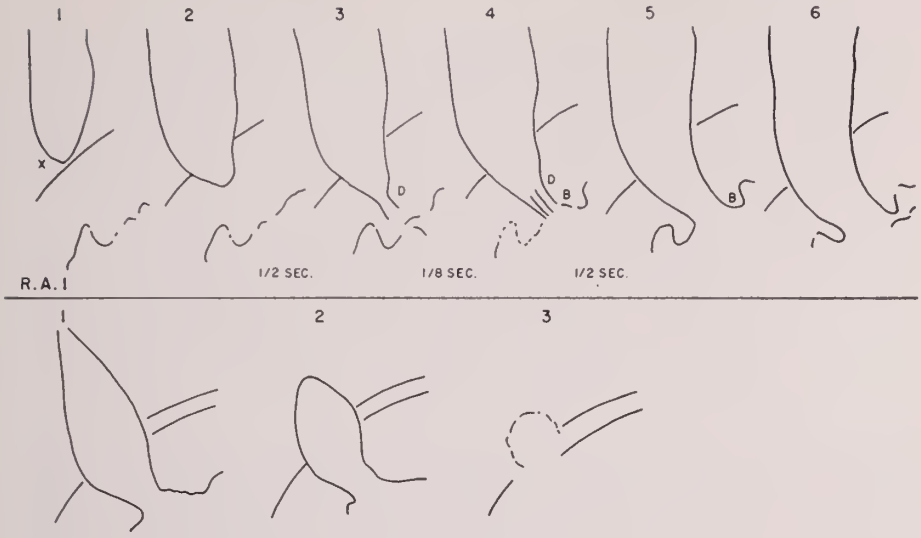

Fig. 12. R. A. Fig. 12A. (Upper Row) Tracings from a movie sequence in a normal patient. Frame 1 shows delay to the passage of the barium column at a point (X) about 2 cm. above the hiatus of the diaphragm. Frame 2 shows progress of the barium column to the level of the hiatus of the diaphragm with transient delay at this level. Frame 3 shows passage of barium through the hiatus. Subsequent frames show the appearances of the barium column in the hiatal canal as it distends. The barium column goes through the cardia (B) into the stomach without delay. The letter D (frames 3 and 4) indicates the level of the hiatus of the diaphragm which is situated well below the dome. The original site of delay (frame 1) presumably represents the proximal margin of the contracted vestibule. Fig. 12B. (Lower Row) Phases during emptying of the final bolus of barium from the distal esophagus. The appearances resemble the phrenic ampulla which diminished in size in stepwise fashion associated with short inspiration and expiration. This sequence may be compared with emptying phases in a patient with a small hernia shown in Fig. 19.

demonstrated by requesting the patient to resume swallowing shortly after emptying. A rather elongated or hourglass constriction can then often be demonstrated above a small phrenic ampulla (Fig. 18). A constriction of this type has sometimes been referred to as the inferior esophageal sphincter but it does not resemble the ring-like contraction described above in patients with small hernias (Fig. 6).

The phrenic ampulla phenomena during emptying may also be seen in patients with small sliding hernias. However, in some of these patients, the emptying mechanism often has a different appearance suggesting that the vestibule may play a rôle during emptying as well as filling (Fig. 19). When swallowing stops, the primary peristaltic wave rapidly strips the tubular esophagus down to the proximal margin of the vestibule. Then the appearance changes and the vestibule empties more slowly and appears to collapse as a unit, sometimes maintaining a surprisingly flat superior surface. The small hernial sac may contract simultaneously with the vestibule and this combined contraction may succeed in emptying the barium into the stomach below the diaphragm. Often, however, a small

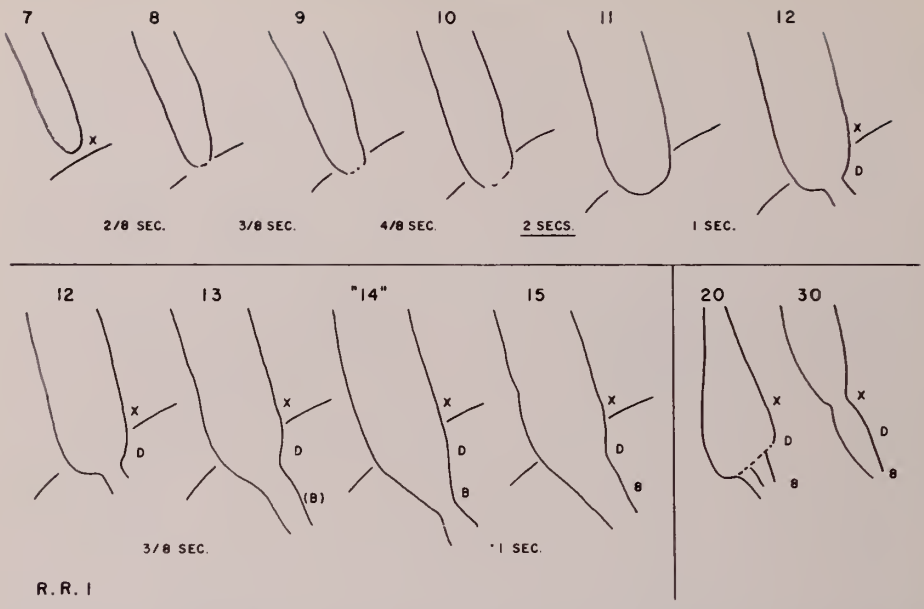

Fig. 13. R. R. Normal; no hernia. Tracings from movie sequence showing delay in passage of barium about 2 cm. above the hiatus (at X in frame 7), progress during filling down to the level of the hiatus (frames 7 to 11), passage through the hiatus (D) and entrance into the stomach (B). Frame 20 indicates the X, D, and B levels during inspiration and phrenic ampulla formation. In one fleeting frame (30), a spindle-shaped configuration was seen extending from X to B through the hiatus (vestibule in normal location).

Fig. 14A Fig. 14B

Fig. 14. The pinchcock action in a patient with a wide hiatus and a small hiatus hernia. Fig. 14A shows a wide barium column traversing the hiatus of the diaphragm (arrow) and outlining the thick gastric folds of the hernial sac. Fig. 14B. In inspiration, there is complete cut-off (arrow) of the barium column through the hernial sac at the level of the hiatus of the diaphragm.

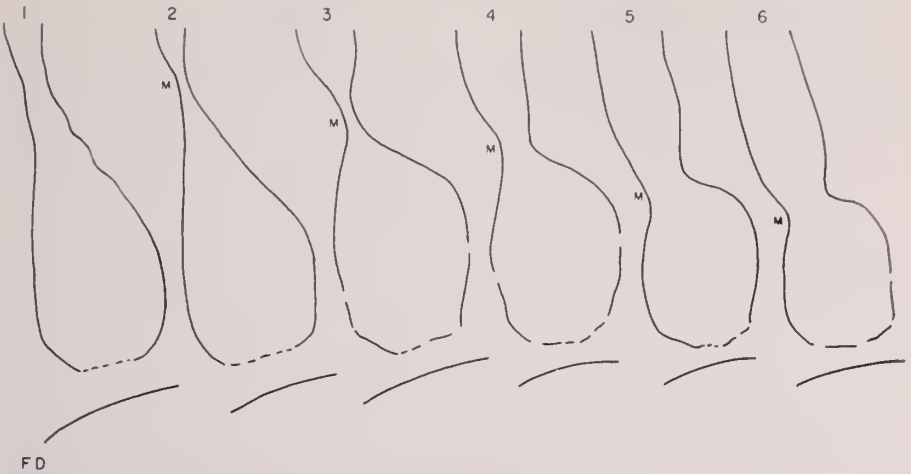

FIG. 15. F. D. Tracings from a movie sequence showing the formation and change in size of the phrenic ampulla during maintained deep inspiration. The elongated constriction (M) represents the stripping peristaltic wave which is slowed up in the distal esophagus as it progresses into the ampullary formation and displaces barium proximally. Note that the width of this constriction increases as it progresses distally and that the wave stops about 3 cm. above the diaphragm. The presence of a small hernia in this patient is not evident in these tracings but was suspected from other views. Faint notches about 2 cm. above the diaphragm were occasionally seen in fleeting fashion.

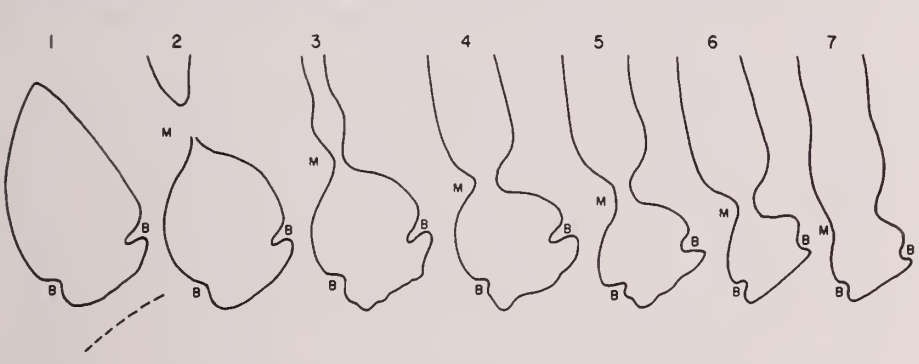

FIG. 16. S. Z. This is the same patient illustrated in Fig. 8 in whom opaque material was injected into the wall of the esophagus down to the esophagogastric mucosal junction confirming the presence of a small hiatus hernia beginning at the BB ring. Sequence of events during deep inspiration and the formation of the phrenic ampulla demonstrates that the BB ring remains unchanged in location while the constriction associated with the peristaltic wave (M) travels distally but stops 1 cm. or so above the B level. Note complete cut-off at level of hiatus (dashed line in frame 1) despite the presence of a hernia.

amount of barium remains in the hernial sac for a considerable period of time and occasionally some barium may also be retained in the contracted vestibule as well.

Special interest is attached to the phenomenon of regurgitation in patients with hiatus hernias since regurgitation of acid gastric contents into the esophagus is involved in the pathogenesis of inflammatory changes of the esophagus (9). In some patients with small direct hernias, barium will flow freely from the

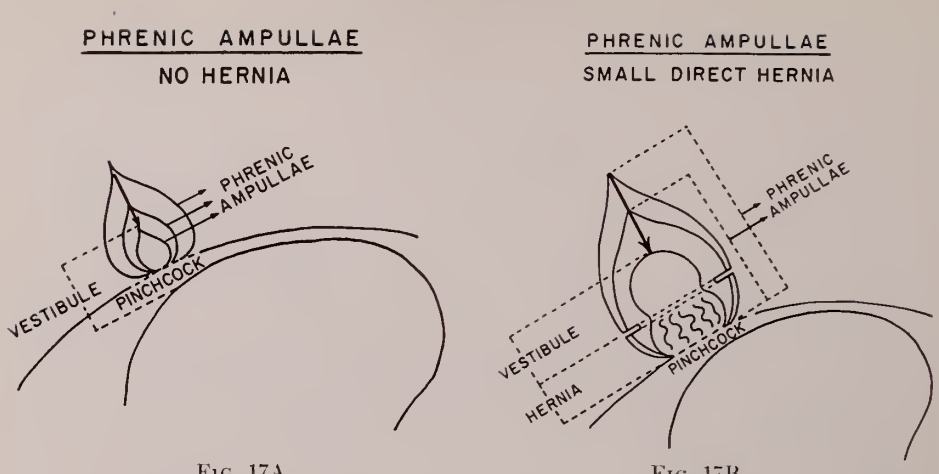

FIG. 17A FIG. 17B

FIG. 17. Diagrammatic representation of phrenic ampullae. FIG. 17A. Normal; no hernia. While the pinchcock action at the hiatus is effective, pear-shaped sacs of diminishing size are seen as barium is displaced proximally. The distal part of the vestibule is occluded by the pinchcock action. If the pinchcock action is not completely effective, barium may enter the stomach while the sac diminishes in size. FIG. 17B. Small direct hernia. The pear-shaped sacs are larger and include the vestibule and herniated stomach distally. Notches between the vestibule and the hernia may or may not be evident.

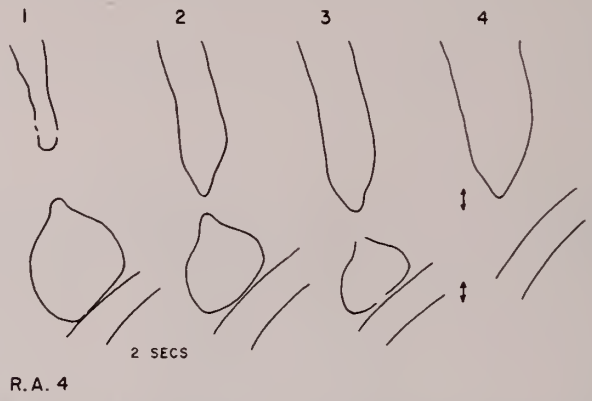

FIG. 18. R. A. A patient without a hiatus hernia showing residual barium in the phrenic ampulla and a persistent elongated constriction proximal to it demonstrated by additional barium entering from above. During this sequence, the phrenic ampulla diminished in size and emptied completely although the barium column was held up about 2 cm. above the hiatus. This level presumably corresponds to the proximal margin of the vestibule and to the proximal margin of the smallest of the phrenic ampullae. The vertical arrows in frame 4 show up and down excursion of the barium column synchronously with the diaphragm during expiration and inspiration. The delay to the passage of barium under these circumstances is not due to pinchcock action since it is above the hiatus and independent of the phase of respiration.

infradiaphragmatic portion of the stomach into the hernial sac and into the esophagus simply under the influence of gravity. This is demonstrated by placing the patient in the Trendelenburg position after filling the stomach with fluid barium. Prompt reflux under the influence of gravity may be referred to as "free regurgitation". In other patients, with small or large hernias, reflux does not

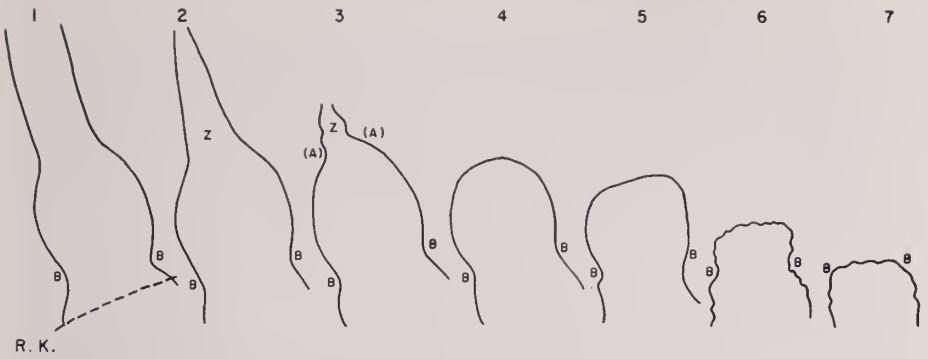

Fig. 19. R. K. Emptying phases in a patient with a small hernia. Filling phases in this patient are shown in Fig. 5. The vestibule extends from AA to BB (frame 3). The first three frames show the rapid entrance of the peristaltic wave into the tubular esophagus. The conical configuration of this region (frame 2) suggests preparatory contraction for a short distance in advance of the stripping wave. A small cap (Z in frame 3) is often seen at the transition from tubular to vestibular emptying. Between frames 3 and 4, a contraction in the AA region may be attributed to the inferior esophageal sphincter. The flat top seen in frame 5 is maintained during subsequent frames, suggesting simultaneous longitudinal and circular contraction.

occur or can be induced only by special maneuvers which serve to increase remarkably the differential pressure between the abdomen and the mediastinum. In tests for regurgitation, it therefore must be clearly specified under what conditions reflux can be made to occur and whether barium enters not only the hernial sac but the esophagus as well. Reflux of barium in some patients with small hernias may be delayed as a result of failure of the vestibule to relax (Fig. 2A). This mechanism of preventing regurgitation, however, appears to be easily overcome. More commonly when reflux into the esophagus is delayed, both the vestibule and the hernial sac fill with barium (Fig. 20). If intraabdominal pressure is further increased, barium may enter the tubular esophagus in a thin streak (Fig. 20B) or fill the tubular esophagus while a short narrowed segment remains at the junction of the tubular esophagus and the vestibule (Figs. 20C, 20D). This appearance suggests the possibility that the inferior esophageal sphincter plays a rôle in preventing reflux but it is likely that a more general contraction of the tubular esophagus also participates. The markedly distended sac seen above the diaphragm when reflux into the tubular esophagus is obstructed recalls the description of Lerche of ballooning-up of the vestibule during expulsion of gastric contents. However, this sac consists of the vestibule plus a herniated portion of the stomach. Moreover, there is no constriction at its distal end. On the contrary, it is evident that the ballooning-out is the result of free communication with the stomach below the diaphragm (Fig. 20B, 20D).

The most common site at which reflux in patients with hiatus hernias is obstructed is at the level of the hiatus of the diaphragm (Fig. 21). Since the stomach occupies the hiatus under these circumstances, this mechanism must be of extrinsic origin. It cannot be the result of pinchcock action per se since it is independent of the phase of respiration. In fact, obstruction at this level can sometimes be overcome by deep inspiration The amount of stomach which

FIG. 20A

FIG. 20B

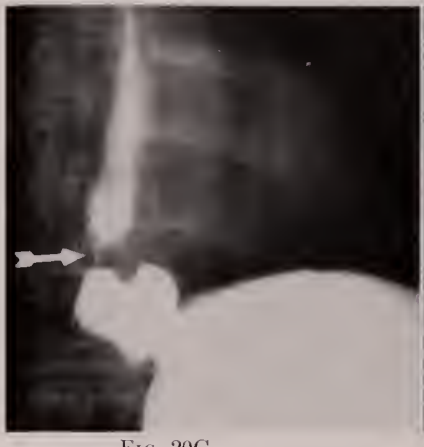

FIG. 20C

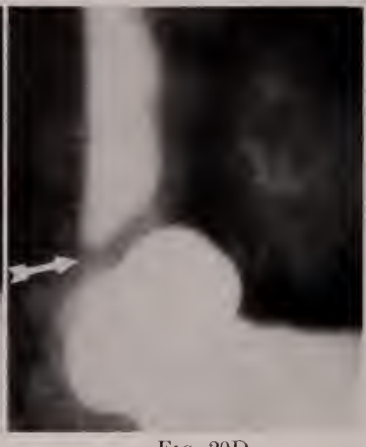

FIG. 20D

FIG. 20. Patients with small hernias. Appearances during delayed reflux in the Trendelenburg position. FIG. 20A. Reflux of barium from the infradiaphragmatic portion of the stomach into the small hernial sac and into the vestibule is present. The notch on the left side (arrow) is indicative of the demarcation between the vestibule and the hernial sac. A streak of barium is noted in the tubular portion of the esophagus. FIG. 20B. In another patient, filling of the hernial sac and the vestibule without any evident demarcation between these two regions is present. A thin streak of barium fills the tubular esophagus over a long distance. An appearance such as this does not indicate the reason for the obstruction to the retrograde flow of barium from the vestibule into the tubular esophagus since it may be due to a localized constriction at the proximal margin of the vestibule or a more extensive contraction of the tubular esophagus. FIG. 20C. Another patient shows reflux into the hernial sac and into the vestibule. After a period of time, barium entered the tubular portion of the esophagus. A rather ill-defined, short segment of narrowing (arrow) is seen between the poorly distended tubular esophagus and the vestibule. FIG. 20D. Another patient shows filling of the hernial sac and the vestibule which are not demarcated from each other. Barium entered and distended the tubular esophagus but a persistent short constriction between the tubular esophagus and the vestibule persisted (arrow). This suggests the possibility that the obstruction to the retrograde flow of barium from the vestibule into the tubular esophagus may be due to a rather isolated contraction of the so-called inferior esophageal sphincter, at least in some patients.

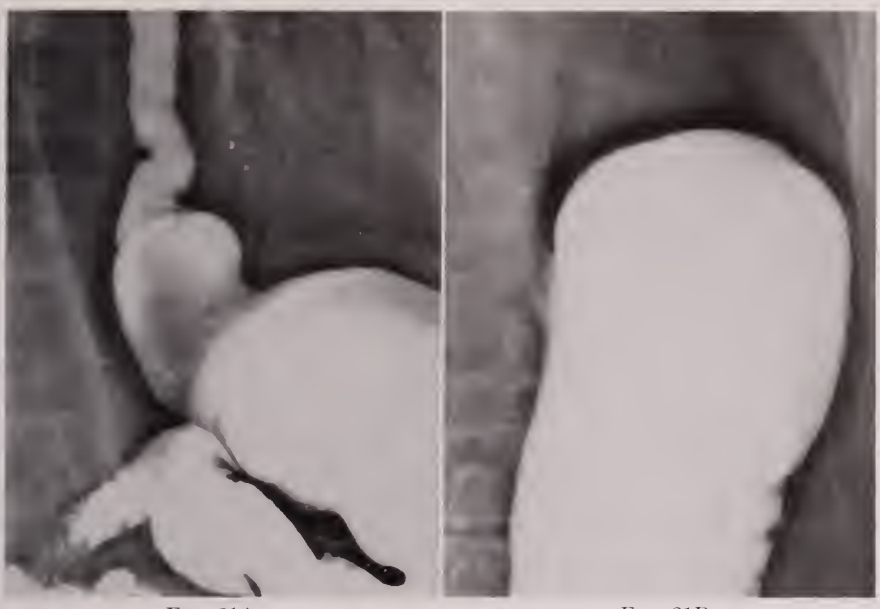

FIG. 21A FIG. 21B

FIGS. 21A and 21B. FIG. 21A. A. D. Film taken during swallowing of fluid barium in the prone right oblique position demonstrates marked widening of the hiatus with a moderate sized hernial sac. FIG. 21B. Same patient in Trendelenburg position showing no reflux through the hiatus. It is assumed that the hernial sac is still present above the hiatus since it is unlikely that a sac of the size seen in Fig. 21A could be reduced with the patient in the Trendelenburg position.

intervenes between the dome of the diaphragm and the level of the hiatus when the patient is inverted into the Trendelenburg position seems to play a rôle in this mechanism. In patients with sliding hernias but without reflux through the hiatus, the distance between the dome and the hiatus is greater than in those patients who show such reflux (Figs. 20, 21B, 21D). When the dome is near the hiatus, the infradiaphragmatic and herniated portions of the stomach are "in line" with no acute angulation at the hiatus to obstruct retrograde flow. These observations confirm the concept of a valvular nature of the mechanism at the hiatus which seems to prevent reflux.

In addition to the gastroesophageal vestibule, Lerche believed that another segment of the esophagus, about two centimeters in length, immediately proximal to the vestibule also showed special features. He believed that this segment could also balloon out and form a discrete saccular dilatation and referred to it as the "ampulla of the esophagus". Unfortunately, at times, he used the term phrenic ampulla presumably to apply to this same segment. He did not indicate any specific landmark for its proximal extent. However, this particular portion of the tubular esophagus has not been observed to distend as a unit and does not show sufficiently unique functional characteristics to warrant a special designation. If the term phrenic ampulla were applied to it, this would serve only to increase the confusion already surrounding this particular name. As pointed out above, the terminal portion of the tubular esophagus occasionally shows some

FIG. 21C FIG. 21D

FIGS. 21C and 21D. FIG. 21C. B. C. Film taken during swallowing shows a moderate sized hiatus hernia with markedly widened hiatus. FIG. 21D. Same patient as 21C, in Trendelenburg position. Reflux beyond the level of the hiatus of the diaphragm is not present.

delay in distending, particularly if it has been recently emptied by a stripping peristaltic wave (Fig. 6C). Under these circumstances, a rather elongated contraction of this area may resemble and be mistaken for the contracted state of the vestibule itself (Fig. 22). Occasionally a short circumferential constriction of a very transient nature may be seen about two centimeters proximal to the vestibule (Fig. 23) but this resembles a tertiary contraction rather than a sphincteric band. Very rarely, a thin ring or small profile notches may be evident at this level which may resemble the ring and the notches more commonly seen at the proximal margin of the vestibule. A rather characteristic feature of the terminal portion of the tubular esophagus is the fact that it becomes quite tortuous when maximum herniation has been produced by maneuvers to increase intraabdominal pressure (Fig. 24). The remainder of the tubular esophagus may remain straight and relatively taut under these circumstances suggesting the possibility that the fascial attachments to the diaphragm (phrenicoesophageal ligament?) insert into the esophagus several centimeters above the proximal margin of the vestibule.

A ring apparently identical with the ring described above as the distal ring was included in the original description of the phrenic ampulla by Templeton (2). The present conclusion, that it is indicative of a small direct hernia, was not drawn by this author. A similar ring was also described by Schatzki and Gary

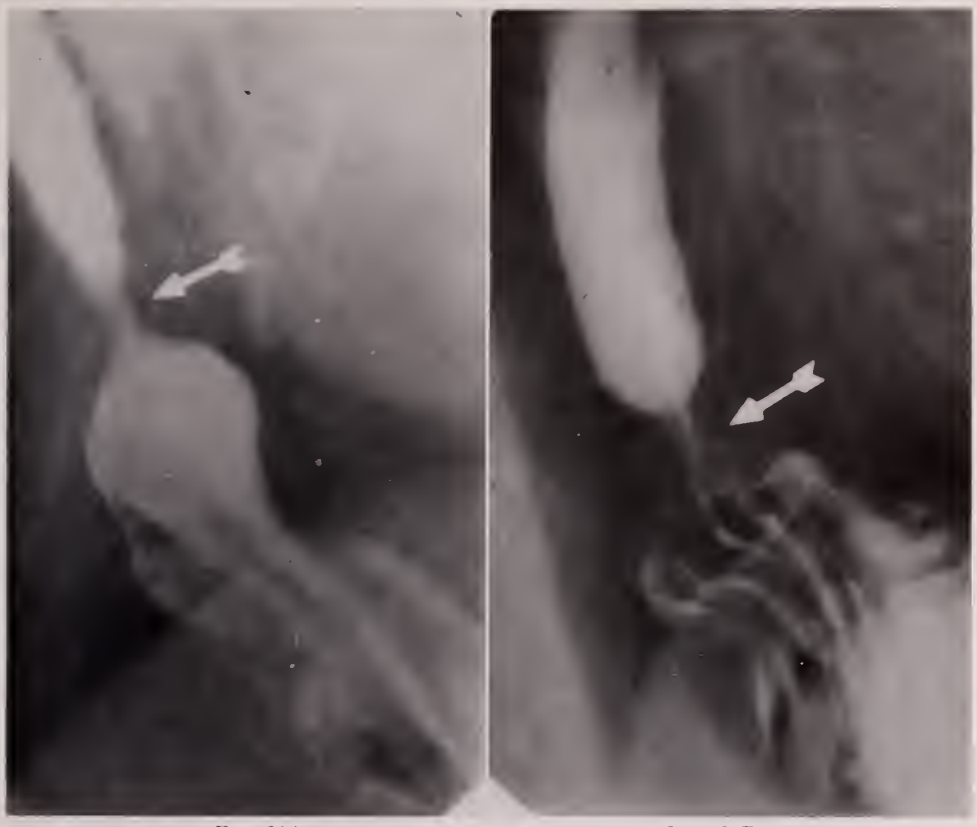

FIG. 22A FIG. 22B

FIG. 22. FIG. 22A. M. B. This is the same patient illustrated in Fig. 10A but in this phase the distal tubular esophagus is incompletely distended. A contracted segment (arrow) about 1½ cm. in length is seen proximal to the vestibule. This is not a sharply demarcated ring. FIG. 22B. Another patient showing a small hernial sac with beginning filling of the contracted vestibule (arrow) which measures about 1½ or 2 cm. in length. Except for its location, the contracted vestibule at such an instant is similar in appearance and in length to the contraction in the distal portion of the tubular esophagus seen in Fig. 22A. However, the contracted vestibule after filling distends to a diameter greater than the tubular esophagus and may also elongate.

(10, 11) and by Ingelfinger and Kramer (12). These authors pointed out that the caliber of this ring might be reduced to a point where swallowing of large boluses of food might be obstructed. The present authors have no case with an incompletely distensible ring in this region which has been sufficiently well studied to prove conclusively its location. Motion picture studies of a patient with such a ring, however, confirm the observations of Schatzki that this ring is static in character rather than contractile and that it is unchanging in location in relationship to the esophagus although its relationship to the level of the diaphragm may change with filling and emptying of the region (Fig. 25). In this patient, the esophagus for a short distance proximal to the ring often showed some delay in distending and assumed a conical configuration; the typical appearance of a vestibule or of the inferior esophageal sphincter was not apparent.

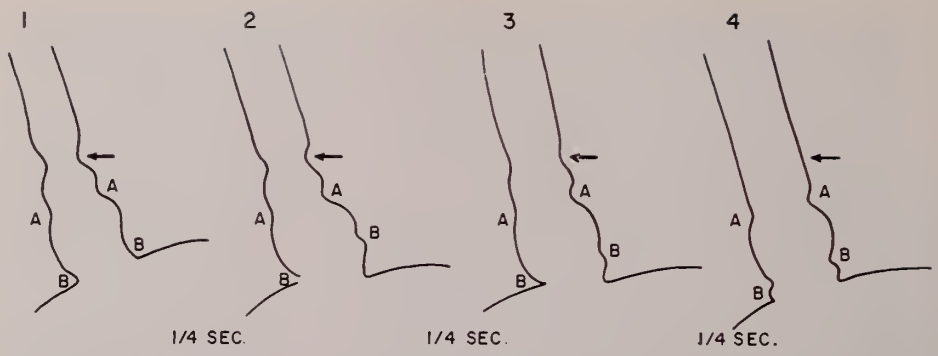

FIG. 23. D. W. Tracings from a movie sequence showing fleeting slight constriction (arrows) 1 to 2 cm. proximal to the vestibule, in the tubular esophagus. A constriction such as this was rarely seen in this patient. The vestibule extends from AA to BB.

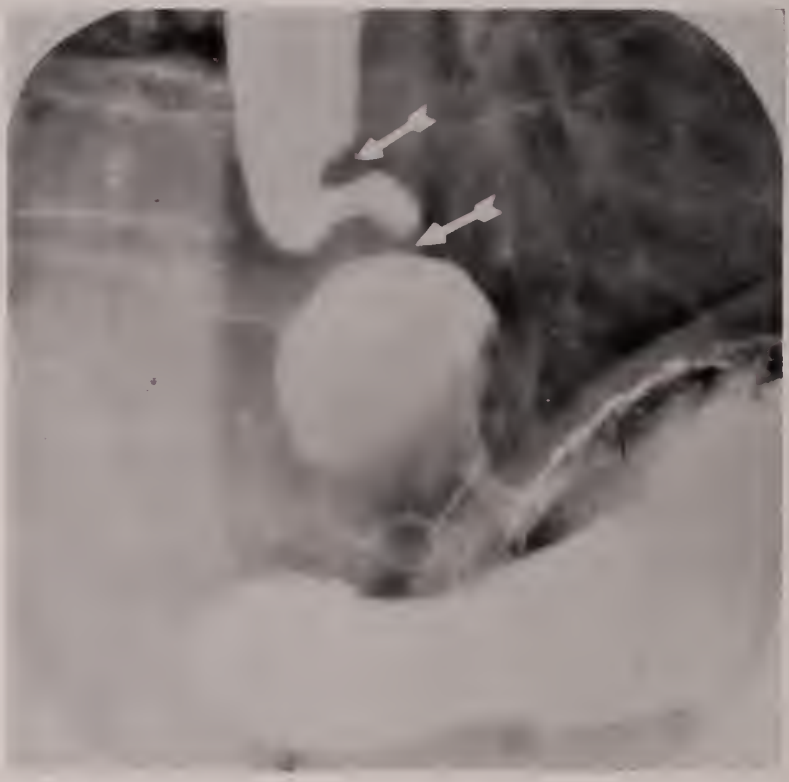

FIG. 24. A patient with a small hernia is swallowing barium in the right oblique prone position while lying on a radiolucent bolster. The sac above the diaphragm consists of the markedly distended vestibule as well as the hernial sac. The tubular esophagus proximal to the sac over a distance of about 2 cm. (between arrows) is markedly tortuous. With the bolster removed, the sac was smaller and the tortuosity absent. Incidentally, over a short distance at the junction of the tubular esophagus and the sac (lower arrow), there is a complete contraction (inferior esophageal sphincter?).

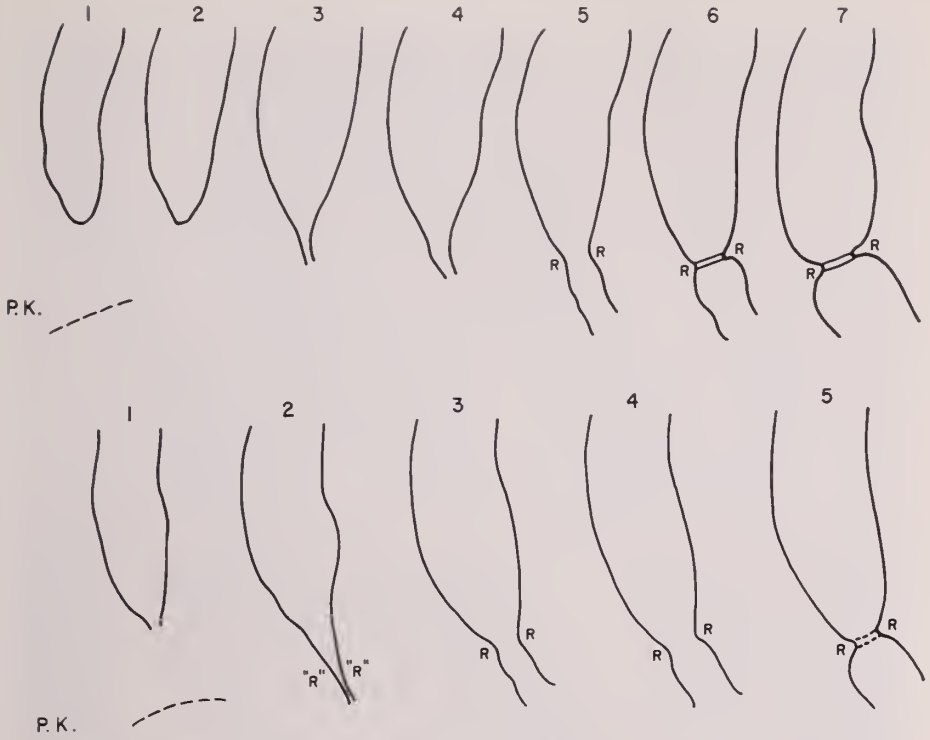

FIG. 25. Tracings from two sequences in a patient with a nondistensible ring (RR) show phases during filling. There was no specific level at which the barium column was delayed but a general delay in distending for 2 or 3 cm. proximal to the ring was noted. The width and length of the ring were constant and it did not travel or move independently of the adjacent regions. With emptying, the region distal to the ring shortened and, as a result, the ring assumed a position closer to the diaphragm. At the same time, the esophagus proximal to the ring was stretched longitudinally. The general delay in distending the esophagus proximal to the ring seemed to be related to this stretching since, with filling, the ring was pulled proximally. The excursion of the ring between filling and emptying was about 2 cm.

It should be emphasized that a small hiatus hernia of the direct type may be present without the appearance of a ring or notches of any type. Nevertheless, a completely distensible distal ring occurs so frequently in this group of patients, if efforts to demonstrate it are made (13), that it cannot be considered of pathological significance (14). It is assumed at present that an incompletely distensible ring is superimposed on and replaces the normally distensible distal ring. However, the possibility that stenotic rings of similar appearance may occur at other sites in the distal esophagus is not excluded.

With a large hiatus hernia of the direct type, the vestibule as a discrete distensible region is rarely evident. In these patients, a portion of the esophagus, one or two centimeters in length, immediately proximal to the hernial sac often shows a localized contraction (4). When this segment relaxes, however, it usually assumes the same caliber as the remainder of the esophagus. The contracted state may represent a foreshortened vestibule and the failure to achieve maximum distention may be due to the fact that the pressure within it cannot be

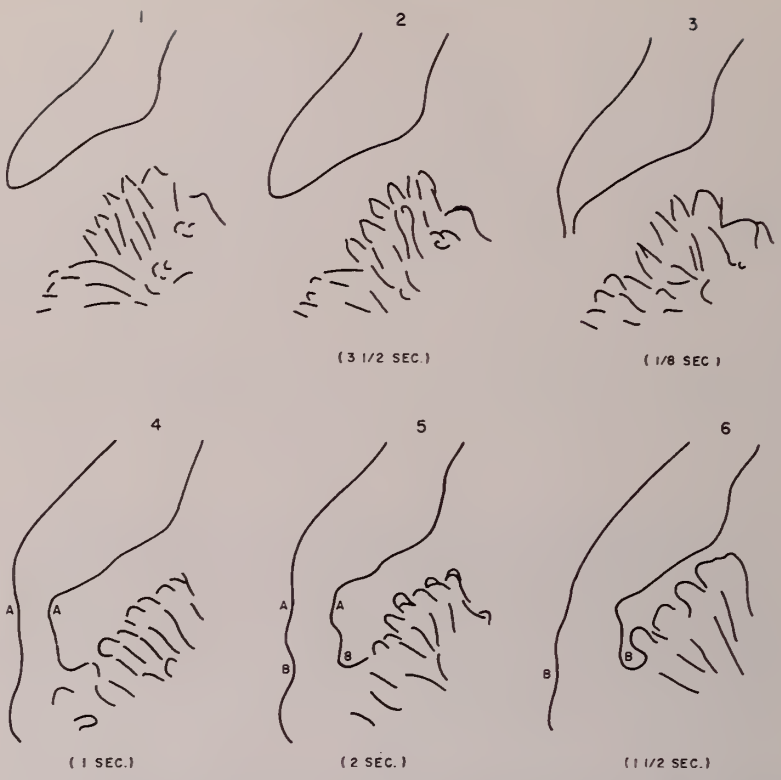

FIG. 26. Tracings from a patient with a combined type of hernia. The paraesophageal component is considerably larger than the direct. A segment, AA to BB, which acts like the vestibule is present. There was moderate delay at the proximal margin of the vestibule but none at its distal margin.

built up to a sufficiently high point when the hernial sac is large and extends well into the mediastinum. In instances of the combined type of hiatus hernia in which the direct component is relatively small, a somewhat atypical vestibule may be evident immediately proximal to the direct sac (Fig. 26). In the presence of inflammatory changes in the distal portion of the esophagus, the vestibule as a distensible structure cannot be recognized. It is of interest to note that in some cases of cardiospasm, a small sac-like structure of variable configuration may be noted just above the hiatus, intervening between two constricted segments (Fig. 27). In one instance of this type, the fact that the esophagogastric mucosal junction was at the distal margin of this saccular area was confirmed by applying a clip at endoscopy. In such cases, the small sac has been referred to as the vestibule and cardiospasm has been attributed to vestibular dysfunction. However, the presence of such a structure in cardiospasm is the exception rather than the rule. In a typical case, only a short segment immediately proximal to the stomach with a characteristic beak-shaped configuration is noted.

The roentgen observations described above appear consistent with the observations of pressure changes in the distal esophagus and esophagogastric region

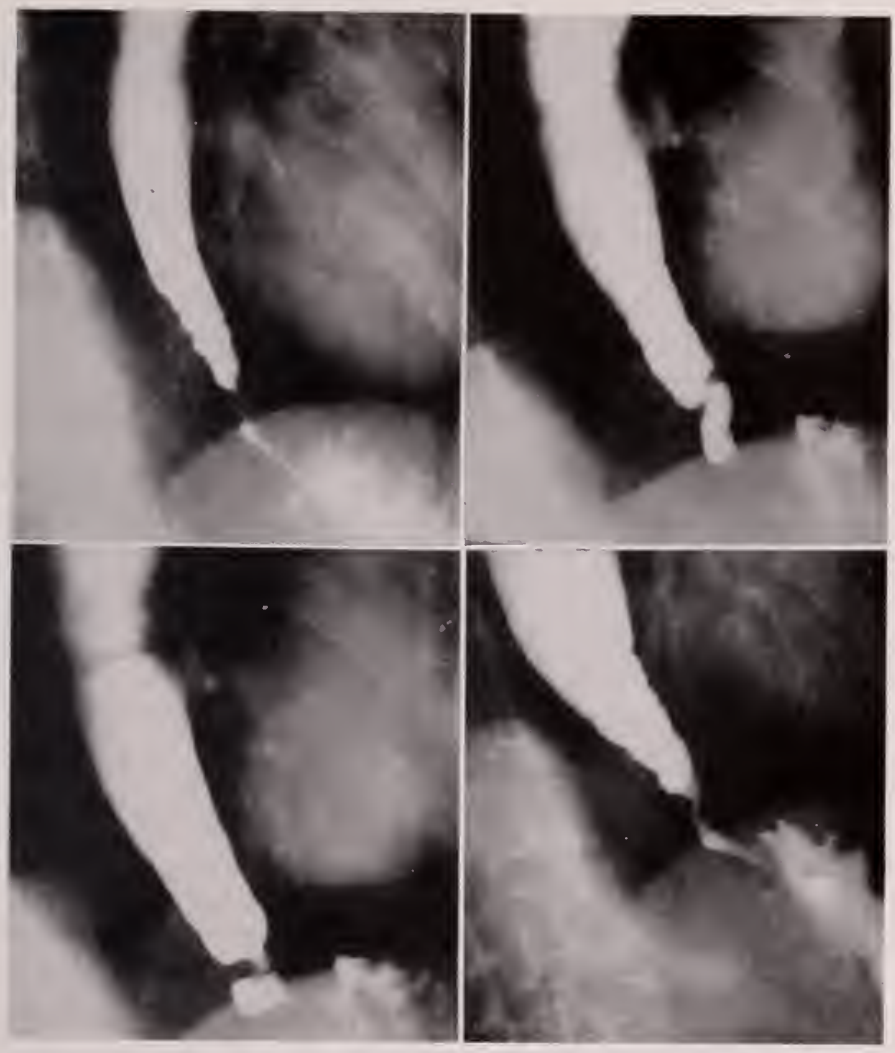

FIG. 27. Four views of the distal esophagus in a patient with cardiospasm. A small sac with a constriction at either end and a variable configuration is seen just above the hiatus. The constriction at the proximal end may represent the inferior esophageal sphincter. The constriction at the distal end is considerably longer and presumably includes the region of the so-called cardiac sphincter.

recorded under a variety of conditions (15–19). Studies of pressure changes have the advantage that the resting or interval state can be observed prior to swallowing and reflex effects of the pharyngeal phase of deglutition on the distal esophagus may be recognized. This can rarely be demonstrated by roentgen examination (Fig. 28). The vestibule appears to correspond to the "high pressure zone" which normally includes an area both below and above the hiatus of the diaphragm (20). This zone has also been referred to as the gastroesophageal sphincter or the vestibular sphincter. The use of the term "vestibular sphincter" for

FIG. 28. K. A. Selected frames from a movie sequence showing abrupt relaxation of a segment about 2 cm. in length which traverses the hiatus. This segment presumably corresponds to the vestibule in its normal location. In frame 1, the barium column is delayed by the contracted vestibule. With resumption of swallowing, the vestibule abruptly relaxes, barium squirts from the stomach into the lower part of the vestibule (frame 2) and then the barium column becomes continuous as it freely enters the stomach (frame 3). Frame 4 demonstrates that the hiatus is unusually wide in this patient (hiatal insufficiency?).

this entire region measuring two to three centimeters in length is inconsistent with the terminology of Lerche who placed greater emphasis on sphincteric action at either end of the vestibule and emphasized the unusual distensibility of the area between these sphincters. Nevertheless, the observations recorded in this report as well as the pressure studies suggest that it is more common for the entire vestibule to play the rôle of a sphincteric mechanism than one or both of its margins. From the roentgen point of view, the term vestibule rather than vestibular sphincter appears more suitable in order to include both the contracted and relaxed states of this segment.

The function of the vestibule during swallowing appears to be to delay, by persistent contraction, the passage of swallowed material until the head of pressure is sufficiently great to prevent reflux. Contraction of the vestibule and/or of the inferior esophageal sphincter may prevent reflux during maneuvers designed to induce regurgitation. However, an extrinsic mechanism is also present at the level of the hiatus of the diaphragm which reënforces these functions and may, under certain circumstances, be of greater importance.

SUMMARY

1. The terminal two or three centimeters of the esophagus may contract and relax as a unit independently of the adjacent portions of the esophagus and stomach. Lerche's term, the vestibule, may be applied to this segment.

2. The vestibule as a single distensible unit can be observed only in the presence of a direct hernia, since, normally, the distal half of the vestibule is located in and below the diaphragm and is therefore limited in distensibility by extrinsic factors.

3. Notches or a static ring may be seen at the distal margin of the vestibule when the vestibule is herniated and distended. Since these notches indicate the junction between the vestibule and the stomach, their presence above the diaphragm is indicative of a hiatus hernia.

4. Notches or a complete ring may also be seen at the proximal margin of the

vestibule. A ring in this location may show independent contractile activity and therefore may be equated with the inferior esophageal sphincter of Lerche. However, except perhaps during regurgitation, localized sphincteric activity in this area is less commonly seen than contraction of the vestibule as a whole. The description by Lerche emphasized remarkable distensibility of the vestibule rather than the more important functional aspect of contractility.

5. The "high pressure zone" or "gastroesophageal sphincter" or "vestibular sphincter" described as a result of pressure studies in the esophagogastric region corresponds to the vestibule as described above.

6. In the studies reported, there was little or no evidence for the presence of a discrete sphincter at the distal margin of the vestibule, that is, at the cardia. It is possible, however, that the notches and ring seen in this area result from the existence of the specialized muscle bundles designated in the anatomical literature as the cardiac sphincter or the constrictor cardiae. The term sphincter, however, appears to be a misnomer.

7. The beginning of gastric mucosa or rugae correponds sufficiently well to the level of the so-called distal notches and ring seen on roentgen examination to make these equivalent criteria for the junction of esophagus and stomach.

8. The term phrenic ampulla was introduced into the roentgen literature by Templeton to apply to the sac-like collection of barium trapped above the diaphragm in deep inspiration. The phrenic ampulla, however, is not a unique structure since it has a variable size determined by the pinchcock action of the diaphragm and the progress of the primary peristaltic wave. In the presence of a small direct hernia, the phrenic ampullae include the vestibule and the herniated portion of the stomach. The term phrenic ampulla as used by radiologists should not be confused with the original anatomical description which presumably included features currently ascribed to the "vestibule".

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PANTOPAQUE® FOURTH VENTRICULOGRAPHY VIA THE LUMBAR ROUTE (REG)

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This is a preliminary report of a new neuro-radiologic procedure for the demonstration of abnormalities in the posterior fossa when pneumoencephalography is not diagnostic. We have been able to fill the fourth and third ventricles with Pantopaque® instilled by a lumbar puncture. For convenience we call this procedure a REG or rhomboencephalogram.

Positive contrast studies of the ventricles with Lipiodol® and recently with Pantopaque® have been useful for many years. All studies published in the past twenty years have used the burr-hole direct ventricle approach to achieve internal filling.

In 1923 Sicard (1) in France, using light and heavy Lipiodol®, described in detail x-ray studies of the spinal canal. He noted casually that occasionally Lipiodol® (the form that was lighter than spinal fluid) would rise into the ventricles giving excellent definition of their anatomy. He mentioned that this might be a better method than Dandy's comparatively new technique of pneumoencephalography; however this observation was not followed up.

In 1930, Balado (2), an Argentine neurosurgeon, reported 90 cases of ventricular study in which Lipiodol® was instilled by burr-hole and ventricular puncture. In 1938, Reeves (3), in a review of Thorotrast® studies, mentioned that Thorotrast®, if instilled in the spinal canal would rise into the ventricles and give some information. Because of the fear of reaction to Thorotrast® this was not continued.

For the past ten years Pantopaque® has been widely used by neurosurgeons for positive contrast ventriculograms. Articles by Bull (4) and Horowitz (5) have emphasized the low incidence of morbidity and the excellent studies of the third and fourth ventricles.

In our hands the pneumoencephalogram is an excellent procedure for demonstrating posterior fossa masses. In all cases with suspected posterior fossa pathology, with or without papilledema, pneumoencephalography is done with little morbidity and no mortality. Using standard techniques we usually fill the third and fourth ventricle and the various cisternae of the region. Frequently there is difficulty in interpretation of the films because of confusing air shadows from cisternae which superimpose on the ventricles. This is particularly true of the posterior-anterior projection, in which outlines of the cisterna magna, third ventricle, fourth ventricle, vallecula, and the interpeduncular cisterna may be

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TABLE I

Successful ventricular filling

Case Number	Pt.	Diagnosis	PEG	REG	Comment
1	55M	Syringomyelia (unverified) Klippel-Feil deformity	No	Yes	* Normal fourth ventricle and posterior cisternae
2	59M	Amyotropic Lateral Sclerosis Syndrome	—	Yes	Normal Study.
3	55M	Cervical Myelopathy (unverified)	—	Yes	Normal Study.
4	67F	Cerebellar-Pontine Angle Neurinoma (verified)	Yes	Yes	* PEG was equivocal, whereas REG was considered abnormal. Operation verified the tumor.
5	29F	Cerebellar-Pontine Angle Neurinoma (verified)	Yes	Yes	The shift of the fourth ventricle seen in the PEG was verified by the REG (Fig. 1).
6	58M	Cerebellar-Pontine Angle Neurinoma (verified)	No	No	Normal cisternae
7	40M	Cerebellar-Pontine Angle Neurinoma (unverified)	Yes	Yes	* The PEG was equivocal, the REG shows a definite shift of the fourth ventricle. (Fig. 2)
8	55F	Posterior fossa disease ? metastatic (unverified)	Yes	No	PEG was normal. We were unable to fill the ventricles with Pantopaque®. The 6 cc. used may have been an insufficient amount.
9	17F	Posterior fossa disease ? neoplasm (unverified)	Yes	Yes	* Both studies were thought to show bowing back of the aqueduct and fourth ventricle. The REG shows excellent definition of the fourth ventricle (Fig. 3-4).
10	40M	Brain stem vascular disease (unverified)	Yes	No	Again 6 cc of Pantopaque® was unsuccessful in a patient without a neoplasm. More Pantopaque® was needed.
11	36F	? Cervical myelopathy, brain stem disease (cause unknown)	—	Yes	Normal study.
12	7M	Posterior fossa tumor (unverified)	Yes	Yes	* The PEG was considered equivocal whereas the REG showed that the fourth ventricle was definitely in normal position.
13	70F	Cerebellar-Pontine Angle Neurinoma (unverified)	Yes	No	Unable to fill ventricles on two attempts.
14	60F	Cerebral tumor (unverified)	No	No	* REG shows definite herniation of the cerebellar tonsils. (Fig. 5)

* REG gave valuable information not gained in PEG in these cases.

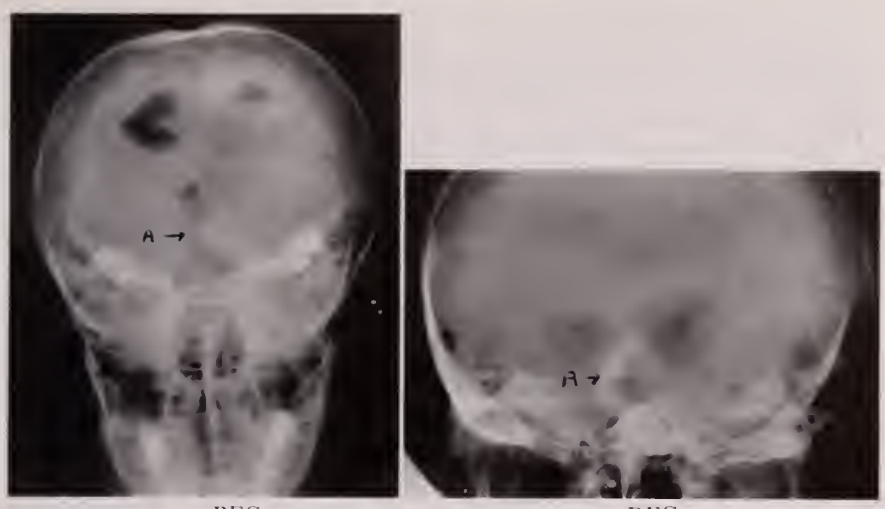


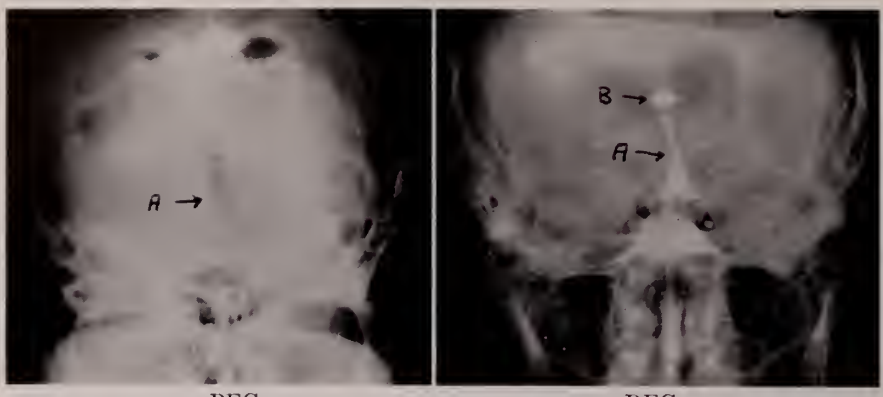
FIG. 1. Case (5). Verified acoustic neurinoma. The REG shows the same defect as seen on PEG. The fourth ventricle (A) is better defined by the Pantopaque® study.

superimposed. In cases with large mastoid air cells, the fourth ventricle is difficult to see on a lateral view, and laminography, which is not always successful, must be done. The superior definition made possible by Pantopaque® becomes necessary in equivocal cases.

The following technique was discovered during an attempt to visualize the posterior aspect of the foramen magnum. Six to nine cubic centimeters of Pantopaque® is instilled into the lumbar subarachnoid space. The needle is then removed and the patient is placed on his back with his head flexed. He is then tilted downward to 80–90 degrees for one minute and then brought to 70 degrees where lateral and anterior-posterior views are taken without fluoroscopy. If the films are satisfactory the patient is placed in the erect position for five minutes. Pantopaque®, which leaves the ventricles in minutes, is then removed from the lumbar region. There usually are a few droplets of Pantopaque® left in the ambient or pontine cisternae. The entire procedure takes approximately twenty minutes.

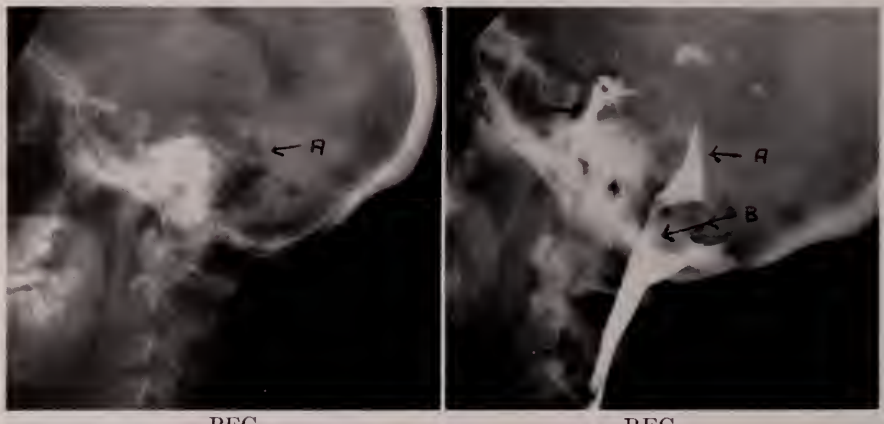
Aside from ventricular filling we get excellent definition of the posterior aspect of the foramen magnum, the posterior cerebellum, and cisterna magna. This information may be as valuable as the views of the ventricles.

We have studied fourteen patients with this technique. In nine cases the fourth ventricle was successfully filled. In all cases we received information (sometimes valuable) of the anatomy of the posterior cisternae. Most of our cases had pneumoencephalography before the study. In one case, in which the pneumoencephalogram was unsuccessful in filling the internal structures, the rhomboencephalogram gave excellent definition of the fourth ventricle. In three cases in which pneumoencephalography was successful, the rhomboencephalogram was unsuccessful in filling the ventricles. With more experience we expect a higher incidence of success.



PEG REG

FIG. 2. Case (7). Unverified acoustic neurinoma. The PEG was considered equivocal because the fourth ventricle could not be well defined. The REG shows the fourth ventricle (A) to be shifted from right to left. (B) is Pantopaque® in the suprapineal recess.



PEG REG

FIG. 3. Case (9). Unverified posterior fossa neoplasm. The PEG shows bowing back of the aqueduct; however the floor of the fourth ventricle is not well defined due to the mastoid air cells. REG shows excellent definition of the fourth ventricle (A). The impression into the floor of the ventricle is unusual and probably is abnormal.
The tonsils, which are not herniated, are well seen (B). Pantopaque® (C) represents the interpeduncular cistern.

Table I gives a short summary of our experience. Five cases (Cases 4, 5, 6, 7, 13) of the fourteen were cerebellar-pontine angle neoplasm suspects, three of which have been verified by operation. In three cases we were able to fill the fourth ventricle. In two cases (Cases 4, 7), in which the PEG showed equivocal shifting of the fourth ventricle the REG showed a definite abnormality. In one case (Case 12) of suspected posterior fossa neoplasm the PEG showed a questionable fourth ventricle shift, whereas the REG showed a well defined normal midline fourth ventricle.

The neurosurgical use of Pantopaque® instilled directly into the ventricles has not been complicated with morbidity (4, 5). Pantopaque® arachnoiditis in

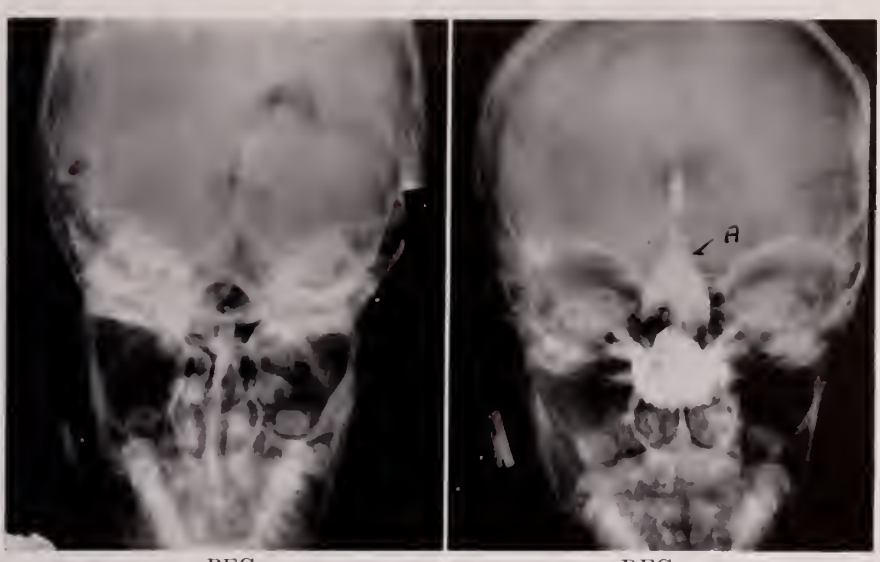


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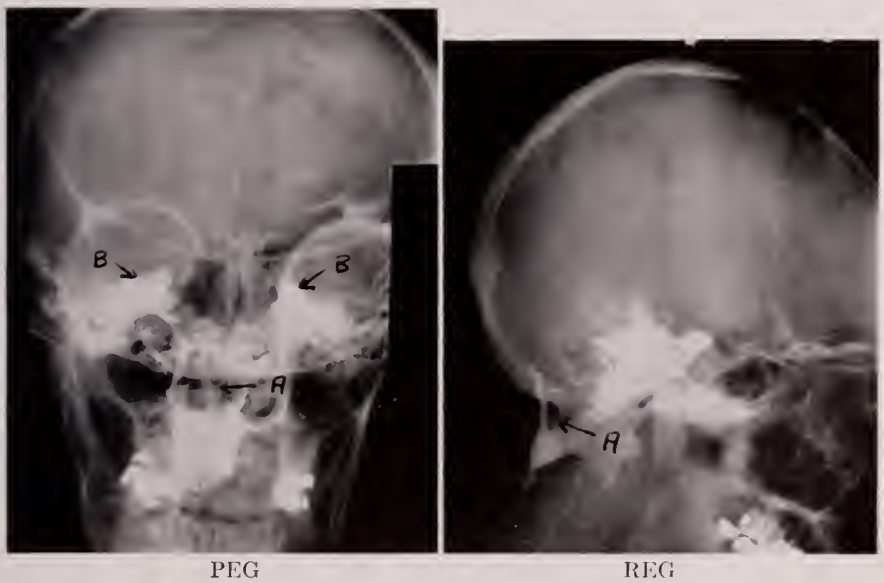
FIG. 4. Case (9). Unverified posterior fossa neoplasm. The pneumoencephalogram shows various superimposed air shadows that make it difficult to define the entire fourth ventricle.

The rhomboencephalogram does not give confusing shadows as the fourth ventricle (A) is clearly defined in the midline. No definite abnormality is seen on the anterior-posterior views.



PEG REG

FIG. 5. Case (14). Unverified neoplasm of posterior corpus callosum. REG shows herniated tonsils (A) well below the foramen magnum. Pantopaque® (B) is seen in both cerebellar-pontine angle recesses.

myelography has been reported and if the reports are correct, it is an extremely rare complication (6, 7, 8). In our fourteen cases there was one reaction. This patient had fever meningeal signs, and cerebrospinal fluid pleocytosis. The spinal fluid showed 2500 white blood cells, many of these containing small doubly refractile droplets. His general condition was unchanged and the meningitic signs and fever disappeared within a week. We have observed similar reactions with routine myelography. There were no other reactions or sequela noted.

CONCLUSION

The Rhomboencephalogram is a new method of studying the structures of the posterior fossa. Burr-hole Pantopaque® ventriculography has been a valuable procedure for the past years. In the event of an equivocal pneumoencephalogram and the clinical suspicion of a posterior fossa mass, we believe a rhomboencephalogram is indicated. Burr-hole ventriculography can now frequently be avoided for positive contrast studies of the fourth and third ventricles. The procedure is also useful in outlining the posterior foramen magnum and lesions associated with this région such as neoplasms, Arnold-Chiari malformations and tonsilar herniation.

Further studies are in progress to expand the usefulness and ease of the procedure.

ACKNOWLEDGEMENT

The authors wish to thank Dr. Bernard Wolf and Dr. Charles Newman of the Department of Radiology, The Mount Sinai Hospital for their helpful advice. We are especially grateful to Dr. Morris B. Bender for his encouragement and help.

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POSTERIOR MEDIASTINAL PARATHYROID ADENOMA

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Felix Mandl, in 1925, was the first to demonstrate the etiological relationship between the presence of a parathyroid adenoma and the symptom complex of hyperparathyroidism, or, as it was popularly termed, Von Recklinghausen's disease of bone. Following Mandl's removal of a parathyroid adenoma, clinical cure was substantiated by the return of all the preoperative abnormal blood findings to normal and by remineralization of all the involved long bones.

Since that time a very large experience with this disease has accumulated throughout the world. In the great majority of instances the diagnosis can be made on the basis of the history of muscle weakness, loss of strength, occasionally loss of height, the characteristic blood findings of elevated calcium, lowered phosphorus, elevated alkaline phosphatase, recurrent renal calculi, roentgenological evidence of bone cysts or marked demineralization of the long bones and calvarium and, finally a marked negative calcium balance on controlled intake and output studies. In the accumulation of this experience, there has accrued a somewhat clearer understanding of the basic pathological physiology of the parathyroid gland system.

In the course of a large experience with the surgical therapy of this disease, we have noted, in recent years, a change in the clinical and metabolic characteristics of hyperparathyroidism. There have been fewer instances with the characteristic bone findings and a proportionate increase in the number of cases of recurrent nephrolithiasis. In addition, we have, in recent years, seen a few instances of surgically proven hyperparathyroidism without bone changes or kidney calculi and minimal metabolic abnormalities as measured by the usual tests. A few of these patients had major gastrointestinal symptoms, nausea, vomiting and severe abdominal cramps. There has been one example of parathyroid psychosis, admitted to the hospital too late in the course of the disease for recovery following removal of a large adenoma.

While in the great majority of cases, the diagnosis of hyperparathyroidism could be made on the basis of hypercalcemia, hypophosphatemia, hypercalcuria, marked negative calcium balance and increased alkaline phosphatase, a few patients presented almost normal blood chemical determinations. Attempts to supply other methods to aid in the diagnosis under such circumstances have given rise to the calcium tolerance and tubular reabsorption of phosphate tests. More extended experience with these new diagnostic procedures will be needed before their value can be adequately appraised. This lack of an absolutely reliable diagnostic test, has led to the occasional need for exploration of the neck and mediastinum to establish the presence of a parathyroid adenoma.

While the clinician sometimes finds it difficult to make a preoperative diagnosis

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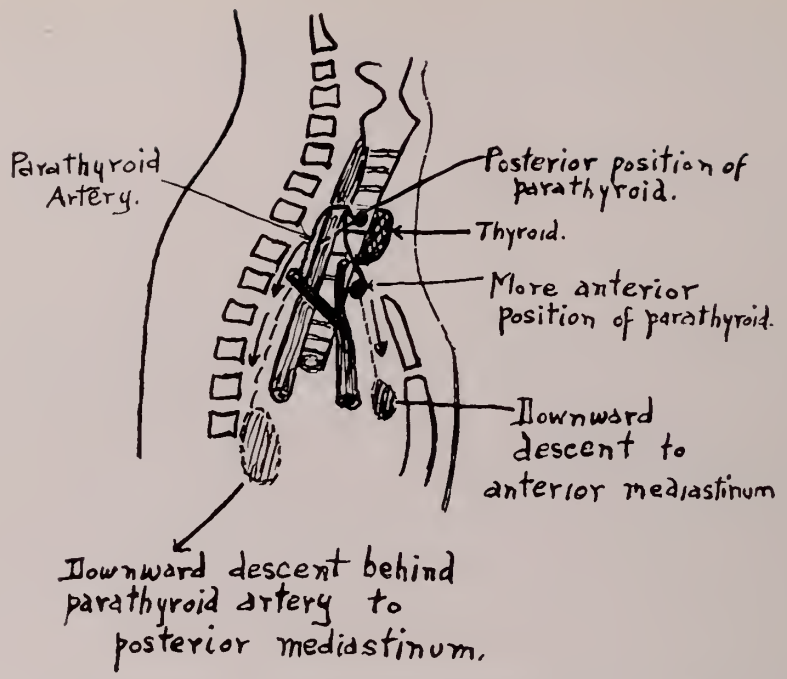

FIG. 1. Diagrammatic sketch of the route of descent of the inferior parathyroid bodies. In the vast majority of instances, an inferior parathyroid descends anterior to the inferior thyroid artery and is finally lodged in the anterior mediastinum. Rarely, when the parathyroid is more posteriorly located in the neck, it may descend behind the inferior thyroid artery and come to rest in the posterior mediastinum, out of reach through the usual cervical and anterior mediastinotomy incisions.

of hyperparathyroidism because of the factors above enumerated, the surgeon is occasionally confronted with the difficulty of locating the adenoma in spite of the fact that the diagnosis is self evident. The following case report is an excellent example of the anatomic vagaries of the parathyroid bodies. As far as I am able to determine, there is only one other similar experience, reported by A. J. Walton in The British Journal of Surgery for 1931.

CASE REPORT

I.S., a man of 56 years was admitted to the medical service of the hospital on October 23, 1950 with a long history of kidney trouble culminating in the removal of several urinary calculi by cystoscopic manipulation. He had noted the gradual onset, 3 months before, of rapidly increasing weakness in both legs and upper extremities and marked loss of strength of such degree that he found it difficult to walk more than a few steps. During this period there had occurred a loss in height of approximately 3 inches.

Physical examination was essentially negative except for a marked thoracic kyphosis and a barrel-shaped chest. Neurological appraisal revealed marked generalized weakness of all muscle groups.

Laboratory findings: Hemoglobin 12.5 gms. with normal white blood cell count. Urine on many examinations showed sp. gr. 1.010, after concentration to 1.016, albumin one plus, occasional hyaline and granular casts and a markedly positive Sulkowitch test

	Blood Calcium (mg. %)	Phosphorus (mg. %)	Alk. Phosphatase (K. A. units)
Oct. 24, 1950	17.1	2	55
Oct. 26			48
Nov. 1	15.8		51
Dec. 12	13.6	1.3	51
Dec. 13	14.4	1.3	62

Roentgenographic examination of the long bones and skull revealed an extreme degree of osteoporosis, compression of the body of the 4th lumbar vertebra and an irregular cystic lesion in the upper shaft of the left tibia. The esophagus was x-rayed, but pressure defects were not noted anywhere.

With the obvious diagnosis of a parathyroid adenoma, operation was undertaken on November 7, 1950 under endotracheal anaesthesia. Through the usual collar incision, the neck was thoroughly explored. Two small normal parathyroid bodies were identified, but no adenoma could be found. A subtotal thyroidectomy was performed on the basis of a possible adenoma being located in the substance of the thyroid gland. When the laboratory report was negative in this regard, an anterior mediastinotomy was carried out through the Sauerbruch approach. All areas as far down as the origin of the aortic arch were thoroughly dissected, including separation of the mediastinal pleura on each side. No adenoma could be demonstrated. The operative wound was closed to the great disappointment of all concerned. The patient recuperated quickly from this extensive procedure, but his severe generalized weakness continued and the blood figures remained high.

A short course of radiation therapy directed to the neck and anterior mediastinum was given without demonstrable favorable results. The patient went home for a short convalescence and returned January 18, 1951 for another operation.

On January 23, 1951, the right chest was opened after removal of the sixth rib. After separation of the incision with a rib spreader, there came into view beneath the pleura a bulging in the posterior mediastinum immediately above the azygos vein, behind and to the right of the esophagus and vertebral bodies. When the pleura over the bulge was incised, a large fleshy tumor, measuring 3 x 1¾ x 1 inches was easily dislodged. A well-defined vascular pedicle extending upwards behind the esophagus was ligated and divided and the tumor was removed. The pleura was resutured and the chest was closed without drainage. Postoperatively, therapy included the administration of calcium gluconate, parathormone, dihydrotachysterol, viosterol and calcium lactate. The operative wound healed per primam and the patient was discharged on the tenth day, markedly improved, especially from the standpoint of his prior extreme weakness.

The adenoma weighed 16 grams, an unusually large one, and consisted mainly of chief and clear cells.

	Calcium (mg. %)	Phosphorus (mg. %)	Alkaline phosphatase (K. A. units)
Jan. 24, 1951	10.5	2.7	37
Jan. 26th	9.3	1.7	25
Jan. 31st	8.4	3.3	21
March 1st at follow-up	8.4	4.6	16.7

The blood figures postoperatively were as follows:

During the succeeding few months, all the preoperative symptoms disappeared and the patient considered himself restored to normal health. He has been quite well ever since.

On October 14, 1952, the blood calcium was 11.6 mg., the phosphorus was 3.9 mg. and the alkaline phosphatase 14 K.A. units. Roentgen examination of the skull, long bones and spine on October 13, 1952 "showed a remarkable change since the preoperative films in that the

severe osteoporosis was no longer present. The large cystic area previously noted in the left tibia was now replaced by a sclerotic density. These films indicate complete healing following removal of the parathyroid adenoma."

SUMMARY

1. The general problem of hyperparathyroidism is briefly discussed.

2. A report is made of a patient with severe hyperparathyroidism due to an unusually large adenoma located in the posterior mediastinum behind the esophagus at about the level of the third thoracic vertebra with complete cure following its removal.

3. One other instance of a similar location has been reported in the surgical literature.

PRIMARY ANASTOMOSIS OF THE TRACHEA AFTER RESECTION OF A WIDE SEGMENT

An Experimental Study

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AND

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The surgical treatment of stenotic or neoplastic lesions of the trachea has been hampered in the past by the inability to accomplish wide excision of a tracheal segment with successful primary restoration of continuity. Many ingenious procedures (1–14) for bridging large tracheal defects have been devised, including various semi-rigid prostheses and reinforced auto-grafts. All of these prosthetic operations are doomed to failure because cartilage does not regenerate around the prosthesis and the new epithelium grows not on the inner surface, but around the outer surface of the supporting tube. As a result, the polyethylene or tantalum tube cannot be removed with maintenance of the patency of the trachea.

The use of wire to support dermal grafts, or bronchial and aortic autografts, has all but been abandoned because of the subsequent development of strictures at the line of anastomosis.

The ideal method for the surgical treatment of lesions of the trachea would seem to be excision with primary anastomosis, if this were feasible. Attempts to obtain this objective date back as far as 1895, when Colley (15) excised three tracheal rings in the human and approximated the remaining portions of the trachea by primary suture. However, the patient developed a stricture at the site of the anastomosis.

In 1940, Taffel (16) excised windows from the wall of the trachea and securely sutured patches of fascia over these defects. Tracheal mucosa covered the windows and the patency of the lumen was maintained.

In an experimental study in the dog, T. L. Jackson (17), in 1949, reported good results with primary anastomosis after excision of a small segment of the trachea, provided he used a cuff resection with mattress everting sutures. Maisel and Dingwall (18), in 1950, removed up to 2.5 cm. of the dog's trachea and successfully obtained primary anastomosis.

In 1950, Ferguson, Wild and Wangensteen (19) presented documented, experimental evidence of the feasibility of primary tracheal anastomosis in dogs. They proved that permanent elongation of the trachea could occur and that more length could be excised in staged operations than in one procedure. They demonstrated that severe stenosis occurred in all attempts at tracheal reconstruction by means of grafts, but that stricture need not result in end-to-end anastomosis.

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Rob and Bateman (2), in 1952, stated that end-to-end anastomosis in the human trachea is impossible after removal of more than 2 cm. of its length. In 1953, Kurlieck and Merendico (20) resected four to eleven tracheal rings in the dog and reconstructed the proximal and distal portions of the trachea by primary anastomosis. In all instances, however, the sutures tore through because of the resultant tension. In 1954, Pacheco (13) tried to obtain primary anastomosis in the dog's trachea. He attempted to prevent stenosis by means of a U-incision, and the use of steel sutures. All the dogs died due to disruption of the suture line.

Abbott (21), in 1955, successfully implanted the human main bronchus into the trachea after the partial excision of a segment of the trachea. In 1957, Barclay, McSwan and Welsh (22) performed tracheal reconstruction without the use of grafts. They found that only 2 cm. of trachea could be resected and end-to-end anastomosis achieved.

We have attempted to study the difficulties and limitations of primary tracheal anastomosis, and to learn how these might best be overcome. Previous experimental evidence has demonstrated that stricture formation and leakage of air at the suture line may be avoided by performing a cuff anastomosis using meticulously placed everting sutures. Discrepancy in the diameter of the proximal and distal segments of the remaining trachea can be dealt with by suturing the membranous posterior wall first, and then approximating the rigid cartilaginous anterior and lateral walls. At least one recurrent laryngeal nerve must be preserved. Also, the blood supply of the trachea, which stems from the esophagus, must not be compromised or stripped from the remaining tracheal segments.

These precautionary measures notwithstanding, there still remains the serious problem of tension when one attempts to approximate the transected ends of trachea after excision of a wide segment. The trachea is a relatively fixed organ, its extensibility limited by its attachment to the larynx above and the pulmonary hilum below in the mediastinum. Mobilization of the entire length of trachea from adjacent structures adds but little to its tractability. Extension of the head upon the neck will also increase the distance between the cut ends of the trachea, and thus complicates further the problem of tension at the attempted anastomosis.

The factor of tension in the restoration of tracheal continuity is therefore directly related to the inelasticity of the tracheal wall itself. A review of the gross anatomy of the trachea reveals the well known fact that the rings of cartilage comprising its anterior and lateral walls are snugly bound together by fibrous tissue designated as the annular ligaments (Figure 1). These vertical ligaments can be stretched but little, if at all, so that the trachea must be regarded as a longitudinally inelastic tubular structure.

The idea presented itself that additional length of trachea might be attained if the annular ligaments were circumferentially incised down to the underlying mucosa. By means of this maneuver, and by viture of the elasticity of the mucosal layer and the membranous posterior wall of the trachea, the spaces between the cartilaginous rings would be widened. Theoretically, therefore, tracheal length

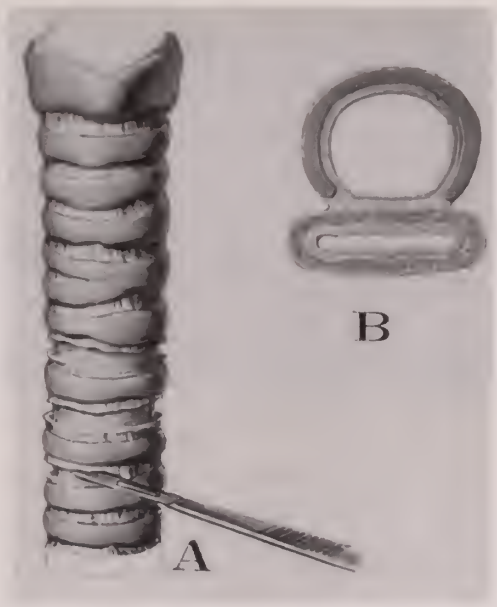

FIG. 1. A. Trachea showing annular ligaments between the cartilaginous tracheal rings, and the separation of the rings after circumferential incision of the annular ligaments down to mucosa. B. Cross section of trachea showing antero-lateral wall supported by cartilaginous ring and membranous posterior wall attached to the anterior wall of the esophagus.

could thus be increased to a degree equal to the sum of the additional distance obtained in each interspace between the tracheal rings.

Accordingly, a segment of a human trachea obtained at autopsy was measured after it was stretched as much as possible in its longitudinal axis and fixed to a board by pins (Figure 2). The intercartilaginous annular ligaments were then carefully incised circumferentially down to the mucosa as illustrated in Figure 1A, and the tracheal segment again stretched and measured (Figure 3). It was now 1.6 cm. longer than before.

Applying this technique in vivo in dogs, it was found that sufficient increase in tracheal length could be obtained to permit primary suture anastomosis, without tension, following excision of wide segments consisting of as many as thirteen tracheal rings.

The surgical procedures were performed under nembutal anesthesia administered intravenously. The animals were placed flat in the supine position with the head and neck maintained horizontally upon the operating table in the same plane as that of the body. Care was taken to avoid flexion or extension during the operative procedure.

The cervical incision was made in the mid-line, extending from the level of the larynx to the suprasternal notch. The pretracheal musculature was separated also in the mid-line, affording excellent exposure of the trachea in the neck.

The length of trachea to be excised was then mobilized and separated from the esophagus, being careful to avoid injury to the blood supply of the remainder of

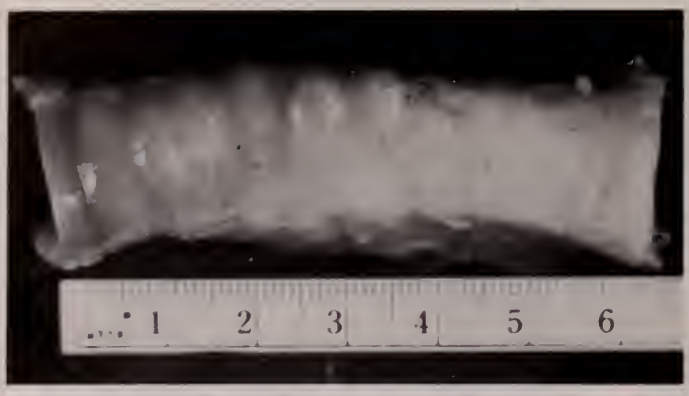

FIG. 2. Segment of human trachea stretched maximally in its longitudinal axis.

the trachea. Following the excision of the tracheal segment, the annular ligaments between the cartilaginous rings in the trachea above and below the transected ends were incised as illustrated in Figure 1A. Usually five annular ligaments were incised in the proximal portion of the trachea, and from five to seven in the distal segment. On occasion, one or more small openings were inadvertently made through the mucosa into the tracheal lumen while incising the annular ligaments. These were effectively sealed, however, by placing a small patch of gelfoam over the openings.

Following resection of the tracheal segment, it was noted that the transected ends of the remaining upper and lower portions of the trachea could usually barely be drawn together, and then only with great tension. However, when increased length had been attained by incising successive annular ligaments, approximation was usually accomplished readily with but little, or no tension.

In the early stages of the work, the anastomosis was made by simple end-to-end suture of the cut margins of the posterior membranous wall of the trachea, and the mucosa adjacent to the opposing cartilaginous rings. Interrupted 4-0 black silk sutures were employed and were tied with the knots on the outside.

The technique of anastomosis was later altered to prevent certain complications which will be described below. In every case, the circumference of the suture line was covered over by a narrow strip of gelfoam.

The wound was closed without drainage. No effort was made to immobilize the head and neck post-operatively. With one inadvertent exception, all the animals received penicillin intramuscularly for several days following operation.

Following the occurrence of moderate narrowing at the anastomosis in one dog, and marked stricture in another, the method of suture was changed. This consisted of placing the silk sutures in mattress fashion so as to evert the tissues at the line of union.

In addition, the use of a short length of polyethylene tubing was tried in two experiments, with the purpose of splinting the anastomosis. A 7 cm. segment of polyethylene tubing, of the caliber of the tracheal lumen, was placed in the trachea at the level of the anastomosis, and fixed by a silk suture at either end.

FIG. 3. Tracheal segment shown in Figure 2, elongated following circumferential incision of the annular ligaments down to mucosa, with separation of the intercartilaginous spaces.

One dog died on the day following operation. At necropsy, the tube was found to have become dislodged upward into the larynx. The second dog died on the third day. Autopsy revealed dislodgement of the tube, necrosis and dehiscence at the anastomosis and peritracheal infection with formation of an abscess at this site.

For the most part, the everting anastomotic sutures were placed only through the apposing soft tissues. On occasion, however, two or three silk stitches were passed to include the edges of the approximated tracheal cartilages. In one instance, supplementary fine #36 stainless steel wire sutures were so employed, and in another two fine wire sutures were passed around the two apposing rings. It was felt, however, that these wire sutures were not necessary to insure successful approximation and healing.

The most satisfactory anastomoses appeared to be those in which the mucosa and the membranous portion of the trachea had been well everted as a cuff by mattress silk sutures, with or without the use of supplementary sutures through the edges of the apposing cartilages. Sufficient mucosa to permit fashioning of the cuff can readily be obtained by dissecting this layer from beneath the most proximal and the most distal ring of the tracheal segment to be excised.

The present communication, preliminary in nature, is concerned with the experience of the authors in performing wide segmental tracheal resection, with primary suture anastomosis, in 18 dogs. The segments of the trachea which were excised consisted of from 9 to 13 cartilaginous rings.

There were three post-operative failures. Two of these were the instances, noted above, in which a polyethylene tube splint was used. In the third, the dog died on the sixth day post-operatively. Necropsy revealed the presence of peritracheal infection about the anastomotic area. Although the suture line was not separated, no healing had taken place, and the anastomosis came apart during the autopsy dissection. It was in this case that prophylactic postoperative antibiotic therapy had been inadvertently omitted.

Stricture developed in one dog. During the seventh week following operation, it was noted that the animal's breathing was accompanied by stridor. Bronchos-

copy was performed, and a marked stricture was seen at the site of anastomosis. Death occurred a few days later (on the 53rd day post-operatively) and this finding was corroborated at autopsy (Figure 4).

Moderate narrowing causing reduction of about one third of the tracheal lumen at the anastomotic site was found at autopsy in one dog that died, apparently of pneumonia, on the 37th day post-operatively.

Four dogs died on the 6th, 14th, 15th and 23rd days respectively after operation. At necropsy, the anastomoses were all intact. The lungs, however, showed patchy areas of pneumonic infiltration. It was thought that this complication might have been due to aspiration of blood and secretions at the time of operation and during the post-operative period.

The remaining nine dogs did well. These were followed for 41, 98, 105, 119, 126, 138, 225, 229 and 132 days respectively. The latter dog was studied again after a period of two and a half years had elapsed since the operation.

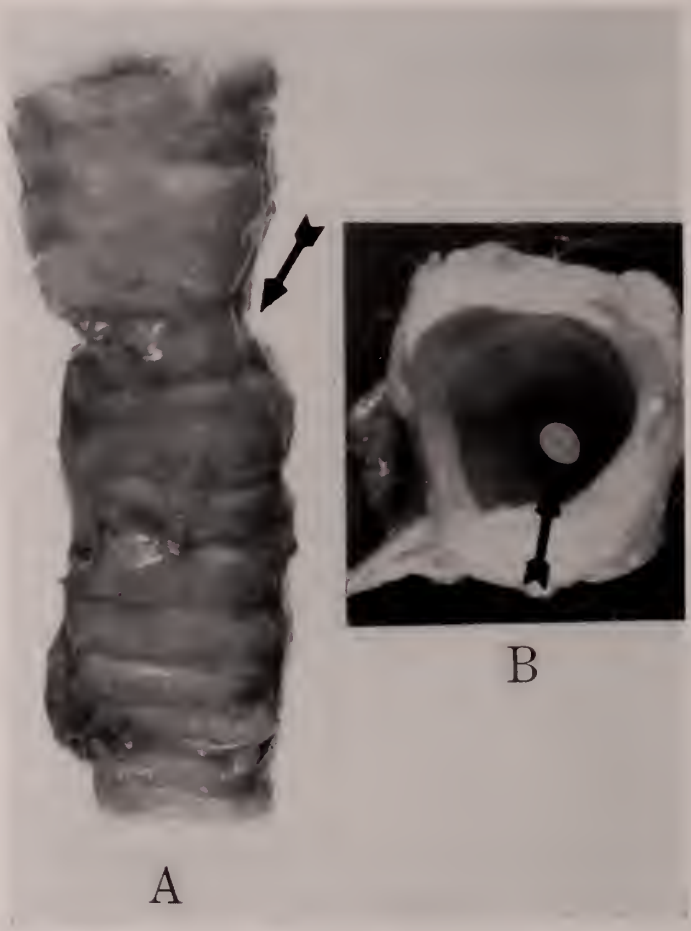

FIG. 4. A. Autopsy specimen of trachea showing post-operative stricture at site of anastomosis, as seen from within the opened trachea. B. Stricture as seen in on-end view of lumen of the unopened trachea.

To determine the condition of the trachea and the anastomosis, bronchoscopy was done in all cases at the times specified, followed by roentgenographic examination. The trachea was viewed in its antero-posterior and lateral projections, the studies being made with air contrast technique and after instillation of radio-opaque iodized oil. With the exception of the dog so examined on the 132nd day post-operative, the animals were then sacrificed and autopsy performed. In all of them, the tracheal anastomoses were well healed, and without stricture. The spaces between the cartilaginous rings, where the annular ligaments had been incised, were noted to be filled in by fibrous scar tissue. These findings are exemplified by the antemortem tracheogram and the necropsy specimen in a dog examined on the 126th day following the operation (Figures 5 and 6).

The animal that was examined on the 132nd day was further followed and re-examined at two and a half years post-operatively. The bronchoscopy and tracheograms were repeated, the dog was then sacrificed, and studied at autopsy. These examinations showed the operative procedure to have been anatomically and functionally successful.

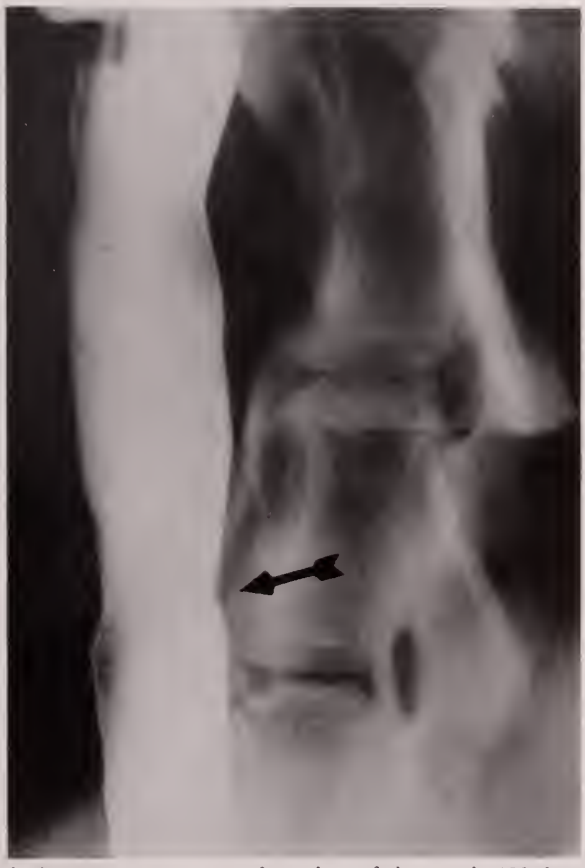

FIG. 5. Lateral view roentgenogram of trachea of dog made 126 days following operation, using iodized oil as contrast medium. Note minimal deformity at anastomotic site and adequate tracheal lumen.

Two tracheal specimens, which were obtained from the dogs sacrificed at 138 days and 2½ years respectively following the operation, were examined microscopically. It was found that healing at the suture anastomosis was complete. The cartilaginous rings of the transected ends of the trachea were held in close apposition by partially hyalinized fibrous tissue, and the mucosal epithelium was noted to have grown over the suture line.

The contrast medium for the tracheograms in the latter cases of the series consisted of barium powder insufflated into the trachea through the bronchoscope. The powder adhered to the moist mucosal lining of the trachea, affording excellent contrast in the roentgenograms.

The experimental protocols, the roentgen examinations, and the gross and microscopic studies in this work will be presented in detail in a future communication.

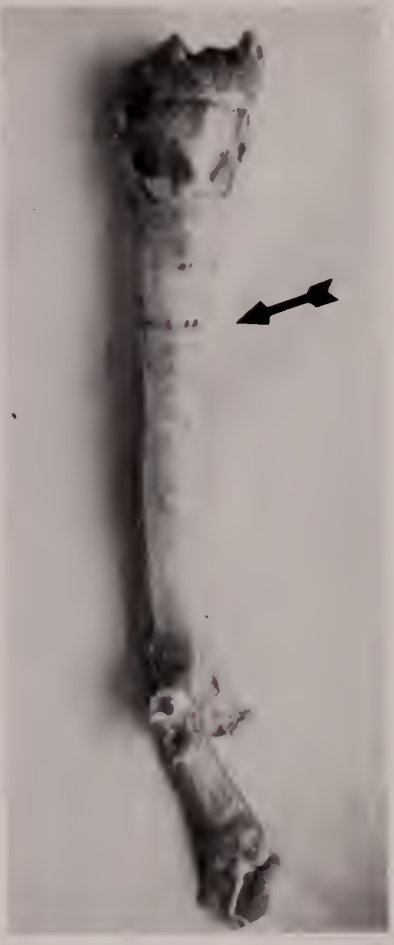

FIG. 6. Necropsy specimen of trachea shown in Figure 5. Note the normal tracheal contour, and the intercartilaginous spaces filled in by fibrous tissue.

DISCUSSION

It has been demonstrated experimentally in dogs that a wide segment of the trachea, consisting of from nine to thirteen tracheal rings, can be resected in one stage, with successful accomplishment of primary end-to-end suture anastomosis.

The major obstacle heretofore encountered which has resulted in failure of healing, and disruption of the suture line, has been the marked tension required to bring together and hold the remaining tracheal segments.

A technique is described whereby the normally inelastic trachea can be elongated sufficiently to permit approximation without tension of the transected ends of this tubular structure following excision of a wide segment. The method consists of making circumferential incisions in the inelastic annular ligaments which bind together the cartilaginous rings of the tracheal wall. Increase in tracheal length is obtained by virtue of the normal elasticity of the underlying mucosal layer, and of the membranous posterior wall of the organ.

Errors in operative technique which caused failures early in the work have been described. Intraluminal splinting of the anastomosis by means of an indwelling polyethylene tube is apparently not only unnecessary, but seems to be actually harmful. Stricture formation can be avoided by constructing the anastomosis with mattress sutures which evert the tissues in the manner of a cuff. As in intestinal surgery, it is important to insure proper healing at the anastomosis by avoiding excessive mobilization of the organ and impairment of its blood supply.

The authors are of the opinion that the attainment of successful tracheal anastomosis following wide segmental resection may now be uniformly anticipated, since it is possible to obviate tension at the line of suture by means of the method described.

It is hoped that this procedure may find clinical application, and permit adequate extirpative surgical therapy of various lesions of the trachea in the human subject. Should such an opportunity present itself, it is planned to employ complementary tracheostomy, through which tracheobronchial secretions may be aspirated to prevent post-operative atelectasis and pneumonia. Drainage of the operative area would also be instituted to reduce the possibility of peritracheal and wound infection.

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I. C. RUBIN, A GYNECOLOGIC EPONYM*

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A myriad of factors affect conception but only a few are understood sufficiently to merit investigation in the routine clinical study of infertility. Of transcendent importance are the anatomical pathways that must be pursued by the egg and sperm until their nuptial tryst in the fallopian tube and by the fertilized ovum in the subsequent journey to its uterine haven. Tubal obstruction is one of the commonest causes of infertility and one of the few demonstrable barriers to conception amenable to correction. "A plug of hardened mucus of the most insignificant character—the merest débris of the Fallopian secretion—may cut off an illustrious race, or change a dynasty." Thus wrote Tyler Smith (1) more than one century ago, when he proposed catheterization of the oviducts with a curved metal tube and fine whalebone bougie.

The office diagnosis of tubal patency or obstruction before World War I depended on the clinical acumen of the physician, and was hence subject to frequent error. Discussing diseases of the adnexa as a cause of sterility in the female, Howard Kelly wrote in his *Medical Gynecology* (2), published in 1908: "This is an interesting group of cases belonging to a class which are peculiarly difficult to investigate on account of the inaccessibility of the organs, namely, those cases in which the sterility is due to disease of the uterine tubes or the ovaries. It is because it is difficult to get at these organs and therefore to obtain an accurate knowledge of their condition that they are frequently forgotten in the clinical examination." Some gynecological texts of the late nineteenth century failed even to mention the fallopian tubes in their discussion of female sterility.

"The determination of patency of the fallopian tubes," Rubin wrote later (3), "has hitherto been possible only by direct inspection and palpation obtained by laparotomy. Physical examination was wholly inadequate because it still left the question of patency a matter of speculation. This is especially true when, as in certain instances, the tubes are sealed tight at their fimbriated end, although no distention of the lumen is present. In other instances it is hard to diagnose occlusion of the tube due to hydrosalpinx when the walls are flaccid. Some tubes are closed by adhesions secondary to a peritonitis that arises outside of the gynecological domain. No matter how clear the history, the question as to whether such a tube is patent or not is always a matter of doubt. The same holds true in cases in which the tube may be occluded by a tumor."

The problem had already been outlined by Carey (4) in similar terms: "In taking up the question of sterility in the individual case we can seldom feel that our diagnosis is accurate or any prognosis warranted because of our inability to

* This article, adapted from a chapter in the forthcoming book, *Obstetric and Gynecologic Milestones* (The Macmillan Co.), is published separately here in honor of Dr. Rubin's seventy-fifth birthday.

FIG. 1. Isidor Clinton Rubin (1883–).

determine if the tubes are obstructed. An occasional case presents a history of tubal infection with signs of diseased adnexa so evident that a temporary unfavorable prognosis is warranted. Other frank lesions may be present which prevent fertility. More frequently, however, we are consulted by the patient who has no reason to suspect pelvic disease and in whom we find no gross lesion. . . . If in this large group of causes of sterility we can now bring to bear definite knowledge regarding the patency of the tubes, the most important single factor is determinable so far as the woman is concerned. An intelligent prognosis may be given."

Independently of each other Carey and Rubin (5, 6) carried out experiments in 1914, the results of which were published almost simultaneously, outlining the uterine and tubal lumens with the radiopaque silver colloid, collargol. This substance proved objectionably irritating to the tissues, however, and was soon abandoned in the search for a suitable method for testing tubal patency.

Air insufflation of the fallopian tubes was first suggested in 1849, by the *Revue Médico-Chirurgicale de Paris* (7), in an editorial on Tyler Smith's catheterization procedure. "After all," the reviewer wrote, "even if catheterization proves impossible, should the therapeutic idea be lost, and could one not try to open up the tube by means of an injection of water or air as is done with the Eustachian tube? Liquid injections that have sometimes been made into the tube have caused serious accidents; but these were irritating injections, and pure water would not necessarily produce the same effect. There should be no objec-

tion to starting with injections of air, which, as experimentation has shown, can be made into the serous cavities without the least inconvenience."

Not until seventy years later, on November 3, 1919, was tubal insufflation, the first Rubin test, actually performed, oxygen being used as the test medium. As Rubin later recalled this experiment (8): "The quantity was measured roughly by gauging the number of bubbles passing through the wash bottle per minute. The intrauterine pressure was not controlled by a manometer; the gas was allowed to enter the peritoneal cavity until a moderate amount of visible abdominal distention resulted. . . . Theoretically we expected to see the abdominal wall rise in case the oxygen gas succeeded in gaining access through open tubes into the abdominal cavity. Those were indeed tense moments as [the physicians] . . . who happened to be present, were observing this first patient through whose uterus I ventured to insufflate oxygen. The actual rise of the abdominal wall was corroborated by everyone present. This constituted first-hand proof that the oxygen actually passed through the tubes and into the peritoneal cavity. Nevertheless it was deemed necessary to establish the presence of the oxygen gas in the abdominal cavity by subjecting the patient to fluoroscopy and radiography. In every respect the x-ray evidence was the same as that which was obtained when oxygen had been introduced into the peritoneal cavity by direct abdominal puncture.

"The patient, having been insufflated with several liters of oxygen, was comfortable in the recumbent posture, but we noticed that she had great epigastric distress and severe shoulder pains when she stood up before the radioscopic screen. She was kept on her back for a little while and, as she was ambulatory, she was brought home about one hour later and put to bed with the foot of the bed elevated. This gave her tolerable comfort. The discomfort rapidly disappeared so that at the end of the third day she was able to report to the x-ray department complaining only of slight uneasiness in the shoulder regions. A small amount of oxygen was still present under the diaphragm. The patient became gravid within two months after the insufflation and was delivered of a full-term baby."

Rubin reported his discovery in a preliminary note to *The Journal of the American Medical Association* (9) and presented the results of his further experiments before the Section on Obstetrics, Gynecology and Abdominal Surgery of the A.M.A. on April 29, 1920 (3). His description of the technique: "The cervix is exposed by means of the speculum; the vagina is carefully wiped clean and the cervix is cleansed dry and painted with tincture of iodin. If there is any uncertainty regarding the direction of the uterine cavity, it may be determined by passing the sound. The cervix is steadied with tenaculum forceps grasping its anterior lip. The oxygen, which has been released from the tank and regulated, is now allowed to pass from the water bottle through the glass and rubber connecting tubing to which the metal cannula is attached. By pinching the rubber tubing near the cannula one can make sure that all the joints are air tight. The mercury immediately rises in this case. . . . This is a very important point to be observed. Having made certain of the pressure, the air valves in the manom-

FIG. 2. Apparatus used in Rubin's early tests of tubal patency. (By permission of *The Journal of the American Medical Association*)

eter are opened and the catheter is then inserted into the uterine cavity to a point well beyond the internal os. This is done so that there is no immediate escape back along the cervical canal and out into the vagina. The rubber urethral tip, placed ordinarily from 1½ to 2 inches away from the cannula tip, is then fitted into the external os, insuring better obturation. This is not essential in the nulliparous intact cervix, but is required in the irregular patulous external os resulting from previous operations or from lacerations attending childbirth. The air valves are now closed. Within a few seconds after the oxygen enters the uterine cavity, the pressure as noted in the mercury manometer will rise; within from one half to three quarters of a minute in the patent cases the mercury reaches its maximum point. It then fluctuates for a few seconds or drops rather sharply from 10 to 30 points, maintaining the last level more or less for the rest of the time. There may be a slight audible escape of oxygen from the external os

Whereas, The Mount Sinai Hospital of New York has been most fortunately graced since 1906, by the inclusion within its medical staff of

Dr. I. C. Rubin

recently elevated to the office of Consulting Gynecologist, after his service beginning as Intern and progressing to the highest rank of Gynecologist to the Hospital; and

Whereas, during his many useful and fruitful years of endeavor he has, in addition to his multitudinous general services, including his painstaking concern and warm sympathy for all patients under his care, and his great interest in the teaching and development of younger men of his profession, conducted extensive research in the subject of human infertility and has originated a method known to the world by his name, for demonstrating the patency of the Fallopian Tubes, and has perfected conservative operative procedures, and safe methods of diagnosis and accurate treatment in this field; and

Whereas, his name, work and reputation are known to and honored by the medical profession in all sections of the globe. Now, therefore, be it

Resolved, that this Board of Trustees expresses to Dr. I. C. Rubin its great regard for his professional attainments, its gratitude, and the gratitude of the Hospital for his loyal service and his scientific achievements which have enabled the Hospital and his professional associates to benefit by reflection from his renown, and its deep affection for him as an individual, as a friend, as an associate, and as a warm kindly and considerate human being whose humanity was never dimmed or overshadowed by the lustre of his professional eminence. And be it

Further Resolved, that this Board welcomes Dr. Rubin as the Consulting Gynecologist, and looks forward to many years of further association with him and to his probable further acclaim resulting from future services.

New York, February 19, 1946

Secretary

President

Fig. 3. Resolution of the Board of Trustees of the Mount Sinai Hospital on Dr. Rubin's appointment as Consulting Gynecologist.

in the cases of patent tubes, but as a rule there is none until the cannula is removed, when slight regurgitation is present.

"In the nonpatent cases, the pressure usually rises steadily for three quarters of a minute to a minute or longer, and then drops sharply as the gas regurgitates into the vagina. As the time required for sufficient oxygen to pass into the abdomen where it can be detected by fluoroscopic examination is one and a half minutes, the cannula is not withdrawn till this time limit is reached. If the pressure reaches 200 mm. in one minute, it is well to open one of the air valves (needle valve) to prevent it from mounting higher. In all our patent cases this high level was not reached. . . .

"With the manometer attached to the water bottle we can decide, knowing the rate of flow beforehand, how much we wish to inject into the abdomen. From the moment the pressure falls, we allow the gas to flow for from one-half to one minute. . . . In the positive cases the pressure need not exceed 40 mm. The average pressure is from 60 to 80; occasionally the pressure rises to 100 or more before the oxygen will pass through the uterine ostium of the fallopian tubes. When the pressure reaches 150 or more, the likelihood is that the tube lumen is closed completely or stenosed, but not necessarily in every case. A pressure of 200 is tolerably certain to be due to closed tubes."

Rubin soon discovered that carbon dioxide was preferable to oxygen as the insufflating agent, for the former, being resorbed more rapidly, caused less discomfort and eliminated the danger of embolism. He also introduced a number of modifications in his apparatus, the most notable being a kymograph for better interpretation of the functional status of the tubes.

No innovation is ever without its detractors. History has proved how wrong was John Polak, then Professor of Obstetrics and Gynecology in the Long Island College of Medicine, when in his discussion of Rubin's paper he predicted that the method would fail to achieve general use, and stated that in cases of suspected tubal obstruction "it would be safer to do abdominal section than to inflate the tubes or uterus with gas." On the contrary, tubal insufflation was enthusiastically adopted by others, and in one of the early papers confirming the value of the procedure Furniss (10) gave it the designation of "Rubin test," by which it has since been known. Many gynecologists regard it as the twentieth century's most important contribution to the clinical study of female infertility.

Isidor Clinton Rubin, born January 8, 1883, was educated at the College of the City of New York, which subsequently honored him with its Distinguished Alumnus Award. He studied medicine in the College of Physicians and Surgeons of Columbia University, and after graduating in 1905 served for three years on the house staff of The Mount Sinai Hospital. The following year was spent in Schottländer's laboratory of gynecological pathology in Vienna's II Universitäts-Frauenklinik. Upon his return to New York Dr. Rubin was made Associate Pathologist and Adjunct Gynecologist at the Beth Israel Hospital and from 1934 to 1937 he served as director of its gynecological service. In 1916 he was also appointed to the visiting staff of The Mount Sinai Hospital, where he ultimately rose to the rank of Attending Gynecologist (1937–1945). During this

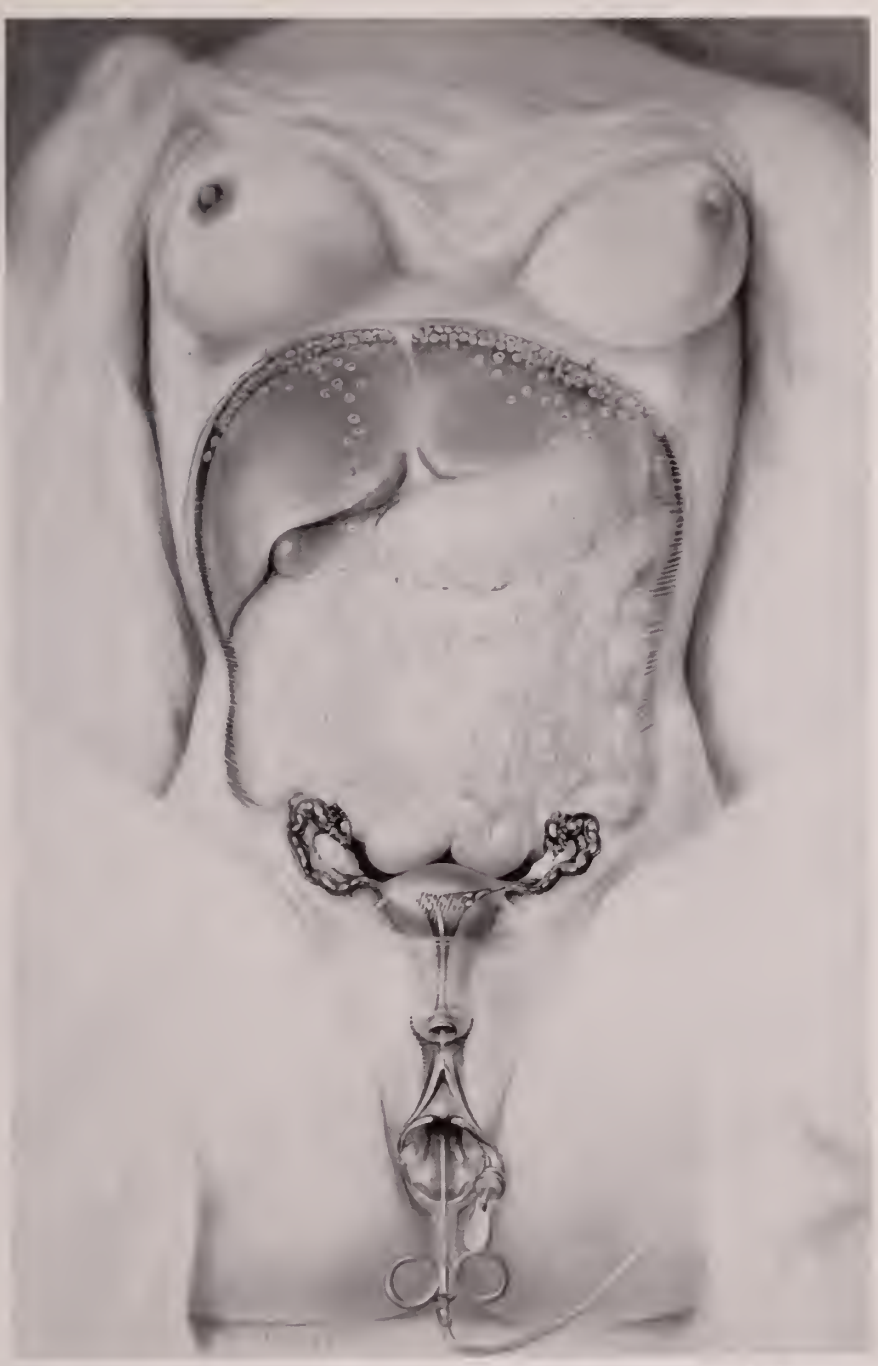

FIG. 4. Frontispiece from Rubin's book, *Uterotubal Insufflation* (C. V. Mosby Co.), demonstrating the production of subdiaphragmatic pneumoperitoneum.

period he held the title of Clinical Professor of Obstetrics and Gynecology in his alma mater. He was elected President of the New York Obstetrical Society in 1928 and served the American Gynecological Society in a similar capacity in 1955–1956. In addition to his book, *Uterotubal Insufflation* (1947), he published *Symptoms in Gynecology* (1923) and, together with Josef Novak, a 3-volume text, *Integrated Gynecology* (1956). The American Society for the Study of Sterility commemorated Dr. Rubin's seventy-fifth birthday with a special issue of *Fertility and Sterility* (vol. *8*, no. 6, 1957).

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VIRAL MENINGITIS

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The aseptic meningitis syndrome is gradually becoming better understood as recovery of an etiologic virus is becoming easier and more common. It is the purpose of this communication to present briefly the case histories of several children with this syndrome in whom a virus was isolated, and to review the latest advances in the field.

CASE REPORTS

Case #1

Eric H. (MSH #54182) a private patient of Dr. Donald Gribetz is a five year old white boy who was admitted because of nuchal rigidity. Five days prior to admission he complained of substernal pain, had fever of 104°F and on examination was seen to have pharyngitis for which he was treated with tetracycline. His fever subsided within two days, but two days later he complained of abdominal cramps and the next day he was admitted to the hospital because of nuchal rigidity and fever of 101°F.

The physical examination at the time of admission revealed stiffness of the back, and generalized muscular weakness, more marked on the left.

The complete blood count showed a hemoglobin of 15 grams per cent, a white blood count of 10,000 cells per cubic millimeter with 54 per cent neutrophils, 42 per cent lymphocytes, 1 per cent eosinophils, and 3 per cent monocytes. The sedimentation rate was 22 mm. per hour. The urinalysis was normal. The cerebrospinal fluid was clear; it contained 21 white blood cells per cubic millimeter of which 16 were neutrophils and 5 were lymphocytes; the protein was 25 mg per cent; the sugar was 62 mg per cent. Nasopharyngeal, throat and blood cultures revealed no pathogens, and one out of three tubes of the cerebrospinal fluid culture grew out streptococcus viridans which was considered a contaminant. The patient did well and became afebrile on the third hospital day without treatment. Subsequent serological studies failed to reveal antibodies to eastern equine encephalitis, St. Louis encephalitis, lymphocytic choriomeningitis and mumps. The tuberculin test was negative.

Michael H. the younger brother of the above patient was concurrently suffering from an upper respiratory infection. The stool of each brother was inoculated into monkey kidney tissue culture media and a cytopathogenic agent was recovered from each on the fourth day. Each agent was passaged several times and

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then inoculated into suckling mice in whom it produced convulsions on the fourth and fifth days.

Comment. The history of chest pain, abdominal pain and meningitis as part of a biphasic illness was strongly suggestive of a Coxsackie-B virus infection and epidemic pleurodynia with meningitis. The pathogenicity of the isolated agents for suckling mice confirmed that suspicion. Subsequently the virus from each brother was identified as Coxsackie B-2.*

Case # 2

Anthony C. (MSH # 52878) is a 4½ year old boy who, three days prior to admission, developed fever and sore throat for which he was treated with a sulfonamide. Two days prior to admission, he seemed normal and had no fever. One day prior to admission he began to vomit and complain of abdominal pain and on the day of admission he was seen at another hospital, where a positive Brudzinski sign was noted. The diagnosis of poliomyelitis was made and he was transferred to The Mount Sinai Hospital.

Physical examination at the time of admission revealed injection of the pharynx and tonsils, and exudate on the left tonsil. No neurological abnormality could be demonstrated, but because of the admission diagnosis a lumbar puncture was performed.

The cerebrospinal fluid contained 34 cells per cubic millimeter, 32 of which were lymphocytes; protein and sugar concentrations were 18 mg per cent and 48 mg per cent respectively. Subsequent to admission, the patient exhibited no symptoms. A repeat cerebrospinal fluid examination the next day showed 40 cells per cubic millimeter which were mostly lymphocytes, again with normal protein and sugar concentrations. The blood count revealed a hemoglobin of 11.8 grams per cent, and a white blood count of 6,100 per cubic millimeter with 57 per cent neutrophils, 28 per cent lymphocytes, 5 per cent eosinophils and 10 per cent monocytes. Urinalysis was normal. The sedimentation rate on admission was 52 mm. per hour, but on the following day it was 12 mm. per hour. Throat culture revealed staphylococcus aureus. Agglutination studies against mumps, eastern equine encephalitis, St. Louis encephalitis and lymphocytic choriomeningitis were negative.

The patient's stool was inoculated into monkey kidney tissue culture media and a cytopathogenic agent was isolated which was cultured serially. Several attempts to grow the agent in suckling mice failed.

Comment. The virus isolated from the last patient behaved somewhat differently in tissue culture than the viruses recovered from the two brothers. The latter destroyed the culture gradually beginning on the fourth day, but requiring another four days to achieve complete destruction of the tissue culture. The virus from Anthony C. showed lesions on the fourth day which quickly became widespread and destroyed the culture in two days, thereby being slower than poliovirus.

All three viruses were neutralized by gamma globulin. None of them were neutralized by any of the three type specific polio antisera.

* G. Dalldorf, personal communication.

Upon testing the virus isolated from each patient against the various patients' initial and convalescent sera, it was shown that the two brothers' convalescent, but not acute, sera neutralized each other's viruses but not the Anthony C. virus. Conversely, Anthony C. convalescent serum neutralized only his own virus. Acute serum from this patient was not available. Identification of the Anthony C. virus has been performed, and it has been shown to be ECHO type 6.*

Case #3

Calvin T. (MSH #71613) is a 12 year old Negro boy who, four days prior to admission, complained of abdominal cramps, sore throat, tearing, anorexia and fever between 103°F and 104°F. There was no vomiting, diarrhea or jaundice. He was given an injection of penicillin but continued without improvement for four days, when he began to cough and came to the hospital for admission.

Physical examination revealed a red pharynx and vesicles on the anterior tonsillar pillars. Only one observer felt that there might be nuchal rigidity. The patient had some right upper quadrant tenderness.

The cerebrospinal fluid was clear, under normal pressure, contained 82 cells per cubic millimeter of which all were lymphocytes, and the protein and sugar concentrations were 27 mg per cent and 47 mg per cent respectively. Other laboratory studies showed a hemoglobin of 12.9 grams per cent, a white blood count of 9,800 per cubic millimeter with a differential count of 62 per cent neutrophils, 30 per cent lymphocytes, 5 per cent monocytes and 3 per cent atypical lymphocytes. The sedimentation rate was 30 mm. per hour; total protein was 8 grams per cent (albumin, 4.8 grams per cent and globulin, 3.2 grams per cent); total bilirubin was 0.48 mg per cent (0.13 mg per cent direct); serum amylase was 49 units. Liver function tests and urinalysis were normal; sickle cell preparation was negative; nose, throat and blood cultures yielded no pathogens.

The cerebrospinal fluid and the stool were inoculated into suckling mice and tissue culture of HeLa cells. A cytopathogenic agent was recovered from each specimen in each medium. Subsequently all were cultured serially in monkey kidney tissue culture. They were neutralized by gamma globulin, but not by the three types of poliomyelitis antisera. Pooled Coxsackie serum neutralized the virus and it was subsequently identified as Coxsackie B-5.† The patient's convalescent serum showed a rise in complement fixing antibody to pooled Coxsackie virus. The patient's serum showed a rise in neutralizing antibody from 1:10 to 1:20 against 1000 $TCID_{50}$ of the cerebrospinal fluid agent, and a rise from 1:40 to 1:80 against 1000 $TCID_{50}$ of the agent recovered from the stool. The use of a smaller amount of virus in performing the neutralization tests might have afforded a more sensitive estimate of the patient's antibody response.

Case #4

Peter G. (MSH #70122) a private patient of Dr. Else Kaufmann is a five year old boy who, two and one half days prior to admission, awoke with a stiff

* G. Dalldorf, personal communication.

† The virus isolation and identification and the antibody studies were performed in the Virology Laboratory by Dr. Betty Aronson.

neck, nausea, vomiting and fever of 100.4°F. Four days prior to his illness, his nineteen month old sister had developed vesicular pharyngitis and had been treated with a tetracycline drug. On the day of onset of the patient's illness, his sister's fever subsided; a rash appeared behind her ears and on her trunk which faded after one and one half days. The patient showed no improvement in two and one half days and was admitted to the hospital.

On examination he had a vesicular pharyngitis and positive Kernig and Brudzinski signs.

The hemoglobin concentration was 12.9 grams per cent, the white blood count was 5,500 per cubic millimeter with a differential count of 65 per cent neutrophils, 30 per cent lymphocytes, 2 per cent eosinophils, 2 per cent monocytes and 1 per cent myelocytes. Urinalysis was normal. The cerebrospinal fluid was clear; it contained 21 cells per cubic millimeter, half of which were neutrophils and half lymphocytes; the protein concentration was 21 mg per cent and sugar content was 65 mg per cent. Blood and cerebrospinal fluid cultures were sterile. Throat culture yielded Hemophilus influenza type B. The tuberculin test was equivocal. The patient became symptom free in two days and was discharged to the care of his personal physician while still receiving chloramphenicol and Gantrisin® therapy.

Seven days later he had to be readmitted because of recurrence of fever and meningeal signs. Physical examination at that time showed a red pharynx with occasional petechiae on the fauces and positive Kernig and Brudzinski signs. Examination of the blood showed the hemoglobin to be 11.7 grams per cent, the white blood count to be 9,100 per cubic millimeter with a differential count of 75 per cent neutrophils and 25 per cent lymphocytes. The cerebrospinal fluid contained 80 cells per cubic millimeter of which all were lymphocytes. The concentrations of protein and sugar were 20 mg per cent and 68 mg per cent respectively. The patient again became asymptomatic in two days when a repeat blood count showed no significant change. Another cerebrospinal fluid examination showed 35 cells per cubic millimeter of which all were lymphocytes. The concentrations of protein and sugar were unchanged. Cerebrospinal fluid cultures were negative including guinea pig inoculation. The tuberculin test was again equivocal. The chest x-ray was normal except for the presence of an azygous fissure.

Cerebrospinal fluid obtained from the first lumbar puncture was inoculated into tissue culture and yielded an agent cytopathogenic for monkey kidney cells. It could also be passaged in suckling mice. The virus could not be neutralized by the three poliomyelitis antisera but could be neutralized by gamma globulin. The patient's initial serum failed to neutralize the virus, but the convalescent serum neutralized 100 $TCID_{50}$ in a dilution of 1:64. Subsequently, identification* revealed it to be an ECHO type 14.

Case # 5

Raffa J. (MSH # 72859), a six year old negro boy, was well on the evening before admission but woke up during the night with a headache, and vomited. The next morning he complained of stiff neck and anorexia.

* G. Dalldorf personal communication.

He was admitted to the hospital with a temperature of 102.8°F, pulse rate of 140 per minute and normal respiration and blood pressure. The only positive physical findings were minimal back pain on marked neck flexion and bilateral unsustained ankle clonus. The Kernig and Brudzinski signs were negative.

The past history revealed that tuberculous lymph nodes in the neck had been removed at the age of 11 months. No chest pathology was noted at that time, nor in x-rays taken at six-monthly intervals since then.

The blood count on admission revealed a normal hemoglobin, a white blood count of 13,800 per cubic millimeter with a differential count of 83 per cent neutrophils, 14 per cent lymphocytes and 3 per cent monocytes. Urinalysis was normal. A lumbar puncture was performed and slightly turbid cerebrospinal fluid was obtained under an initial pressure of 420 mm. of water and a closing pressure of 240 mm. of water. The fluid contained 1,000 white blood cells per cubic millimeter, of which 90 per cent were neutrophils; sugar concentration was 78 mg per cent and protein content was 42 mg per cent. No microorganisms were seen on gram or acid fast stains of the sediment but therapy was instituted for meningitis of unknown etiology. This consisted of penicillin, chloramphenicol and sulfadiazine.

The next day the temperature climbed to 103.8°F and nuchal rigidity seemed more marked, but there were no neurological abnormalities. One day thereafter, the patient was afebrile and asymptomatic. On the fourth hospital day, coincident with the omission of penicillin, fever spiked to 102°F and returned to normal when penicillin therapy was reinstituted.

Cerebrospinal fluid examination seven days after admission showed 100 white blood cells per cubic millimeter, all lymphocytes, and 55 mg per cent sugar and 27 mg per cent protein concentration. Nasopharyngeal, pharyngeal and blood cultures revealed no pathogens and neither cerebrospinal fluid culture showed microorganisms, including tubercle bacilli. The patient's second strength tuberculin test was positive, but his chest x-ray was negative. A blood count one week after admission was normal.

A virus was isolated in monkey kidney tissue culture from the cerebrospinal fluid and passaged several times after which it was successfully passed in suckling mice. The virus failed to be neutralized by the three types of polio antisera or fourteen ECHO antisera, but was neutralized by gamma globulin. It was neutralized by Coxsackie B4 serum, but not by any other Coxsackie B antisera, thereby identifying it as Coxsackie B4.*

Case #6

Arthur M. (MSH #85685), a private patient of Dr. Ralph Moloshok, was admitted with fever and nuchal rigidity. His illness began six days prior to admission with frontal headache, photophobia and fever of 100.6°F. He was seen by his physician on the next day when he was afebrile, but lethargic and anoretic. There followed spontaneous improvement until one day prior to admission when anorexia, headache, lethargy and photophobia returned together with fever of 102.4°F. He vomited twice and his physician noted nuchal rigidity, and positive

* Serum kindly provided by Dr. B. Aronson.

Kernig and Brudzinski signs, and admitted him to The Mount Sinai Hospital. The past history revealed that he had had measles two years prior to admission and three injections of poliomyelitis vaccine had been given, the last one four months before admission.

The examination at the time of admission was unremarkable except for marked decrease in nuchal rigidity and the absence of neurological signs. The temperature was 101.6°F, but later rose to 103°F and thereafter fell by lysis to become normal on the third hospital day. The blood count showed the hemoglobin concentration to be 13.6 grams per cent and 8,000 white blood cells per cubic millimeter. The differential count was 49 per cent segmented neutrophils, 14 per cent band-forms, 27 per cent lymphocytes, 7 per cent monocytes, 2 per cent atypical lymphocytes and 1 per cent eosinophils. Urinalysis was normal. The cerebrospinal fluid was not under increased pressure and contained 200 cells per cubic millimeter, all of which were lymphocytes. Nuchal rigidity returned after the lumbar puncture, but disappeared in 36 hours, and the patient thereafter was asymptomatic. Nasopharyngeal, throat and cerebrospinal fluid cultures revealed no pathogenic bacteria.

A virus was isolated in monkey kidney tissue culture from the cerebrospinal fluid and passaged several times after which it was successfully passed in suckling mice. It was neutralized by the patient's convalescent serum. The virus failed to be neutralized by the three types of polio antisera or fourteen ECHO antisera, but was neutralized by gamma globulin. It was neutralized by Coxsackie B2 serum, but not by any other Coxsackie B antisera, thereby identifying it as Coxsackie B2.*

DISCUSSION

Since 1925 Wallgren's definition of the aseptic meningitis syndrome (1) has served as a useful clinical guide but his criteria have been adhered to by few writers. Steigman (2), thirty years later takes a much broader view of the subject; however, the developments of the last few years are bringing the syndrome into focus.

Our concern is with untreated patients who present signs and symptoms of meningitis from whose cerebrospinal fluid no bacteria can be isolated. During the "poliomyelitis season" such patients are often said to have non-paralytic poliomyelitis; it is now known that other viruses may be responsible, and at all times of the year.

A review of 854 cases of aseptic meningitis seen at the Army Service Graduate School between 1947 and 1952 (3) revealed the following causes:

Lymphocytic choriomeningitis	9%
Mumps	12%
Leptospirosis	7%
Herpes simplex	5%
Undiagnosed	67%

* Serum kindly provided by Dr. B. Aronson

With the use of the suckling mouse and the introduction of tissue culture methods, an increasing number of viruses have been reported as causative agents and the cases of unknown etiology are becoming less frequent. A virus has been held responsible when it was isolated from the patient's stool or throat washings and if, during convalescence, a rise in the patient's serum antibody titre could be demonstrated. The virus can be labeled as causative even more definitely if it can be isolated from cerebrospinal fluid.

Recently reported outbreaks of "poliomyelitis" have emphasized the recovery of other enteric viruses. Melnick in 1955 (4), from non-paralytic cases, recovered poliovirus in 41 per cent, Coxsackie viruses in 23 per cent and ECHO viruses in 36 per cent. The frequency of the various virus types varies from place to place and year to year. Rhodes (5) reported 18.8 per cent Coxsackie virus isolation between 1950 and 1955 at the Toronto Childrens Hospital, and Kirby (6), 27.4 per cent Coxsackie virus isolation in Seattle in 1954.

Encephalitis has been reported to be associated with Bornholm disease for over 20 years (7). The association was noted again recently in Belgium (8), Great Britain (9), Australia (10), and Sweden (11, 12) so that Johnsson (11) suggested that Bornholm disease manifests itself as aseptic meningitis in children and epidemic pleurodynia and myalgia in later life. Evidence for Coxsackie B virus causing aseptic meningitis is provided not only by recovery of the virus from stool and associated rise in antibody titre but also by isolation from cerebrospinal fluid (5, 13). In seventeen cases reported (14), the cerebrospinal fluid cell count averaged less than 180 per cubic millimeter with a preponderance of lymphocytes and the cerebrospinal fluid protein concentration was under 45 mg. per cent. All Coxsackie B types have been isolated from cerebrospinal fluid (15, 16). Coxsackie A types have been recovered from feces of patients with aseptic meningitis but only type A9 has been isolated from cerebrospinal fluid (17, 18). An undetermined type has been responsible for a large outbreak in Italy (19). Conversely Coxsackie A infection, such as herpangina need not be associated with pleocytosis, rise in protein or presence of virus in the cerebrospinal fluid (20). Problems of causal relationship arise with Coxsackie A virus due to its frequent association with other viruses, especially poliovirus. This is rarely the case with Coxsackie B, which is thought to interfere with poliovirus (5). Coxsackie virus may, at times, cause more than meningitis. Steigman (21) reports the occurrence of mild residual paresis following Coxsackie B5 infection, and central nervous system neuronal damage due to Coxsackie B2. From the spinal cord of a newborn infant who died of myocarditis and meningoencephalitis, Coxsackie B3 has been isolated (22). Coxsackie virus was isolated from the stool of a newborn infant who died of myocarditis and encephalitis at The Mount Sinai Hospital. Stools from four of seven patients with Guillain-Barré syndrome studied by Gear (23) yielded Coxsackie A virus. Dalldorf has recently demonstrated neuropathogenicity similar to poliovirus in group A Coxsackie virus type 14 (24), and the same has been suggested for Coxsackie A7 (24–26).

The ECHO viruses have been isolated from the stools of healthy children and children with diarrhea, and from the stools and cerebrospinal fluid of children

with aseptic meningitis (27–33). Sabin (27) states that he has not found them in the stools of normal individuals between the ages of 20 and 30 years. The types most frequently associated with aseptic meningitis have been ECHO 4, 5, 6, 9 and 14, and all of them have been isolated from cerebrospinal fluid (34–37).

Outbreaks of ECHO 6 aseptic meningitis have been reported by Melnick (4), Kibrick (36) and Karzon (38). Their descriptions of the illness agree in all important respects; it is biphasic in about one fourth of the patients, most of whom complain of headache, stiff neck and/or back and gastrointestinal symptoms, especially vomiting. Fever usually lasts a few days. The blood count is generally within normal limits with a slight "shift to the left." The cerebrospinal fluid cell count is usually under 300 per cubic millimeter of predominantly polymorphonuclear cells early in the disease but with a rapid change to lymphocytic preponderance. The cerebrospinal fluid protein is often within normal limits. Muscle weakness is common, though transient.

In the Marshalltown, Iowa epidemic, ECHO 4 virus was recovered from 52 per cent of patients with aseptic meningitis, 20 per cent of patients with "minor illness" and 18 per cent of family contacts without illness (35, 37). In the Milwaukee area, ECHO 9 reportedly caused an outbreak of aseptic meningitis associated with a rash (39) after having been implicated in several outbreaks in Europe (29–33, 40, 41). Dalldorf and Rhodes (42, 43) believe it to be a new type of Coxsackie virus. Further evidence to this effect has come from Melnick (32, 34) and Boissard (29), yet an antigenic relationship of the virus to herpes simplex has also been reported (44).

Karzon, most recently, studied an outbreak of aseptic meningitis due to an ECHO virus which most closely resembled ECHO type 4, but was antigenically related to ECHO 1, 8 and 13, some Coxsackie types A and B and poliovirus II (26, 45).

Svedmyr (46) reports isolation of ECHO 6 and 9 from patients with paralytic disease. Steigman reports isolation of ECHO 2 from a typical bulbo-respiratory polio-like case (21) and Wenner and Rhodes agree that ECHO 2 and 6 attack neurones like polio-virus (35, 43).

The adenoviruses too may play a role in the causation of the aseptic meningitis syndrome. A virus related to the adenovirus group (36) and three new antigenic types were isolated in the 1951 Massachusetts outbreak; however no rise in antibody titre was demonstrable. The 1951 illness was biphasic in one case only, fever was low-grade (100–102°F, orally) and the predominant symptoms were headache, stiff neck and back, vomiting and sore throat. The white count was below 10,000 per cubic millimeter with a slight shift to the left. Cerebrospinal fluid showed usually less than 100 cells per cubic millimeter of which most were lymphocytes and the protein was normal.

Viruses long associated with the aseptic meningitis syndrome are mumps, lymphocytic choriomeningitis, and herpes simplex; poliovirus is still a leading cause. Leptospirosis, tuberculosis and coccidioidomycosis as well as the arthropod-borne viruses have been implicated (28, 47, 48).

The above reviews emphasize that in viral meningitis it is common to have moderate cerebrospinal fluid pleocytosis, predominantly lymphocytic with little or no increase in protein concentration. In making the diagnosis, inadequately treated bacterial meningitis has to be excluded. To establish the diagnosis of viral meningitis, the recovery of a virus should be accompanied by a demonstration of a rise in specific antibody titre. A significant increase of antibody titre to a viral antigen shown to occur in serial examinations of the serum is strong presumptive evidence of viral etiology even if a virus is not isolated.

The isolation of a virus from the cerebrospinal fluid is most suggestive of etiologic culpability. However, Steigman (21) mentions the isolation of Coxsackie virus from cerebrospinal fluid of five patients, one with severe pneumonia, one with encephalitis, one with fever of unknown cause, and two with brain tumors and he raises the questions whether any severe disease may lower the blood brain barrier and whether virus may be attracted to tumor because of its rapidly growing young cells.

SUMMARY

Six illustrative cases of viral meningitis are presented. The literature is briefly reviewed and the newer viral agents of etiologic significance are discussed.

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THE EFFECT OF GLUCAGON ON THE EXOCRINE PANCREATIC SECRETION OF MAN*

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Acute alterations in blood sugar level have been reported to stimulate the elaboration of enzyme but not fluid by the pancreas (1, 2). This report is a study of the effect of glucagon-induced hyperglycemia upon external pancreatic secretion in man.

METHOD

Fourteen patients without pancreatic disease and ten patients with proven chronic pancreatitis were subjected to the same experimental procedure. All subjects were studied in the fasting state. A double-lumened gastro-duodenal tube was positioned at the ligament of Treitz under fluoroscopic control. Gastric and duodenal specimens were obtained separately with constant suction. In half the cases, after two control periods of 20 minuts each, a secretin test was performed using a standard intravenous dose of 1.0 unit of secretin per kilogram of body weight, following which 2.0 milligrams of glucagon were given intravenously and duodenal drainage was collected in divided specimens for five hours. In the remaining patients, the hormones were administered in reverse order.

The volume of duodenal drainage was measured, its bicarbonate concentration determined with the van Slyke apparatus, and its amylase concentration analyzed by a photo-colorimetric modification of the Somogyi starch substrate method (3). Blood was drawn before and at twenty minute intervals after the administration of glucagon in most of the patients, and in some others not subjected to intubation. Glucose and amylase determinations were made upon these sera. A minimum elevation of 40 milligrams per cent, observed in all patients, was considered a satisfactory response to glucagon.

RESULTS

The effect of glucagon induced hyperglycemia on the exocrine pancreatic secretion is presented in Figure 1, wherein the average percentage change from the basal control rates of pancreatic flow, bicarbonate concentration, bicarbonate secretion, and rate of amylase elaboration are given both for patients with and

* The Glucagon and Secretin used in this study was furnished by the Eli Lilly Company, Indianapolis, Indiana.

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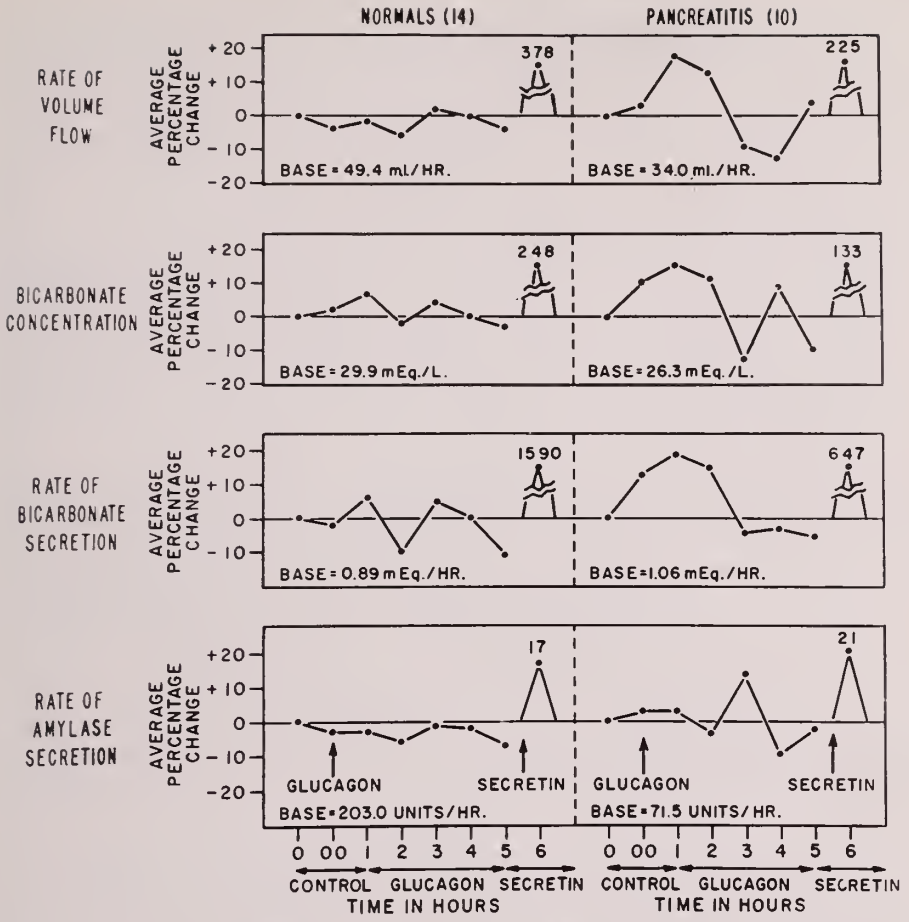

FIG. 1. Average percentage change of pancreatic flow, bicarbonate secretion, and amylase secretion following intravenous glucagon in 14 patients without pancreatic disease and in 10 patients with pancreatitis.

without pancreatic inflammatory disease. The graphs clearly indicate that glucagon induced hyperglycemia results in no change in rate of flow, bicarbonate secretion, and enzyme secretion. This lack of effect is found both in patients with and without pancreatic disease.

In Figure 2 the average percentage change in blood sugar and blood amylase values following intravenous glucagon are given for 16 patients without pancreatic disease and for 13 patients with chronic pancreatitis. In both groups, the rise in blood sugar following glucagon is accompanied by a depression of the blood amylase. As the glucagon effect deteriorates and the induced hyperglycemia wanes, the blood amylase is reciprocally elevated towards the basal level. These changes were of similar magnitude in patients without pancreatitis as in patients with chronic pancreatitis. The inverse relationship observed between blood glucose and amylase is statistically significant at the .001 level.

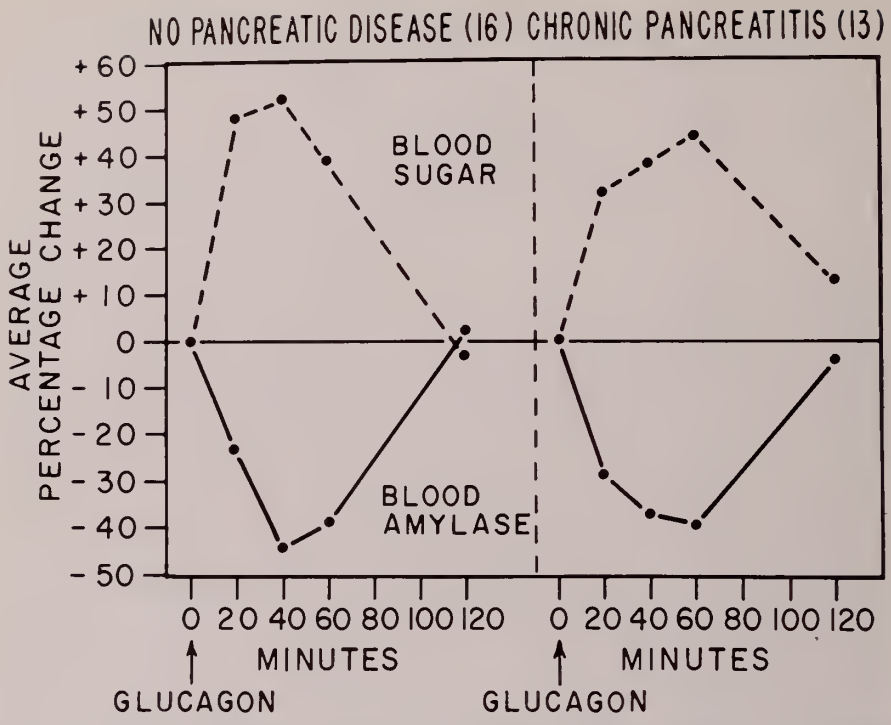

FIG. 2. Average percentage change in blood sugar and blood amylase concentrations following intravenous glucagon administration to 16 patients without pancreatic disease and 13 patients with pancreatitis.

COMMENT

The failure of glucagon induced hyperglycemia to affect the external pancreatic secretion in man requires little discussion. Hypoglycemia augments enzyme secretion by direct stimulation of the vagal centers (2); its effect is obliterated by vagisection (4). The increase in amylase secretion noted following intravenous infusion of hypertonic glucose was not found in our results but our blood sugar changes were not as acute, of as great magnitude, nor as prolonged as those induced by Crider et al (1).

The depression of blood amylase following glucagon induced hyperglycemia is worthy of comment. There are two possible explanations of this phenomenon: (a) either it is the result of alterations within the pancreas, or (b) it is due to changes in extra-pancreatic factors which control the blood amylase level.

A pancreatic mechanism for blood amylase depression following glucagon cannot be dismissed merely because there is no observed alteration in the external secretion of amylase. This depression might result from an action at the cellular level which produces a change in the endocrine-exocrine partition ratio (5). However, parallel studies of the behavior of the blood amylase following the administration of drugs such as insulin, orinase, epinephrine, glucose, and fructose indicate that the changes in amylase do not follow either the induced alterations

in blood sugar nor the induced changes in pancreatic secretion (6). Indeed, a correlation between the response of blood amylase levels and the non-esterified fatty acid (NEFA) content of the blood would suggest that the blood amylase depression following glucagon noted in this study is extra-pancreatic in origin and dependent upon alterations in the rate of carbohydrate utilization (6, 7).

CONCLUSIONS

1. Glucagon induced hyperglycemia did not effect the rate of flow, bicarbonate secretion, nor the rate of enzyme secretion by the pancreas in patients with and without pancreatic inflammation.

2. Glucagon induced hyperglycemia is accompanied by a reciprocal depression of the blood amylase, an effect apparently extrapancreatic in locus of action, and probably secondary to an induced alteration in rate of glucose utilization.

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PROGRESS AND PROBLEMS IN BRAIN RESEARCH*

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It is a true honor, and a real pleasure to be invited to give the Israel Wechsler lecture. Since my first acquaintance with Dr. Wechsler, as a student through his textbook and history of neurology, and later through his penetrating scientific works in clinical neurology, gleaning from them important ideas concerning the physiology and pathology of the brain, I have always wanted to meet and to know Wechsler, the man. It is only during recent years that I have had this privilege. I now envy his many students who have known him for a longer time, and more intimately, for many have been inspired not only by his great teaching, but by his example of a good way of life. As we would say in Quebec, "il est très sympathique".

Perhaps one reason I find Wechsler particularly sympathetic is that he began his medical career in psychiatry, then turned to neurology with the conviction that study of the brain, its anatomy, physiology, and chemistry, combined with extensive clinical experience would eventually contribute more to the understanding of human behavior and mental disease. Time has proven the soundness of his judgment as witnessed by the prevailing trend in psychiatry today.

But Dr. Wechsler has never abandoned completely his first love. In his own words "psychiatry is a charming and seductive wench which invites occasional flirtation and even deserves some ardent affection." My first love was the same, philosophy and psychology. I then turned to neurophysiology in search of a more concrete basis of understanding. I suspect our eventual goal is the same, though the pathway I chose to follow has been mainly through the laboratory, rather than through the wards or clinics. It is the problem of bringing clinical neurology closer to neurophysiology that I wish to discuss this evening.

We hear a great deal today about the urgent need for more well trained scientists and engineers, stimulated by the remarkable achievements of our Russian colleagues in atomic and geophysics and their inauguration of the age of space travel. Less spectacular but of considerable interest, is the increasing volume of work coming from Soviet laboratories and Institutes of Higher Nervous Activity, but I think I am safe in saying that the most outstanding developments in brain research have been coming from laboratories of the Western world. This opinion is shared by all who have visited Soviet laboratories recently and who are most familiar with their published work. However, the need for reconsideration of educational programs for the development of a new generation of scientists in the field of brain research is equally urgent, in view of the broad and highly technical character of scientific disciplines needed in brain research today and in the immediate future.

* The Israel Wechsler Lecture, presented Dec. 13, 1957 at the Mount Sinai Hospital, New York, N. Y.

The neurologist or neuropsychiatrist of today, as engineers or research workers, must keep abreast of a bewildering array of scientific disciplines and techniques if advances being made in the laboratory are to be brought to bear upon clinical practice and understanding of disorders of brain function: biophysics, genetics, neurochemistry and pharmacology, electronics and communication engineering, electrophysiology, principles of atomic physics and radiation, bacteriology and immunology, electron-microscopy and the behavioral sciences. Most of us of the senior generation of neurologists feel very keenly our lack of adequate training in these fields. Even the present generation as they come to our laboratories each year to qualify for specialty examinations can hardly get started in productive work due to lack of basic training.

Are we reaching a stage when it is no longer possible for one man to hope to master or even to acquire an adequate working knowledge of all the basic sciences needed for a comprehensive understanding of brain research? If so, research advances in bits and pieces, in different directions (some false), with a broadening gap between laboratory and clinical work.

Attempts at integration are being made by the multiplication of symposia which serve a useful purpose. However, too often a few star performers repeat again and again modified versions of the same old stories. The resulting multi-authored treatises are excellent sources of information and opinion but must be baffling to the young student trying to get oriented in the field.

Granted that team work is necessary in modern research, is it not necessary to have an eventual synthesis of information from more than one discipline for any comprehensive understanding of brain function, or for the application of laboratory findings to clinical practice? Is it not necessary that such a synthesis occur in one brain, rather than in a community of brains?

In order to provide specific examples let us review some of the major advances in neurophysiology during recent years with a consideration of the impact they have, or could have, upon clinical neurology and psychiatry. Important progress is being made in two apparently opposite directions; studies of ultra-microscopic structure and function by means of the X-ray diffraction, the electron microscope, ultramicroelectrodes, and microchemistry on the one hand, and, on the other hand, studies of the activity of the intact brain in unanaesthetized animals or man in relation to behavior and conscious experience.

The electron microscope is revealing a vast new world of fine structure in the nervous system. I wonder how many neurologists attending the international congress in Brussels understood what they were looking at in the beautiful exhibit from the Institute of Fernandez-Moran in Venezuela. I must confess that I did not.

From the work of Pallade and Palay, de Robertis and co-workers, Robertson, Schmidt, and Gasser and their co-workers, we learn that the myelin sheath, previously thought of as a relatively simple structure, is composed of a spiral of many double membranes, each of which is a relatively complex structure.

The axoplasm of nerve fibres has been shown to be not a structureless homogeneous substance but a tissue of extraordinary complexity with bundles of

closely packed neuroprotofibrils among which mitochondria and small dense granules are aligned.

Studies of fine fibres reveals an entire new series of axons, with myelin like sheaths, which probably possess distinct and important functional properties. In the brain it seems that what has been considered fluid space is filled with fibrillary nerve and glial elements, many fibres of submicroscopic dimensions (40,60 mu.).

Studies of synaptic junctions have provided a precise picture of the highly complex and varied nature of contacts between neurones, or even between nerve and glial cells. As in neuromuscular junctions, microsomal particles or vesicles are seen which may contain packets of acetylcholine or other chemical transmitter substances ready for liberation at junctional membranes.

It is of interest that the existence of such particles or macromolecules was first predicted by Katz and co-workers from microelectrode studies of the interior of muscle end plates, where miniature end-plate potentials were found popping along continuously in an all or none manner even without the arrival of nerve impulses along the axon. Such a miniature transmitting mechanism between junctional membranes in the nervous system, operating even in the absence of nerve impulses may be of far reaching importance if it is shown to function in a similar manner in the central nervous system, where similar vesicles and particles have been seen, and "synaptic noise" has also been heard with intracellular microelectrodes, though not yet identified with such a mechanism.

The growing use of ultramicroelectrodes to record resting polarization, postsynaptic potentials, and action currents both from the interior and exterior of nerve cells, in relation to their dentritic environment is revealing a wealth of precise new information about the function of single nerve cells, the biophysics of resting and action potentials, and mechanisms of excitation and inhibition at synaptic junctures. Such refinements in electrical recording techniques, when combined with precise measurements of ionic movements and changes in impedance of cell membranes, together with microchemical studies of enzymes, and possibly neurohumoral mediators, is making an exciting and rapidly moving story of progress in our knowledge of the intimate mechanisms of nerve function. Application of such techniques to the brain are only beginning but it is already abundantly clear that brain waves, as recorded in the electroencephalogram or with gross electrodes on or within brain tissue cannot be directly related in a simple manner to the firing of nerve cells, but we will return to this point later.

We need mention only in passing the rapid developments in neurochemistry and neuropharmacology which are the subject of the present meeting of the Association for Research in Nervous and Mental Diseases, and which has been the subject of several recent symposia. There can be little doubt that we are here on the verge of a major "break through", as they would call it in Washington.

You are all familiar with the serotonin story as told so beautifully here by Dr. Wooley two years ago, and elaborated by Marrazzi, Uddenfriend and their

co-workers. Of equal importance is the story of the central actions of adrenaline and its break down products as related to psychotogenic compounds, effects which may be counteracted by an ataraxic drug such as Reserpine. As Dr. Kline has so aptly stated, "At no time in the past has the prospect for the understanding of mental and emotional aberrations been as promising as it is today." I would like to add, that essential to this understanding is knowledge of the physiological action of these drugs being pursued intensively in many laboratories. These chemical substances, some of which can be derived from extracts of the brain itself, provide experimental tools which may make possible the discovery of changes in function of individual elements and synaptic circuits in the brain, which result in psychotic behaviour.

Of equal interest and importance is the story of Gamma Aminobutyric acid or GABA and related amino acids known for some time as being important constituents of brain tissue, and now shown to have strong and selective actions upon the activity of dendrites and cells of the cerebral cortex. Emphasis is placed upon inhibitory substances by these studies, a welcome change from the exclusive emphasis upon excitatory substances in the past. Of particular interest is the fact that substances with a selective inhibitory action, such as LSD, result in hallucinations.

Correlated with this discovery are the remarkable observations made in Professor Hebb's laboratories at McGill, and repeated by Dr. Lilly in Bethesda, of the striking mental disorders with active hallucinations which result from simple prolonged isolation with diminished amount and variability of sensory input in the environment. Such experiments were begun in an effort to understand mechanisms of "brain washing" and the effects of monotonous watches in lonely outposts of our north country. They were almost too successful with some of the college students serving as paid subjects. This was a dramatic demonstration of the dependence of the brain upon a normal varied sensory input for its rational functioning. One can only surmise what the effects might be when distorted sensory input is combined with limitation and monotony of environmental stimuli such as might occur in prolonged space travel.

This brings us to studies of functional systems of neurones in the intact brain, or spinal cord.

Recently I visited an Electronic Research Laboratory on our campus which I thought might help us with some electronic problems in our neurophysiology laboratory. I found that this laboratory was engaged in research on the movements of electrons in the design or use of electronic circuitry. This was done for them by the Engineering Department. So it is with brain research. Those interested in microstructure and function of single elements of the nervous system are seldom interested in functional systems of neurones in the intact brain.

Efferent Control of Sensory Systems

One of the most interesting developments in neurophysiology during recent years is the demonstration of a central control on peripheral sensory pathways. This control is exerted, as you probably know, either upon the sensitivity of

sense organs themselves or as a regulator of the excitability of the first sensory relay station. The most striking example, and the one best documented, is the gamma efferent system controlling the bias or sensitivity of stretch receptors in the muscle. The pioneer work of Leksell, Kuffler, Hunt, Granit, Kaada and others has served to clarify the mechanism of action of this efferent system and its connections with the higher nervous centres.

This mechanism is of major importance to clinical neurology in view of our daily concern with the activity of the stretch reflex and spasticity or tone in peripheral muscles. It is of considerable importance for us to realize that many descending tracts from the cerebellum, brain stem, basal ganglia and cerebral cortex, seem to have their primary action on the gamma motor system affecting the sensitivity of muscles to stretch, and only with somewhat stronger excitation is a direct action shown on the alpha motor system or lower motor neurones.

Just in what manner this new conception of control of spinal reflexes and tone is to be incorporated into our thinking regarding variations and stretch reflexes with various lesions of the central nervous system has yet to be worked out but this is certainly a problem worthy of a co-operative endeavour between the clinical neurologists and the neurophysiologists.

The extension of this principle to other sensory systems such as somatic, auditory and olfactory and visual, as summarized recently by Granit in the Silliman lectures, provides us with a new and somewhat revolutionary conception of central control of sensory processes. It provides a mechanism whereby the sensitivity of our sensory systems may vary as a result of disorders in their efferent control in a manner perhaps similar to the disorders of reflexes and muscle tone so familiar to the clinical neurologist. It certainly has a bearing on studies such as have been carried out by Dr. Bender in relation to parietal lobe function with simultaneous presentation of stimuli to the two sides of the body. Consideration of these efferent mechanisms in other sensory systems as well as the somatic system in relation to cerebral lesions may well give us a great deal of insight and new interpretative principles for certain neurological signs and symptoms. Just to what degree these efferent mechanisms may operate in the functions of attention, remains yet to be shown although they do seem to be rather labile and specific to a degree though perhaps not to a sufficient degree to explain the more complicated selective processes of attention which depend upon the qualitative aspects of a stimulus pattern.

One could hardly select topics of importance to our thinking about research on nervous system organization without mentioning the extensive work during recent years on the brain stem reticular system. I need not elaborate on this subject since as a summary of this field has recently been given in New York City in the Salmon lectures by Professor Magoun, and in the Detroit symposium. I am sure you will all agree that the brain stem reticular system, alias the centrencephalic system of Penfield or perhaps better even, the central internuncial system of Olszewski has been one of the most stimulating developments in neurophysiology during recent years. It has initiated wide variety of research in anatomy, physiology, and psychology, giving us a clearer conception of mecha-

nisms of action of pharmacological agents and mechanisms particularly related at the higher mental processes in conscious behaviour and learning. Not the least of its influences has been its stimulus to extensive speculation about the higher integrative processes of the brain, some which will undoubtedly need to be grossly modified in the light of future work.

The evolution of the conception of the central activating or integrating function of the brain stem reticular formation is a fascinating story of the convergence of clinical observations and experimental studies in the laboratory. From clinical and neurosurgical observations, particularly on patients with epilepsy, and from electroencephalographic studies, Penfield postulated a centrencephalic system as a necessary working hypothesis to explain the manifestations of certain kinds of seizure and the organization of the brain as a whole in conscious mental activity. Working from the lower end of the reticular system, Magoun and his colleagues with Moruzzi, worked out many of the functional properties of all levels of this central internuncial system. Undoubtedly certain of our conceptions of the function of this system are still naive but it is a model of collaborative effort between clinicians, neurophysiologists and anatomists.

Most important for future progress in this field are the combination of studies of the fine structure and function of this system as exemplified by the work of the Scheibels, Moruzzi and Amassian—and the electron microscopists mentioned above; with progress in new techniques of study, new principles of interpretation which will not be long in forthcoming.

Another aspect of the physiology of the sensory system, deserving mention because of the general principles involved, is the recent demonstration of important inhibitory components of sensory excitation. It was first shown in the retina by Kuffler and Hartline that excitation of a central zone was accompanied by inhibition of surrounding retinal elements. Recently Mountcastle has beautifully demonstrated that the same principle applied for tactile stimulation of the skin. Recording the response of single cells in the sensory cortex, he was able to show that a given cell may be related to a small restricted area of the skin while surrounding cells may become inhibited when stimulating this same point. Recently, I understand, a similar principle of a central excitatory zone surrounded by inhibited elements has been shown for reflex activity of the spinal cord.

Some such principle of selective central excitatory state with surrounding inhibition has been postulated by Penfield recently in his Academy lecture here, in order to explain the selective activation of particular recollections to the exclusion of others when stimulating the temporal cortex in man. A similar hypothesis has been used by Russian colleagues in the theories of conditioned reflexes. This is an important generalization which may have widespread implications for understanding of selective functions of the brain with particular reference to mechanisms of reciprocal excitation and inhibition in the refinement of sensory discrimination or in the selection of neuronal circuits involved in the conscious reproduction of specific memories.

There is another fascinating story of brain research which should not be omitted from this brief survey and that is the story of cortical dendrites. This

story is most eloquently told by George Bishop, and in a quite different version by Gründfest, in their recent comprehensive reviews of the evidence that the properties of cortical dendrites are quite specific and distinct from those of axons.

The masses of dendrites which make up the larger part of the brain relative to nerve cells appeared to have properties of graded responsiveness with excitatory states which may be built up by a successive post-synaptic activation and they may retain sustained levels of steady depolarization over considerable periods of time. This then becomes another parameter of central integrative processes which is not dependent upon the circulation of impulses in nerve nets but rather upon the building up of excitatory states in the fibrillary dendritic meshwork of the brain. These may be transient rhythmic waves of depolarization which are probably the major component of the electroencephalogram or they may be long lasting sustained levels of polarization such as are seen when direct current recording is made of the cortical surface relative to the depth. This then gives us what the communication engineer would refer to as an analogue process in the mechanism of cerebral action as distinct from the digital transmission of messages over axonal fibre systems.

This hypothesis has been elaborated in considerable detail by Drs. Gründfest and Purpura, with the addition of the conception that both excitatory and inhibitory post-synaptic potentials may summate in the dendritic system of the cortex. The addition of inhibitory waves is a very important conception and there is a growing body of evidence in its favour. Recently, in our laboratory, we have been trying to test this hypothesis with microelectrode records of the discharge of cortical cells recorded simultaneously with dendritic waves as effected by the local application of Gamma Aminobutyric acid. Although we were quite sceptical at the outset, I must confess that we have now been able to show that not only are the cortical responses changed in electrical sign, from negative to positive, but associated with this change there may be an inhibition of cortical cell discharge. In previous studies we have also observed that certain large long sustained waves or steady states of polarization recorded from the surface of the cortex might be associated with inhibition rather than excitation of cell discharge in the depths of the cortex. It seems quite clear therefore that post-synaptic potentials in cortical dendrites may have either excitatory or inhibitory action. This implies that the waves recorded on the cortical surface in the EEG may be also either of excitatory or inhibitory function relative to the activity of the cortical cells enmeshed in their network. Implications for an understanding of the EEG in certain kinds of epileptic seizure should be obvious, if confirmed in epileptic patients themselves.

I don't mean to imply that progress in our understanding of brain function depends solely upon such highly advanced techniques based upon proficiency in the physical sciences. One has only to cite, for example, the continued productiveness of Dr. Penfield with his astute observations of the responses of a conscious patient to the electrical stimulation of his exposed cerebral cortex, or the observations of Penfield, Scoville and Milner, on loss of ability to record and

recall immediate experience following removal of the hippocampal portions of the brain in man. The significance of such observations for our understanding of brain mechanisms underlying memory recording depends, however, upon a much more detailed and refined neurophysiology and microanatomical study possible only with modern biophysical methods, and even upon such methods yet to be developed. Such neurosurgical observations *set* the problems clearly, but other methods must be used for their *solution*.

One could cite many other examples of the continued productiveness of the ablation method of studying brain dysfunction. But after it has been cut into pieces someone has to put it back together again in a functional whole. This is seldom done in a satisfactory manner.

One might mention also the promising neurosurgical treatment recently developed for Parkinsonism and other dyskinesias, but who would be rash enough to pretend to really understand neurophysiological mechanisms of disorders of motor systems? Here we find some of the foundation stones of traditional clinical teaching and practice, the pyramidal and extrapyramidal syndromes, under serious attack by some of our most experienced and critical colleagues. (I refer here to the recent article by Bucy in Brain, entitled "Is there a pyramidal tract?").

Some clinicians are concerned about the growing dependence upon the laboratory for diagnosis and guides to treatment. It is true that laboratory data may lead us astray, especially when interpreted by inexperienced men. None of us seek the advice of an neurophysiologist if we begin to have fits or weakness in one hand. But the clinician has to have more than a superficial knowledge of laboratory data to be able to use it critically, and to permit real progress in his understanding of neurological diseases.

Conclusions

I have presented this brief review of some of the highlights of brain research today to illustrate the high degree of competence in basic physical sciences needed to do significant work in these fields. The great majority of medically qualified men, specializing in neurology, neurosurgery, or psychiatry are quite unqualified to carry out such research unaided. Electron-microscopy, the use of ultramicroelectrodes, advanced biophysical and neurochemical measurements and analyses require far more training than can be provided in the one year of laboratory work now required for graduate certification in these specialties. Attempts to conduct basic research in institutes with an endless stream of such fellows flowing through our laboratories is becoming increasingly difficult. And yet competence and experience in clinical work is also essential if the work of the laboratories is to be intelligently applied to the understanding of nervous and mental disease in man. Even intelligent communication between the laboratory and clinical worker is often difficult or impossible. This is the modern dilemma.

In spite of the many brilliant and promising advances mentioned above there are some fields of investigation which may well have reached a dead end unless new methods are developed for the analysis or synthesis of the multitude of

detailed data which can now be obtained from the living brain in relation to even simple forms of behaviour, learning and conscious mental processes.

I am thinking particularly of studies we have been currently engaged in which consist of recording the discharge patterns of single brain cells during conditioning experiments in the monkey. With billions of cells in constant interrelated activity, the problem of obtaining statistically significant samples from all portions of the brain participating in the establishment of the simplest form of conditioned response is a formidable one. We are then faced with working out temporal and spacial relationships between activities occurring simultaneously in many parts of the brain. Consideration must be given not only to firing patterns of thousands or millions of individual cells but the longer lasting changes in the dendritic or synaptic network of the brain in which the cells are enmeshed, before one can even formulate satisfactory working hypothesis regarding the true neurophysiological basis of brain function in relation to learning or the higher mental processes. The technique of implanting dozens of stimulating and recording electrodes in the brain to permit studies during a complex behaviour and learning is an important step forward in the study of physiological reactions more closely related to normal function.

Analogies in the form of electronic models or computing machines and the most advanced development in communication engineering deserve serious study but only study of the brain itself will give the true answers, and even with all the ingenuity of modern scientific methods, I suspect the brain will always withold from us its most intimate secrets.

There must be a reason why many of our better scientific minds in neurophysiology tend to avoid brain research as such. Some have started work on the brain and given it up for more simple preparations due to difficulties in obtaining clear, simple, well controlled observation (e.g., Matthews, Lorente de Nó). Others have taken the point of view that the brain was after all only a collection of nerve cells, and therefore, study of isolated nerve cells outside the brain under controlled conditions should give all the answers of importance, assuming properties of nerve cells must be general. This is understandable for men with clear thinking minds and high standards of scientific accuracy. It is also true that principles of nerve cell function derived from exact studies of isolated cells such as the stretch receptor neurone of the crayfish may well yield principles applicable to excitatory and inhibitory processes in the nerve cells and dendrites in the cerebral cortex. However, this must be tested in the cerebral cortex itself and by the same precise methods. It is here much more difficult. And then there are the many problems of the functional organization of systems or assemblies of neurons which have to be studied in the brain itself.

It is unfortunate, however, that those with the highest skills and training in the physical sciences should tend to avoid the more difficult problem of study of the brain itself. (Of course there are notable exceptions to this rule.) With the modern techniques now becoming available, it would now seem that controlled observations may be possible and we would hope that more attention to the organization of cerebral activity be given by the men most competent to deal with the complicated methods necessary in such research.

Finally, I would like to urge that we consider the training of scientists for brain research of equal importance to training for research in intercontinental missiles or space travel. The need for training in the physical sciences for continued progress in brain research is equally important, and woefully inadequate. There is no greater challenge. The rewards are great in both scientific and human values, which must be kept foremost if we are to successfully defend our way of life.

I can no longer speak for this country, but north of the border, in Canada, we are pretty well pleased with ourselves and our way of life, but we are beginning to feel serious concern as to the relative value we are placing upon men and institutions producing men of science, and in medicine, the relative value of men who produce new understanding and methods of treatment as compared with those engaged in its distribution. South of the border, I am told, that opportunities and support for brain research are increasing more rapidly than is the training of competent men to accept them, due largely to the remarkable increase in government support of such work during recent years. I feel confident that once the requirements are recognized they can be fulfilled. We can only hope that some of our best scientific brains will be devoted to brain research itself, and that clinical applications will not fall behind.

OSTEOMALACIA IN A PATIENT WITH CARCINOMA OF THE PANCREAS

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Osteomalacia has been described in the western world particularly in association with renal tubular abnormalities (1, 2, 3) and with intestinal absorptive defects as a result of diseases of the small bowel and biliary tract (3, 4, 5, 6). So far as we have been able to determine after a search of the literature, carcinoma of the pancreas coexistent with osteomalacia has not been encountered. We wish to present such a case and to discuss whether the two conditions may be etiologically related.

CASE REPORT

M. A. (MSH # 56514), a 62 year old German-born waiter, was admitted to the Mount Sinai Hospital for the second time in November, 1955, with complaints of bone pains since about 1940, deformity of his body since about 1953, and dyspnea and weight loss for six months prior to his admission.

In 1940, while in a German concentration camp during World War II, he sustained various physical abuses and subsisted on a diet deficient especially in milk and vegetables. He began to complain of generalized body aches and pains at this time. In 1951, because of persistence of these complaints, and especially of low back pain and weakness of his lower extremities with difficulty in walking, he was admitted to the Mount Sinai Hospital on the neurological service. At that time, neurological examination, including a myelogram, was negative. Roentgenograms of the spine and lower extremities did reveal, however, "osteoporosis" in the feet and spinal osteoarthritis.

Subsequent to his discharge from the hospital, pains in the shoulders, hips, all extremities, and trunk persisted and finally, three years prior to his last admission, he was given cortisone by his physician. This was continued for about one year, in doses varying from 25 to 100 mg. per day. After one year of cortisone administration, his "chest collapsed" resulting in marked deformity of his thoracic cage and a three to four inch loss in height. From this time on, the patient required crutches for walking. About six months prior to the last admission he began to develop peripheral edema and exertional dyspnea, as well as anorexia, emesis of ingested food and fluid, and weight loss (his weight fell from 180 to 120 pounds in the six months prior to admission).

Physical examination on admission to the medical service revealed a temperature of 99.4° F., pulse of 120 with frequent premature beats, respirations of 24 per minute. Blood pressure was 130/80. The patient was an emaciated, somewhat dyspneic white male with a striking deformity of the trunk characterized by a

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marked dorsal kyphoscoliosis to the left, a depressed upper anterior sternum, with leftward deviation and anterior bowing of the lower portion of the sternum. The neck veins were moderately distended with a positive hepato-jugular reflux. The lungs revealed a few fine moist basal rales. The heart was deviated to the left with frequent premature beats audible on auscultation. The liver was palpable two cm. below the right costal margin and was moderately tender. In the left upper quadrant was a hard mass, relatively smooth in contour, extending down from the left costal margin about 10 cm. and descending slightly on deep inspiration. The lower extremities showed weakness and limitation of motion as well as muscle atrophy and diminished deep tendon reflexes.

On admission, the patient presented a problem in relation to congestive heart failure, bony deformity, and the nature of the left upper abdominal mass. Initial laboratory data revealed the following: Hemoglobin 14 grams per 100 ml.; white blood count 5,600 per cu. mm.; urine albumin 1 plus, blood urea nitrogen 16 mg. per 100 ml.; fasting blood sugar 94 mg. per 100 ml.; carbon dioxide content of plasma 27 mEq. per liter; plasma chloride 98 mEq. per liter; serum albumin 3.6 gm. per 100 ml.; serum globulin 3.3 gm. per 100 ml.; serum calcium 9.7 mg. per 100 ml.; serum phosphorus 0.5 mg. per 100 ml; serum alkaline phosphatase 9.4 King-Armstrong units (normal value); prothrombin time 13.51 seconds with control of 11 (two subsequent determinations revealed values of 16.5 and 16 seconds with a control of 12 seconds); erythrocyte sedimentation rate (Westergren Method) 4 mm. per hour; stool guaiac reaction trace. Gastric analysis showed free acid. Radiographic study of the bones showed severe demineralization and symmetrically placed pseudofractures involving the femora, humeri, ribs, tibiae, with true fractures in some areas as well.

Thus initial laboratory data indicated the presence of osteomalacia, with normal serum calcium and alkaline phosphatase levels and markedly diminished serum phosphorus level.

Further studies were done to evaluate the cause of the osteomalacia. On a Bauer-Aub diet, with dietary calcium restricted to about 100 mg. per day, the patient excreted 18 mg. of calcium in a seventy-two hour urine specimen. Phosphorus excretion in this time was 597 mg., a value within the normal to low range on such a diet (where phosphorus intake may vary from 500 to 1000 mg. per day). Various tests of liver function such as cephalin flocculation test and bromsulphalein test were normal. A glucose tolerance test revealed a fasting value of 96 mg. per 100 ml. with values at one-half hour of 117, at one hour of 158, at two hours of 151, and at three hours of 150. Duodenal aspiration for study of pancreatic secretion revealed no evidence of pancreatic secretion even after secretin. A vitamin A tolerance test showed a normal absorption curve, although the fasting vitamin A level was low. Fasting level was 21 micrograms per 100 ml., at four hours 60, at eight hours 152, at ten hours 113. The carotene level of blood was low normal (42 micrograms per 100 ml.). After oral ingestion of Lipiodol,® the urine was positive for iodine in dilutions of 1:1 and 1:2, findings which indicated inadequate absorption of the Lipiodol® (7). Several Sudan III stains of stool were done, some of which revealed excess amounts of neutral fat.

The patient's early course in the hospital was characterized by repeated vomit-

ing and the development of metabolic alkalosis (the serum carbon dioxide content rising to 35 mM. per liter). A gastrointestinal series revealed duodenal obstruction and narrowing at the ligament of Treitz by an extrinsic mass, with proximal gastric and duodenal dilatation. Therefore, on December 23, 1956, about one month after admission a gastroenterostomy was performed. At operation, the surgeon's presumptive diagnosis was carcinoma of the pancreas. The patient's poor condition precluded taking a biopsy.

Thereafter, therapy was mainly symptomatic in nature. Repeated paracentesis became necessary, because of recurrent ascites. Intramuscular vitamin D (Hyderitol®) was given in a dose of 200,000 units per day; orally, the patient was given a multivitamin preparation (Polyvisol® 0.6 cc. per day) as well as supplemental calcium salts.

On this regimen, the patient's serum calcium, after two months, was 8.8 mg. per 100 ml. (at a time when the albumin was 2.6 gm. per 100 ml.), and the phosphorus had risen to 2.0 mg. per 100 ml., with the alkaline phosphatase still at 11. X-ray examination of the bones showed no change. A repeat urine calcium determination on a Bauer-Aub diet showed now an excretion of 134 mg. of calcium in seventy-two hours.

The patient died six months after admission. At postmortem examination, there was an infiltrating scirrhous carcinoma of the body and tail of the pancreas, with invasion of the splenic hilum, the lesser curvature of the stomach, the left renal capsule, the upper pole of the left kidney, and the left adrenal. There was complete occlusion of the portal vein and splenic vein. The main pancreatic duct was completely occluded by tumor, except for the last 2.5 cm. leading into the duodenum. The duct of Santorini was not identified. On microscopic examination, the head of the pancreas was found to be infiltrated by scirrhous carcinoma as well.

The liver and small intestine showed no significant abnormalities.

The bones showed a marked degree of softening and the deformities of the sternum, vertebral column, and ribs described clinically. The number of bony trabeculae was reduced. They were atrophic and the Haversian systems were not well discerned. There was no evidence of osteoblastic or osteoclastic activity. The marrow was diffusely fatty. There were areas of osteosclerosis in the sternum and vertebrae. No typical osteoid tissue was found.

DISCUSSION

This patient presented the classical clinical picture of osteomalacia, demonstrating severe structural deformity, multiple symmetrical "pseudofractures" (8), and the chemical findings of low serum phosphorus, normal to slightly reduced serum calcium, normal to slightly elevated serum alkaline phosphatase, and markedly decreased urinary excretion of calcium. The pseudofractures ("*umbauzonen*"), thought to be due to pressure by nutrient arteries on weakened bone (9), are well shown (Fig. 1). The striking thoracic deformity (Fig. 2), frequently an accompaniment of advanced osteomalacia, is demonstrated in this patient as well, and is associated with cardiac strain resulting in heart failure—a condition seen in comparable cases reported from China. (10)

FIG. 1. Fractures and pseudo-fractures of femora and pelvis. Diffuse decalcification.

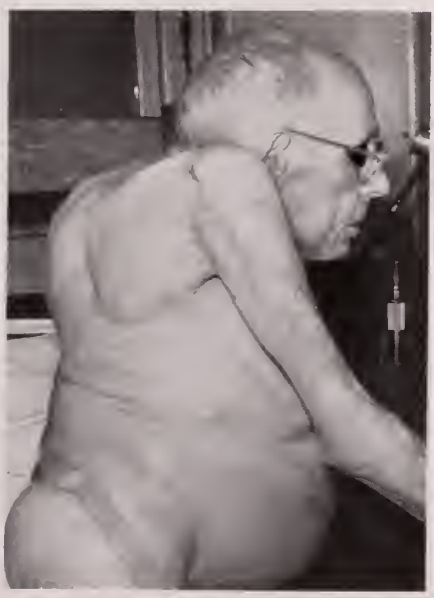

FIG. 2A FIG. 2B

FIG. 2A. Photograph of patient taken in 1951.
FIG. 2B. Photograph of patient taken in December, 1955.

Reports by Dent (1), Fanconi (11), and others (2), have emphasized renal factors in the etiology of the osteomalacic syndromes. A specific defect in the renal tubular reabsorption of phosphate has been present alone, or in various combinations with renal acidosis, glycosuria, amino-aciduria, and hyperkaliuria. The absence of increased total phosphate excretion in our patient at first seemed to rule out a renal cause for his osteomalacia. In the presence of a lowered serum phosphorus, however, a normal total excretion would mean an increased phosphate clearance with decreased tubular reabsorption. The history of bone pain extending over many years would favor such an interpretation. On the other hand, although recently described, increased phosphate excretion as a *sole* evidence of tubular abnormality is not common. This led to a consideration of

another cause for the osteomalacia. On clinical grounds we can exclude osteomalacia due to such rare conditions as von Recklinghausen's neurofibromatosis (12), essential hypercalciuria (3), and "simple" vitamin D deficiency (13, 14).

It is well known that any condition with steatorrhea—whether from faulty small bowel absorption, as in sprue (6), scleroderma (4), or regional enteritis (4, 5); from decreased bile in the intestine, as in biliary cirrhosis (4);—may lead to deficient vitamin D absorption. If this is sufficiently prolonged and severe, osteomalacia will result in the adult. A hallmark of this vitamin D deficiency is decreased urinary calcium excretion.(3, 10, 16).

When the diagnosis of carcinoma of the pancreas was suspected and later proven in our patient, evidence of faulty absorption of fat and fat soluble vitamins was sought (5). There was no gross or microscopic evidence of excess fat in the stool at first. At this time he had incomplete obstruction of the fourth portion of the duodenum, he was vomiting and his intake of food was minimal. After the obstruction had been relieved by operation, the stool was found to contain large amounts of neutral fat, by staining with Sudan III on at least two occasions. Further, the test with Lipiodol® demonstrated minimal absorption of iodine (7). It should be pointed out that qualitative tests for fecal fat may not be continually positive in patients with steatorrhea (17).

The prothrombin time became prolonged to abnormal levels, up to 16 seconds with control of 12 seconds. The vitamin A level in the blood was low, even though the vitamin A tolerance test was normal. Finally, the duodenal secretions obtained by intubation showed no evidence whatever of pancreatic secretion, although bile was present. The elevated rather than flat glucose tolerance curve tended to eliminate the possibility of intrinsic small bowel disease and to support the diagnosis of carcinoma of the pancreas.

All these findings point to steatorrhea with resultant vitamin D deficiency as a possible etiology of the osteomalacia in this patient. In view of the absence of grossly foul, fatty, or bulky stools, it would seem then that this patient would fall into the category of "latent steatorrhea" (6, 18), in which significant amounts of fat may be present in the stool for long periods without being otherwise grossly evident.

The question thus arises whether the carcinoma of the pancreas in this patient was the factor which led to absent secretion of pancreatic enzymes and to the steatorrhea. Bockus, Kiefer, Nothman and others have reported a four to twenty-two per cent incidence of steatorrhea in series of patients with carcinoma of the pancreas (19–22). Brown (23) et al regard it as an early sign. One difficulty resides in the fact that most patients with carcinoma of the pancrease die before a sufficient length of time elapses for the osteomalacic results of steatorrhea to become evident.

On review of roentgenograms taken four years before this admission, evidence suggestive of a mass in the left upper quadrant and of osteomalacia was present is retrospect. This suggests that the length of survival after the development of the carcinoma was longer than usual in our patient. Snapper, however, has emphasized that even in pancreatic steatorrhea of long duration, as in chronic cystic fibrosis, rickets or osteomalacia does not become evident (24).

At autopsy, a short terminal segment of the pancreatic duct was patent, but the entire pancreas showed some degree of involvement by scirrhous carcinoma. These findings appear adequate to account for absent pancreatic secretion from the duodenum and steatorrhea.

Despite the typical clinical picture of osteomalacia, the bones contained no osteoid tissue microscopically. This probably is a reflection of the prolonged vitamin D treatment before his death.

Another contributing factor in the development of bone lesions may have been that he received cortisone for many months after the development of his bone pains—thus adding a potent cause for osteoporosis to osteomalacia.

One may speculate that this man's deficient diet during his incarceration in a concentration camp may have rendered his bones unusually susceptible to a subsequent deficiency of vitamin D.

We thus have presented a patient in whom osteomalacia and osteoporosis and carcinoma of the pancreas occurred together. There are certain findings which suggest that the osteomalacia preceded the development of the pancreatic lesion and was possibly due to the renal tubular loss of phosphate. On the other hand, there was evidence for a latent steatorrhea. Although osteomalacia as a result of pancreatic steatorrhea is rare, the very rarity of this association has prompted us to report this patient.

SUMMARY AND CONCLUSIONS

1. A patient with carcinoma of the pancreas and osteomalacia is described.
2. The possible etiologic relationship of these two conditions is discussed.

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USE OF BARIUM STEARATE TO REMOVE LABILE FACTOR FROM PLASMA

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Substances of diverse chemical composition such as barium sulfate, calcium phosphate, aluminum and magnesium hydroxide (1), and glass (2) are known to

TABLE 1

Effect of Barium Stearate on Plasma Prothrombin Components

Owren Values in *Per Cent*

Sample of Oxalated Plasma	Prothrombin		Stable Factor		Labile Factor	
	Before	After adsorption	Before	After adsorption	Before	After adsorption
Normal, #1	100	100	100	>100	100	8
Normal, #2	100	100	>100	>100	100	<5
Normal, #3	100	>100	>100	>100	>100	8
Patient with postop. bleeding	82	82	92	92	92	<5
Hypofibrinogenemia	100	100	100	100	100	5½
Treated with dicumarol	26	26	15	10	55	<5
AHG-deficient patient, transfused	100	100	89	52	83	8
Normal, #4, collected in silicone	100	100	>100	100	86	<5
Normal, #3, after treatment with Vinylite instead of barium stearate	100	>100	>100	>100	>100	84

1 cc of fresh oxalated plasma was added to 100 mg barium stearate powder in a 75 × 12 mm glass tube; the powder was forced into suspension by brief and gentle stirring with a glass rod and the mixture incubated at room temperature for 20 minutes. It was centrifuged for 15 minutes at 3000 rpm and 5° C and the clear liquid was aspirated from under the floating caked powder. All powders were hydrophobic before, and hydrophilic after contact with plasma.

adsorb preferentially prothrombin, stable factor and plasma thromboplastin component from oxalated plasma. Labile factor is adsorbed poorly if at all by these agents which have in common hydrophilic surfaces.

On the other hand, platelets (3) and a cephalin preparation (4) have been found to adsorb labile factor quite efficiently.

To investigate adsorption by an even more hydrophobic surface, barium stearate powder* (100 mgm ml) was added to several samples of fresh oxalated plasma and forced into suspension with a glass rod. After 20 minutes incubation at room temperature, the suspensions were centrifuged and the clear liquid between the sediment and the caked powder floating on the surface was aspirated;

* Obtained from Witco Chemical Co., New York City.

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upon assay it proved to have only about 5% or less of the original labile factor activity while retaining about 100% of the original prothrombin and stable factor activity (Table 1). Preliminary tests similarly indicate that Hageman factor, plasma thromboplastin component and most antihemophilic globulin are retained, but that plasma thromboplastin antecedent is removed. Further studies, including efforts to recover labile factor presumably adsorbed on the stearate, are in progress.

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PROLONGED HYPOTENSION ASSOCIATED WITH PULMONARY EMBOLISM AND INFARCTION

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In recent years there has been an increased emphasis of the early diagnosis and treatment of pulmonary embolism. A twenty year review of personal experience by White (1) has shown that there is now an increased incidence of pulmonary embolism. In part, this has been due to an increased awareness and recognition of thromboembolic disease. Pulmonary embolism and infarction are not synonymous. Pulmonary embolism occurs when a portion of a thrombus (or other foreign body) lodges in a branch of a pulmonary artery. If there is necrosis of the lung tissue, the term pulmonary infarction is used (2).

INCIDENCE

Pulmonary embolism and infarction are relatively common problems of serious significance. A well known text attributes two to three per cent of all deaths to pulmonary embolism (3). The increased incidence in recent years is due, at least in part, to greater interest on the part of physicians in general. Another factor must certainly be the gradually increasing age of our population. The increased use of antibiotics, potent mercurial diuretics, salt restrictive diets, and other forms of therapy which tend to prolong the life span of seriously ill cardiac patients may play a paradoxical role. They permit the survival of patients with pulmonary congestion and therefore contribute to the likelihood of pulmonary infarction. Israel and Goldstein (4) have recently stated that pulmonary embolism had become the most common disease of the lungs which they encountered in a general hospital. In approximately fourteen per cent of carefully performed autopsies, evidence of pulmonary embolism and/or infarction has been found. In a study of three thousand five hundred autopsies, a nine per cent incidence of pulmonary embolism and/or infarction was found (5). Hampton and Castleman (5) reported that forty per cent of their cases followed surgical procedures, thirty per cent were in cardiac patients and thirty per cent of the three hundred seventy cases of pulmonary embolism and infarction in which they had autopsy studies were in non-cardiac medical patients. Other authors (6, 7) have found an even greater proportion of medical versus surgical patients with fatal pulmonary embolism. Baker and Al (6) reported a ratio of eight to one amongst non-surgical or medical patients as opposed to post-operative patients. Among medical patients with pulmonary embolism an incidence of heart disease of between sixty and seventy per cent was noted (7).

RELATIONSHIP TO PULMONARY CONGESTION

It is well known that the occurrence of pulmonary infarction is to a large degree dependent upon antecedent pulmonary congestion. Thus it was that only

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fifty-eight per cent of patients with postoperative emboli sustained a pulmonary infarction whereas in ninety per cent of cardiac patients with pulmonary emboli pulmonary infarction occurred (5). Chapman and others (8) showed in an experimental study that pulmonary infarction usually occurs in a lung with concomitant pulmonary congestion and edema. Intravascular clots were produced and released from the jugular veins in twelve normal dogs. No pulmonary infarcts were noted when the dogs were sacrificed but in seven there were emboli in branches of the pulmonary arteries. Pulmonary congestion was then produced by the intravenous use of Alph-Naphthylthiourea (ANTU) and pulmonary congestion was produced in four dogs receiving it alone. In an additional eight dogs, in whom pulmonary congestion was produced by ANTU, intravascular clots were produced and released as emboli. In three of these dogs definite pulmonary infarction resulted. In part the importance of this study was the use of intravascular clots rather than foreign body emboli.

SEX AND AGE

The sex incidence of pulmonary embolism has been reported slightly differently by varying authors. Goyette (9) found approximately an evenly divided sex incidence whereas Carlotti (7) found the incidence slightly increased in males over females. Almost eighty per cent of the patients studied were over forty years of age (7, 4).

SYMPTOMS OF PULMONARY EMBOLISM

Pulmonary embolism may produce a series of acute alarming symptoms or symptoms may be entirely absent. The most common symptoms are dyspnea and chest pain. The chest pain may be produced by a pleural reaction or may be substernal and simulate angina pectoris. The latter type pain may be produced by sudden distention of the pulmonary artery itself or may be due to coronary anoxia or insufficiency. There may be cough with or without hemoptysis and the patient may show anxiety or even panic. Fainting, restlessness, or sweating may occur. In a large group of patients with pulmonary embolism, chest pain was found in approximately half, dyspnea in about one third, and hemoptysis in about one sixth (7). In another recent study pleuritic type chest pain was found in fifty-six per cent, precordial pain in twenty-seven per cent, and dyspnea in forty-six per cent of ninety patients (4).

SIGNS OF PULMONARY EMBOLISM

The signs of pulmonary embolism are tachycardia out of proportion to other vital signs, tachypnea, cyanosis, pleural friction rub, and signs of local consolidation in the lungs with subcrepitant rales. The temperature is likely to be elevated. On rare occasions jaundice may occur. There may be signs of thrombophlebitis in the legs and the pulmonary second sound may be accentuated. A state of shock may occur with a thready pulse and a falling blood pressure. The pulmonary embolism may give rise to a plural effusion. In doubtful cases, thoracentesis productive of sterile bloody fluid of fairly high specific gravity (1.014 to 1.018)

with a relative paucity of white cells affords good confirmation of one's suspicions of pulmonary embolism and infarction (10). The incidence of rales in a group of patients with pulmonary embolism was approximately fifty per cent. A friction rub was heard in less than ten per cent. In the same study approximately one third of the patients had a temperature elevation to 102°F. and a rise in pulse rate to 110 (7). A more recent study demonstrated that fever was present in almost eighty per cent, rales in sixty per cent, and tachypnea in fifty per cent (4). Tachycardia was noted in sixty per cent of the patients and in twenty to twenty-five per cent hemoptysis or plural friction rub was present. It is interesting that these authors reported a twenty-five per cent incidence of hypotension.

ETIOLOGY

The etiology of pulmonary emboli is usually the dislodgment of a blood clot in a systemic vein or the right chambers of the heart. There are rare instances of emboli due to other materials such as fat emboli after fractures of the major bones or amniotic fluid during delivery. The clot is usually bland. Patients who are susceptible to venous thrombosis include those with a history of previous thrombophlebitis particularly in individuals who again become post-partum or postoperative. Disturbances in venous circulation such as extensive varicosities favor the development of thrombosis. Individuals with malignancies have more recurrent and frequent thrombosis. Extensive abdominal and pelvic surgery predisposes to venous thrombosis. Fractures of the femur and amputations of the lower extremities are followed by a remarkably high incidence of thromboembolism. Thromboembolism occurs at least twice as frequently in obese individuals as those of normal weight. Blood dyscrasias such as polycythemia are also predisposing factors. The phlebitis which precedes the pulmonary embolism may not be recognized or present clinically. The source of the emboli has usually been found in the leg veins. Only ten to fifteen per cent of cardiac patients with pulmonary emboli had thrombi on the right side of the heart at autopsy. Seventy-five per cent of the patients with pulmonary embolism showed venous thrombosis upon examination of the legs (6). An even higher percentage was found by Hampton and Castleman (5).

The patient to be described presented an unusual manifestation of thromboembolism, in that he sustained a pulmonary embolism (or embolisms) and thereafter was hypotensive for a continuous period of twenty-six days and was maintained on levophed® (levarterenol bitartrate) throughout this entire episode. It was found that the patient required large amounts of vasoconstricting material to maintain his blood pressure and urine output and a critical dose and rate of levarterenol had to be maintained in order to prevent the patient from becoming hypotensive and anuric.

CASE REPORT

A sixty-seven year old white waiter was admitted to The Mount Sinai Hospital on June 10, 1957 with the chief complaint of post-prandial epigastric pain of two months duration during which time a twenty-four pound weight loss oc-

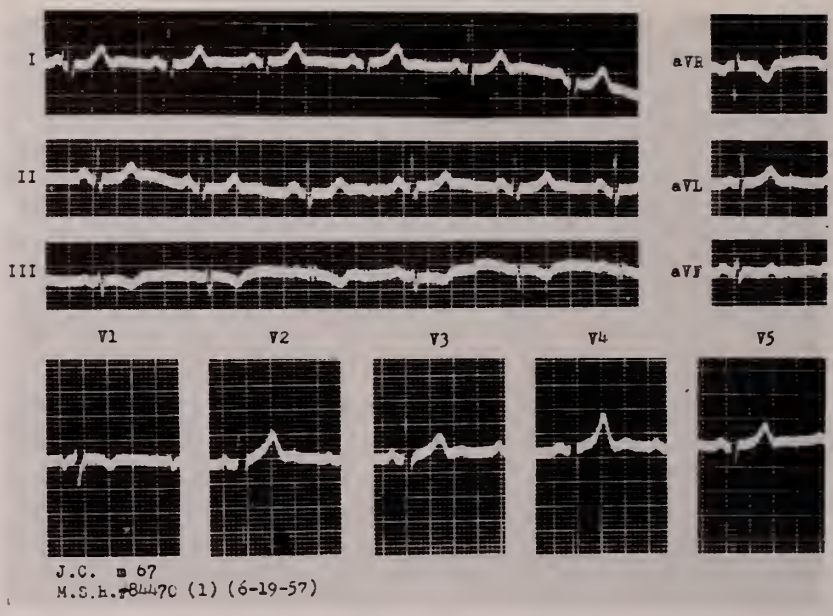

FIG. 1. An electrocardiogram taken preoperatively showing left axis deviation, regular sinus rhythm, at a rate of 80 per minute. The tracing is essentially within normal limits.

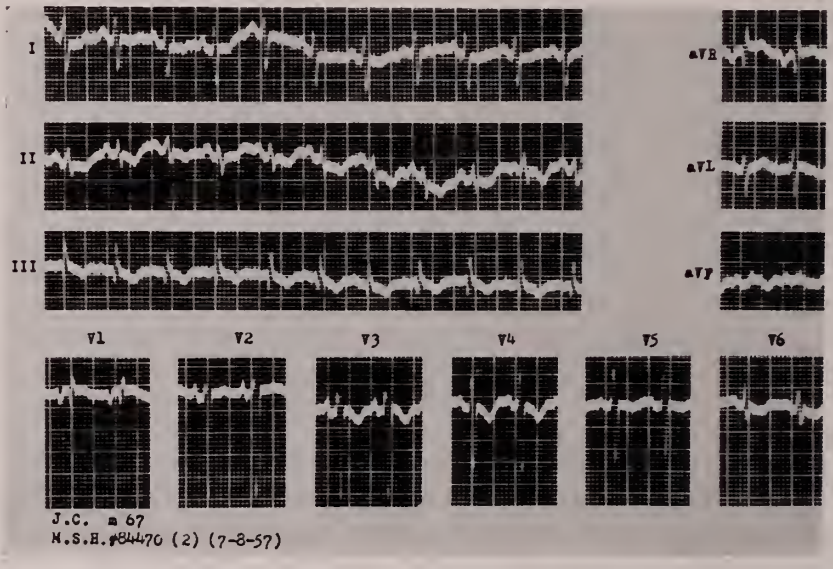

FIG. 2. An electrocardiogram taken 7/8/57 after the patient noted chest pain and dyspnea. Sinus tachycardia at a rate of 130 per minute and right axis deviation is now present. There is an S wave in lead I and a flat T wave. The ST segment is depressed in leads I and II, AVF and V-3 through V-6. The T wave is inverted in leads II, III, AVF, V-3 through V-6. There is a Q wave present in lead III. There is an R′ present in AVR. These changes are seen in pulmonary embolism.

curred. Two months before hospitalization the patient noted post-prandial epigastric pain occurring one hour after eating and lasting about two hours. It was unrelated to position or food ingestion. One month before admission the patient noted anorexia and three weeks before admission the patient became jaundiced. Past history and review of systems was essentially negative.

Physical examination at the time of admission revealed a chronically ill white male who was markedly icteric. The pulse was 60 per minute, respirations were 16 per minute and the blood pressure was 135 75. The skin and sclera were icteric. There was a sense of fullness in the epigastrium, and one observer felt the liver edge two fingers below the right costal margin.

Urine analysis revealed the specific gravity to be 1.017, acid reaction, no albumin, no sugar, 4+ bile, 1:160 urinary urobilinogen, and no formed elements on microscopic examination. The hemoglobin concentration was 13 gm per 100 ml. The white blood cell count was 6800 per mm^3. The differential count was normal. The sedimentation rate was 14 mm per hr. Blood chemistry studies revealed blood urea nitrogen, 15 mg per 100 ml; glucose, 111 mg per 100 ml; total protein, 7.4 gm per 100 ml; albumin, 3.8 gm per 100 ml; globulin, 3.6 gm per 100 ml; total bilirubin, 14.6 mg per 100 ml; direct bilirubin, 7.7 mg per 100 ml; alkaline phosphatase, 33.4 King-Armstrong units per 100 ml; prothrombin time, 12 seconds (control, 12 seconds); cephalin flocculation, 0; serum glutamic oxalo-acetic transaminase, 185 units (normal 40 units). Stool guaiac was negative. Secretin test of pancreatic function with duodenal drainage revealed a normal volume re-

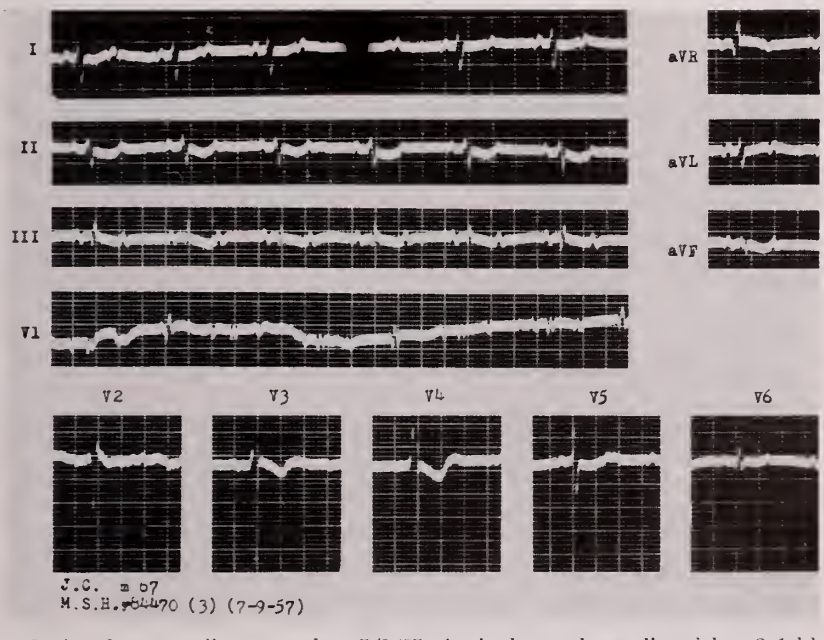

FIG. 3. An electrocardiogram taken 7/9/57. Auricular tachycardia with a 2:1 block is now present. The ventricular rate is 80 per minute, the auricular rate is 160. The T wave is less inverted in leads II, III, AVF, V-5 and V-6. The Q3 is less marked.

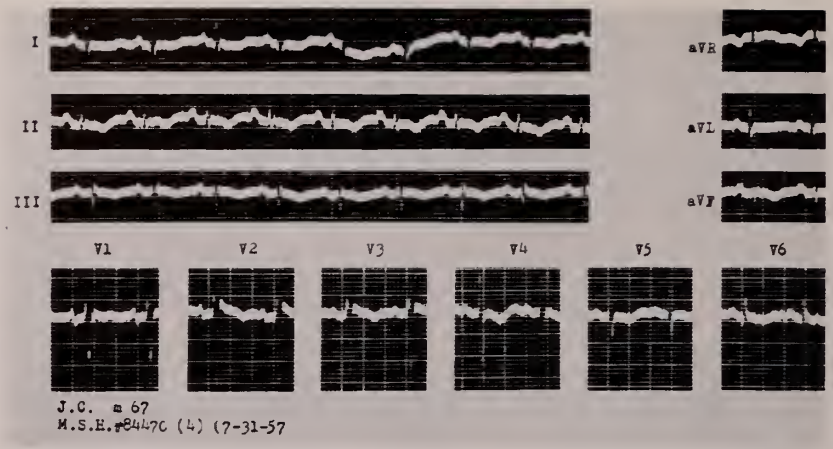

FIG. 4. An electrocardiogram taken 7/31/57. Regular sinus rhythm at a rate of 100 per minute is now present. Left axis deviation is again present. The T waves are less inverted in leads V-2 through V-5. The changes of acute cor pulmonale are no longer present.

sponse and a low maximum bicarbonate concentration. On the basis of the secretin studies, it was felt that the gall bladder could contract normally.

Because of the picture of obstructive jaundice, laparotomy was done on 7/2/57. A five by six centimeter hard mass in the region of the head of the pancreas was seen and there were firm lymph nodes along the superior border of the pancreas. The common bile duct was found to be dilated. A cholecystogastrostomy was performed. During the procedure the patient's blood pressure was 70/40 for a period of about twenty minutes. The patient was returned to the ward and for the week following surgery his blood pressure averaged 90/70. He was maintained with intravenous feedings and appeared to be recovering reasonably well. His urine output averaged 700 cc per day and he did not appear to be in clinical shock.

An initial pre-operative electrocardiogram taken on 6/19/57 showed a slight left axis deviation and no other abnormalities (Fig. 1). On 7/7/57 the patient complained of some precordial chest discomfort and he was noted to be dyspneic with a respiratory rate of thirty-two per minute. An electrocardiogram revealed sinus tachycardia at one hundred thirty-two per minute, a deep S in lead 1, a small Q in lead 3, right axis deviation, a tall R′ in AVR, inverted T waves in V-3 through V-6 and an R′ present in V-1 (Fig. 2). These changes were interpreted as indicating acute pulmonary embolism. The patient was treated with levarterenol because of a fall in blood pressure to 60/40 and signs of shock.

Because of the occurrence of heart failure, the patient was digitalized with intramuscular digoxin and given two cc of mercuhydrin intramuscularly. On 7/9/57 an electrocardiogram showed auricular tachycardia, two to one heart block, right axis deviation, R′ in V-1 and a tall R in AVR (Fig. 3). On 7/11/57 the concentration of levarterenol was increased in order that smaller amounts of intravenous fluid be necessary to maintain his blood pressure. The patient received thirty-two to forty micrograms of levarterenol per minute and an average daily intake of 1500 cc intravenously.

On 7 11 57 an attempt was made to stop the levarterenol when the patient's blood pressure was 120 80. Within four to five minutes of the cessation of levarterenol therapy, the patient's blood pressure dropped to 60 10. Levarterenol was restarted, the blood pressure rose to 130 90 and a transient episode of auricular fibrillation lasting ten minutes occurred. The levarterenol was continued at a slower rate, the patient reverted to regular sinus rhythm and his blood pressure was maintained at 110 80 with an average dose of 40 micrograms of levarterenol per minute. On 7 12 57 the patient had a thirty second decholin (arm to tongue) circulation time. On 7 14 57 because phlebitis and blanching of the skin occurred at the sites of intravenous infusions in his leg, the levarterenol was stopped and the blood pressure carefully observed. The blood pressure dropped immediately from 110 80 to 54 38 and during the ensuing hour of observation the patient was able to maintain his blood pressure at 68 48. He produced no urine (an indwelling catheter was in the bladder and was irrigated before and after the period of observation). The patient remained rational despite the hypotension but his skin became clammy and sweaty. Thereafter, levarterenol was continued intravenously at 40 micrograms per minute. By 7 15 57 the icterus had cleared and thereafter the patient produced an average of 700 to 1000 cc of urine daily.

On 7 17 57 an attempt was made to decrease the levarterenol to 20 micrograms per minute. The patient's blood pressure promptly fell to 60 systolic and a scant 300 cc of urine was produced during the day. On 7 22 57 intravenous therapy was again stopped and there occurred again a prompt fall in blood pressure to 64 48. After twenty minutes levarterenol was again started. An electrocardiogram on 7 22 57 revealed inverted T waves in Leads 1, 2, AVF and V-2 through V-6. On 7 25 57 the patient was started on intravenous solu-cortef® in an effort

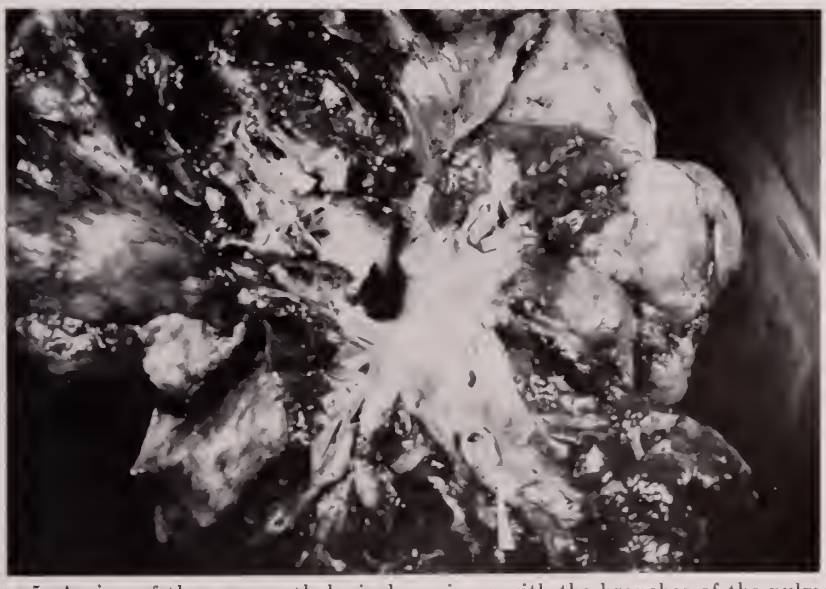

FIG. 5. A view of the gross pathological specimen with the branches of the pulmonary artery laid open showing multiple pulmonary emboli (see white arrows) and pulmonary infarctions.

FIG. 6. A close-up view showing a clot embolus in a branch of the pulmonary artery. (See white arrow).

to ascertain whether any of his hypotension was due to adrenal-cortical insufficiency. After four days of therapy with steroids it was obvious that they had no effect on the hypotension and they were stopped. On 7/27/57 the levarterenol was discontinued for one and one half hours during which time the patient produced no urine and again had a hypotensive episode. During the remaining week the patient was at no time able to maintain his blood pressure without considerable amounts of levarterenol. He developed four plus edema of his left leg with obvious thrombophlebitis and a palpable cord. He developed fever of 101° and some chest pain and began to cough. He was treated with massive amounts of antibiotics, oxygen by nasal catheter and was fed by naso-gastric tube. Despite all efforts, the patient died on 8/3/57 without acute manifestations of a cardiac, cerebral, or respiratory catastrophe after 26 days of continuous levarterenol therapy necessitated by prolonged hypotension.

Post-mortem examination revealed heavy lungs weighing 620 grams each. The pulmonary arteries showed multiple embolization (Figs. 5 & 6). Many of the embolizations were accompanied by pulmonary infarctions. There was a large, firm carcinomatous mass in the head of the pancreas. The right femoral and external iliac veins were occluded by an adherent thrombus. The heart, brain and adrenals were unremarkable.

THE ELECTROCARDIOGRAPHICAL CHANGES IN PULMONARY EMBOLISM

The electrocardiogram was of help in this patient in making the early diagnosis of pulmonary embolism although it is unfortunately not frequently helpful. The classical electrocardiographic changes occurring in pulmonary embolism have

been previously described (2, 12, 13). These include a change to right axis deviation especially if this was not true beforehand as in the patient reported. The electrocardiogram after pulmonary embolism may show a deep S wave in lead 1 with a depressed ST segment, a Q wave and elevated ST segment in lead 3 and clockwise rotation. AVR may show an R wave and an elevated ST segment. AVL may show depressed ST segment and in AVF, ST segment elevation. A prominent R with elevation of ST may occur in V-1 and V-2. In V-5 and V-6 there may be a marked S wave as well as ST segment depression. The occurrence of the classical electrocardiographic pattern after pulmonary embolism is variable but has been reported in approximately 10 to 20 per cent of the patients studied. Some electrocardiographic changes are seen in fifty per cent of the patients with pulmonary embolism who have had two or more tracings taken (4). Only rarely are these changes diagnostic of pulmonary embolism. They are usually positional changes, changes in axis deviation, changes of coronary insufficiency with ST and T wave changes, and changes in rhythm. Atrial fibrillation, atrial tachycardia and changes in conduction with right bundle branch block are also seen.

DISCUSSION

The occurrence of shock after pulmonary infarction has long been recognized. There is a recent report of a case treated successfully with l-noradrenaline (14). Prolonged hypotension as manifested by the case reported appears to be uncommon. There appear to be several mechanisms which may play a role in the circulatory failure which follows large pulmonary emboli. Thus there may be mechanical interference with cardiac output by massive pulmonary embolism. It has been shown that unless more than half of the cross sectional area of the main pulmonary artery is occluded, the increased pulmonary resistance is compensated by a rise in the right ventricular pressure which leads to a stronger right ventricular contraction sufficient to maintain a normal supply to the left ventricle (15). Thus clinically pulmonary embolism of less than massive size is usually insufficient to produce general circulatory disturbance (16). The point at which circulatory failure occurs appears to be sharply defined. Haggert and Walker have shown, with gradual occlusion of pulmonary arteries in dogs, that there were no serious circulatory disturbances until between 52 and 66 per cent of the pulmonary arterial cross section was occluded. Death usually followed 85 per cent occlusion. Part of the circulatory failure following pulmonary embolism has been attributed to myocardial ischemia or hypoxemia. Myocardial anoxia follows as a natural consequence of arterial hypoxemia secondary to the loss of a large segment of pulmonary functional tissue. There may be impaired coronary drainage by way of the thesbian veins because of the elevated pressures on the right side of the heart (17).

The role that reflex vasoconstriction of the coronary arteries mediated by way of the vagus nerve plays has been subject to much debate. Sokolow (12) quoting Villaret et al (18) states that after bilateral vagotomy up to seven times the usual lethal dose of seed emboli was necessary to cause death in experimental animals.

De Takats et al (19) found that atropine would increase the survival of dogs in whom massive pulmonary embolism was produced. However, Love and Brugher (20) felt that reflexes mediated through the autonomic nervous system did not play a major role It has been known that a patient may die of a pulmonary embolism without massive obstruction. Some reflex mechanism appears an attractive hypothesis. It has also been demonstrated recently that pulmonary artery thrombosis can be entirely asymptomatic and be discovered after an unrelated death. Another point of view was expressed after a study of the pulmonary vascular response to precapillary emboli with graphite particles. In vagotomized animals there was no marked alteration of response to such emboli as compared to control animals (21). Atropine, however, appeared to abolish vasoconstriction associated with precapillary embolization. This is attributed to a direct effect of atropine on the blood vessels which was not effected by way of the vagus nerve. The exact role of reflexes mediated through the vagus nerve after pulmonary embolism remains to be determined. Hypotension following pulmonary embolism is due to a group of factors some of which are as yet not completely elucidated.

SUMMARY

A case of prolonged hypotension lasting 26 days following pulmonary embolism is reported and discussed. A brief discussion of incidence, signs and symptoms, and etiology of pulmonary embolism is included. The relationship to pulmonary congestion is outlined. A discussion of the mechanisms responsible for circulatory failure is presented.

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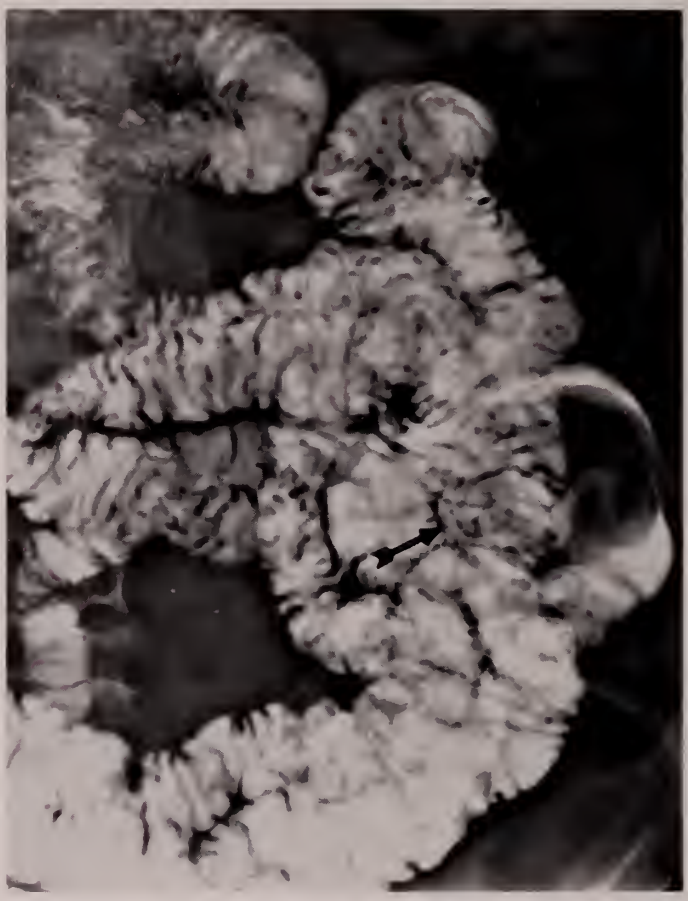
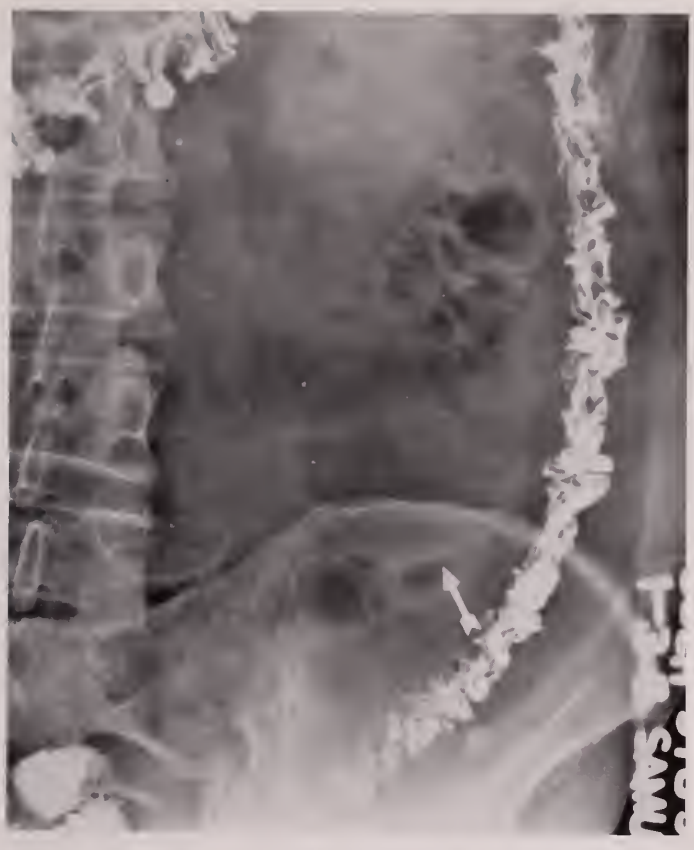
Radiological Notes

CASE NO. 32

B. S., a white female of 65, was admitted with the chief complaint of red and black stool per rectum for 24 hours prior to admission. Three bowel movements were black but, intermixed with the stool, the patient was able to recognize rather dark but reddish blood. Sixteen years prior to admission, the patient had undergone a cholecystectomy. Despite this, however, she continued to complain of recurrent heartburn and gaseous distention especially after fatty meals. Multiple roentgen examinations were reported as being negative. Three months prior to admission, because of dyspepsia, the patient was given some type of powder. After this, her stools became dark but resumed a normal color with



CASE 32, FIG. 1. Black arrow points to a large somewhat lobulated, sharply demarcated filling defect about 2 inches in diameter in the jejunum about 4 feet from the ligament of Treitz. The mucosal pattern over this filling defect is absent but there is no evidence of ulceration. The bowel proximal to the lesion is not dilated and barium passed this area without difficulty.

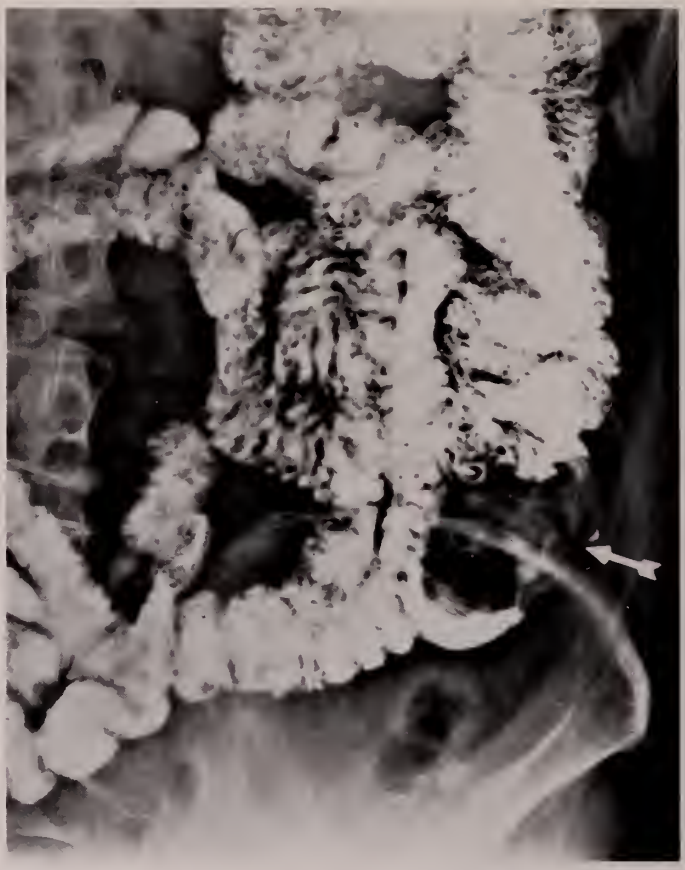


CASE 32, FIG. 2. Film taken after evacuation of the barium enema shows a round lucent area (arrow) about 5cm. in diameter with a thin, denser, sharply demarcated periphery, situated medial to the colon. The density of this area is intermediate between air and muscle, i.e. corresponds to fat or sebaceous material. Its location is the same as the filling defect in the jejunum seen in fig. 1.

cessation of the medication. The patient had been moderately constipated for many years and hypertensive for about ten years. Five years prior to admission, the patient had undergone a hemorrhoidectomy.

Physical examination showed a patient in no distress. Blood pressure was 176 98. A well-healed right upper quadrant scar was evident. No masses were felt within the abdomen and no abdominal tenderness was elicited. On sigmoidoscopy, red blood was seen, coming from above the end of the scope. The distal 10 inches of the sigmoid and rectum showed no abnormality. Hemoglobin on admission was 11.4 grams per cent and, on the subsequent day, 9.5 grams per cent. The patient was transfused with 2 units of blood.

Barium enema examination showed no evidence of any intrinsic lesion of the colon or terminal ileum. However, on the film taken as part of the barium meal examination, a filling defect was evident in the jejunum (Fig. 1). Review of the



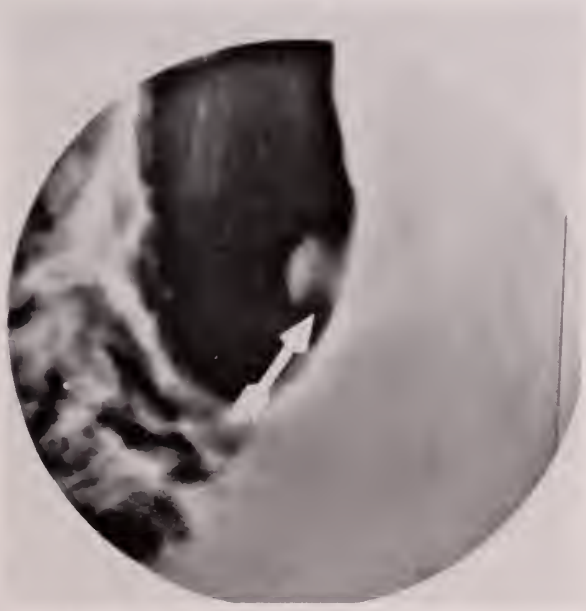
Case 32, Fig. 3. Repeat barium meal examination shows a more ovoid or elongated configuration of the filling defect in the jejunum. During the course of fluoroscopy, the more spherical appearance appeared to be transformed to this ovoid appearance when additional pressure was applied to the abdomen. Barium could be seen to spurt past the filling defect without obstruction.

films taken during the course of the barium enema examination also demonstrated an unusual shadow adjacent to the descending colon (Fig. 2). Repeat barium meal examination was then done with fluoroscopic observations of the filling defect with the aid of the image intensifier. The shape of the mass appeared to be somewhat changeable depending upon the amount of pressure applied to the abdomen and on the peristaltic activity of the adjacent small bowel (Fig. 3).

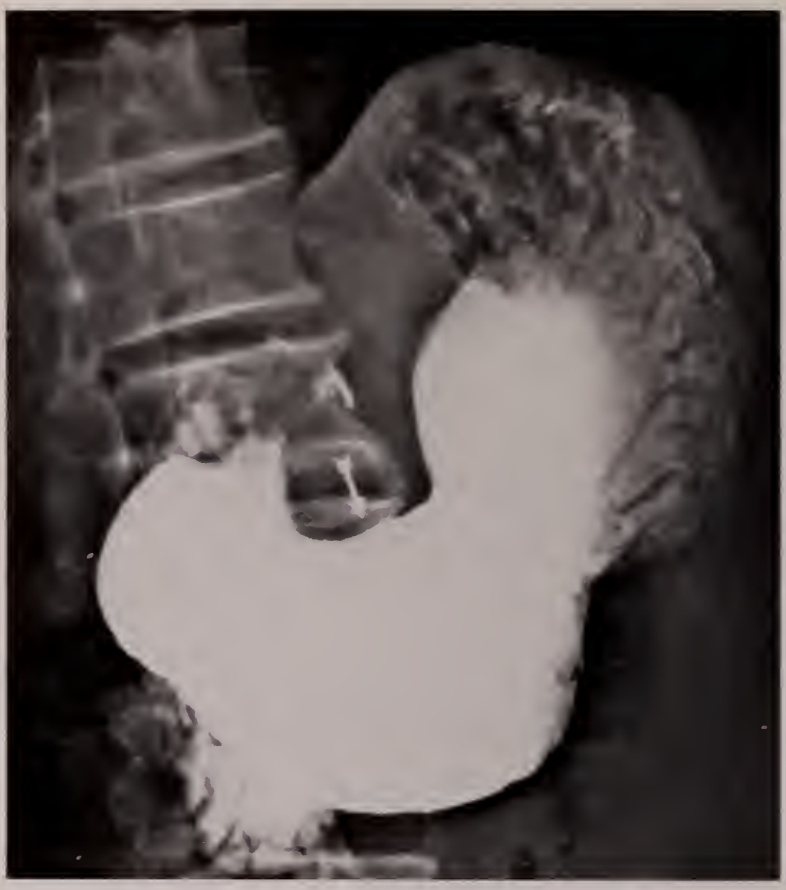
A diagnosis of lipoma of the jejunum was made on the evidence of a lobulated, smooth, relatively radiolucent filling defect. The patient was explored and a lipoma with a broad base was found at the predicted site. The mucosa over the mass was markedly stretched and in places appeared to be eroded. The postoperative course was uneventful.

Final Diagnosis: Lipoma of the jejunum.

Case 33, Fig. 1A. Spot pressure film of the lesser curvature of the stomach just above the reentrant angle shows an ulcer niche. There is a thin, sharply demarcated, lucent line (arrow) at the base of the crater and a conical or funnel-shaped communication with the lumen of the stomach. The appearance of this niche and this lucent line, Hampton's line, is characteristic of a benign ulcer crater.

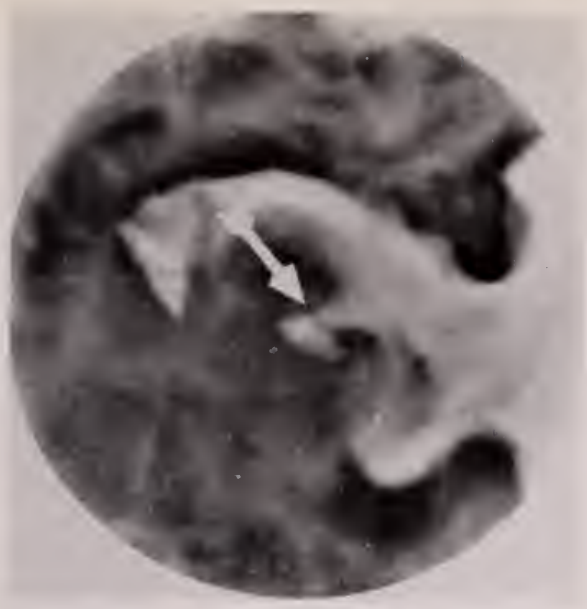


Case 33, Fig. 1B. Another compression view of the ulcer crater again demonstrates features associated with a benign ulcer. A rather thick, relatively lucent collar is seen intervening between the stomach crater and the general lumen of the stomach.



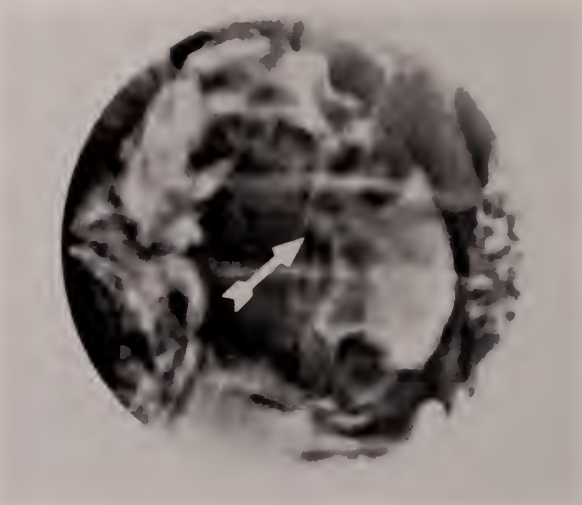
Case 33, Fig. 1C. A film of the filled stomach shows flattening, slight serration, broadening and rigidity of the reentrant angle (arrow) which was interpreted as shortening of the lesser curvature in association with a benign ulcer. The ulcer crater seen on the spot erect compression films is not evident. This patient was explored and a subtotal gastrectomy performed for a large infiltrating flat scirrhous carcinoma involving the lesser curvature of the stomach and extending onto the anterior and posterior walls. The wall of the stomach at the site of the carcinoma was markedly thickened. In the center of the carcinomatous area, there was a punched-out, sharply demarcated, rather deep ulceration which resembled a benign peptic ulcer. At the base of the ulcer, however, on microscopy there was carcinoma as part of the diffuse infiltration.

In the September–October 1957 issue of the Journal of The Mount Sinai Hospital, profile features of benign gastric niches were described with emphasis on the importance of a thin straight lucent line which may be seen between a benign crater and the lumen of the stomach. This line has been referred to as Hampton's line and is excellent evidence of the benign nature of a niche. It was pointed out, however, that in rare instances, Hodgkin's disease or lymphosarcoma of the stomach may give a similar appearance. The present group of cases demonstrate



Case 34, Fig. 1. Compression view of a filling defect of the antrum of the stomach involving the greater curvature. This filling defect appears to be bilobar with a deep ulceration in the middle of it. The arrow points to a thin, straight, lucent line intervening between the deep crater and the funnel-like communication with the general lumen of the stomach. This filling defect is sharply demarcated and, except for the ulceration, there is no evidence of destroyed mucosa over the defect. Roentgenologically, the diagnosis of an intramural tumor, presumably a myoma, was made and this was confirmed at laparotomy. The lucent line fulfills the criteria of a Hampton line.

Case 35, Fig. 1A. Spot view of the duodenal bulb showing an extremely large crater on its posterior right aspect with rather thick folds directed towards the base of the carter. A transverse lucent, sharply demarcated line (arrow) is seen at the junction of the crater and the lumen of the bulb. This resembles the Hampton line described in benign gastric ulcers.



Case 35, Fig. 1B. Re-examination one month later shows marked diminution in the size of the ulcer crater (arrow) with a typical pattern of radiating folds. The lucent line is not evident.

that a Hampton line may rarely be seen in carcinoma of the stomach (Case 33), in myoma of the stomach (Case 34) and also in duodenal ulcer (Case 35).

Final Diagnosis: Case 33—Hampton line in carcinoma of the stomach.

Final Diagnosis: Case 34—Hampton line in myoma of the stomach.

Final Diagnosis: Case 35—Hampton line in a duodenal ulcer.

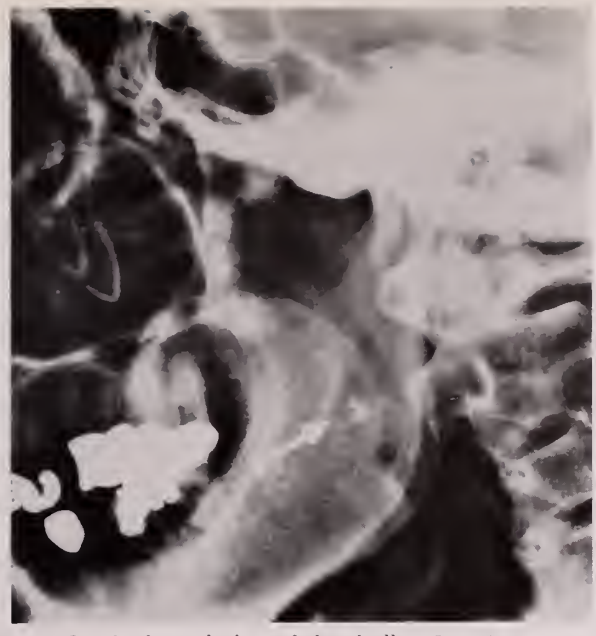
CASE NO. 36

(Submitted by Mansho T. Khilnani, M.D.)

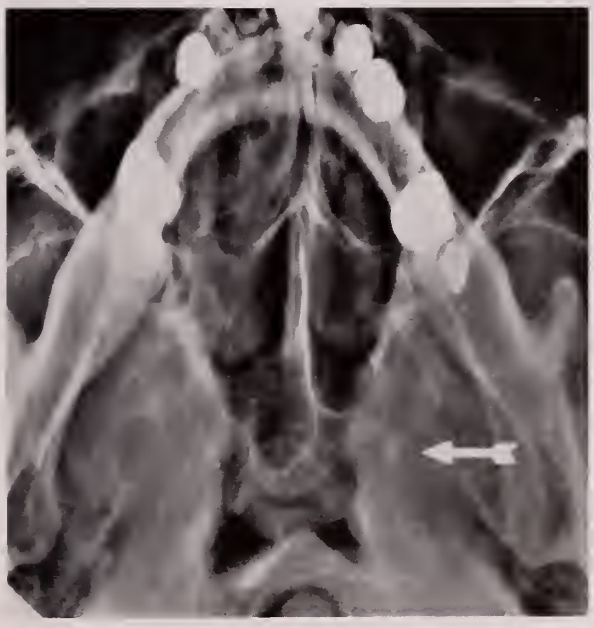
In this patient, examination of the skull and sinuses was requested because of headaches. No abnormality was noted in the skull films but, on the lateral view, near the angle of the jaw, a somewhat amorphous calcification, 3 or 4 mm. in diameter, was noted (Fig. 1). This was also identified in the base view of the skull.

The roentgen findings indicate that the concretion is located in the region of the tonsil and represents radioopaque debris within tonsillar crypts. As far as is known, this finding has no special significance. Its importance lies in the fact that it may be mistaken for a parotid calculus. It is located more posteriorly and much further medially than a calculus in the parotid duct.

Final Diagnosis: Radioopaque debris in tonsillar crypts.

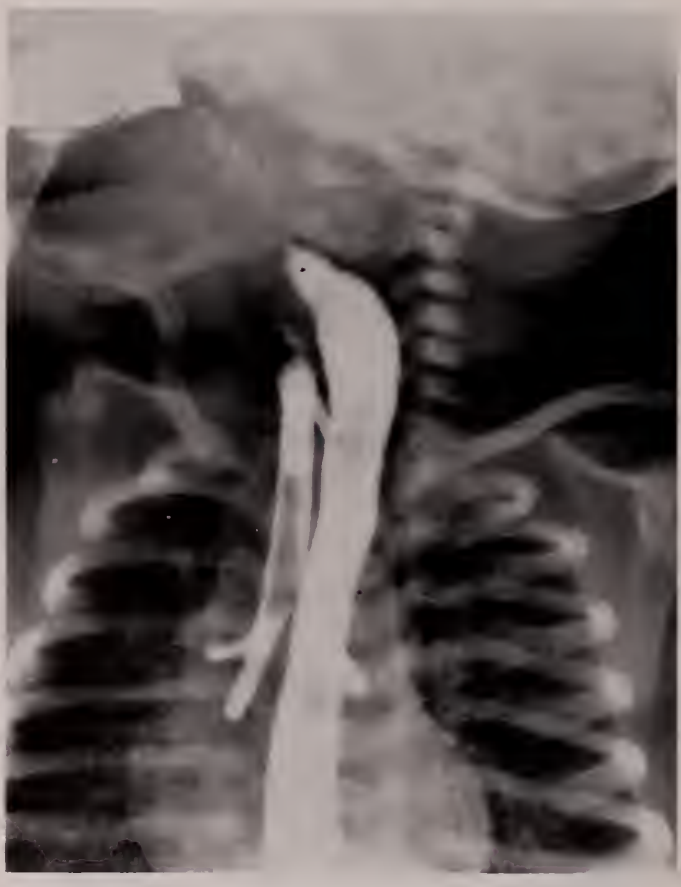


Case 36, Fig. 1A. On the lateral view of the skull, a 3 or 4 mm. amorphous calcification (arrow) is noted just above and anterior to the angle of the mandible. The shadow of the soft palate is seen immediately above it. The location of this calcification is more posterior than is ordinarily seen with a parotid duct calculus.



Case 36, Fig. 1B. Base view of the skull shows that the calcification (arrow) is located medial to the parotid gland and overlaps the soft tissue density of the tonsillar region. It therefore represents radio-opaque, presumably calcific, debris in tonsillar crypts.

CASE NO. 37



CASE 37, FIG. 1. Oily dionosil administered by mouth fills the esophagus and the trachea. An oblique fistulous track is seen to join these organs. The tracheal opening is at a higher lever than the opening into the esophagus. For this reason, a catheter passed into the esophagus will not enter the track while a catheter passed into the trachea is likely to pass easily into the esophagus. There is no esophageal atresia, i.e. this is an example of the rare so-called H type of tracheo-esophageal fistula. This fistula is located higher (between C7 and T1) than the ordinary type and repair through the neck seems preferable.

C. N., a five day old infant was admitted with the tentative diagnosis of a tracheo-esophageal fistula. Difficulty in taking feedings was noted immediately after birth. Gurgling sounds could be heard in the chest while the patient attempted to swallow. Despite this, however, a catheter passed into the stomach without difficulty. Physical examination of the child was not remarkable. His weight was 3.1 kilograms. The observation that a catheter could be passed into the stomach without difficulty was confirmed clinically and roentgenologically.

A roentgen examination of the chest showed some increase in the prominence of the markings at the right base. Because of the possibility of a tracheo-esophageal fistula, without esophageal atresia, oily dionsil was administered by mouth. It was evident on fluoroscopy that the opaque material entered the trachea from the upper esophagus through a short communication just above the level of the thoracic inlet. This fistula coursed forward and upwards from the esophagus to enter the trachea. There was no evidence of atresia or stenosis of the esophagus.

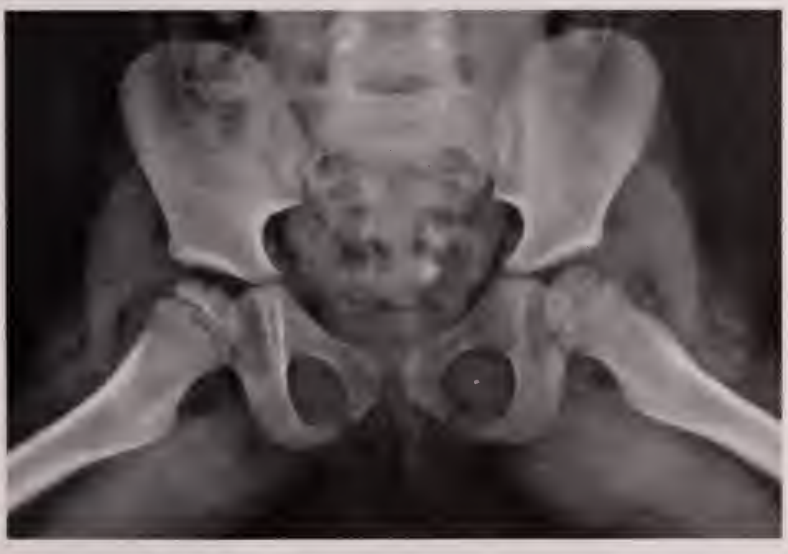
After preparation with antibiotics and parenteral fluids, an attempt was made transpleurally to expose the fistula. This turned out not to be satisfactory and during the course of the operation the child showed considerable respiratory difficulty. Post-operatively, the child did poorly and succumbed within 10 days. Post-mortem examination confirmed the roentgen findings.

Final Diagnosis: TRACHEO-ESOPHAGEAL FISTULA WITHOUT ESOPHAGEAL ATRESIA.

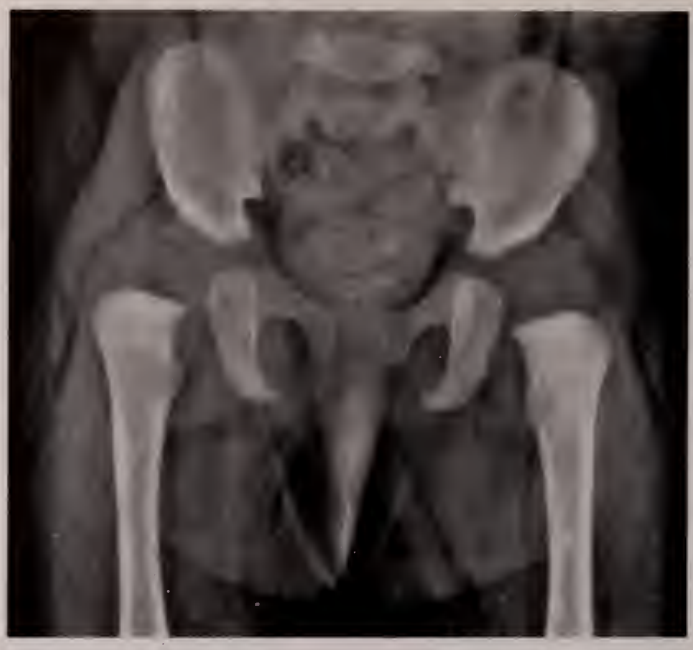
CASE NO. 38

(Submitted by John E. Moseley, M.D.)

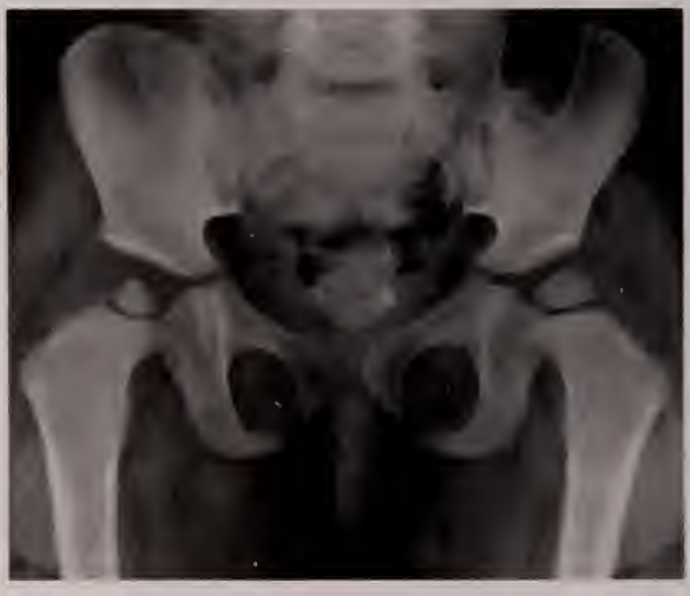
C. R., a 4 year old white female, was referred for x-ray examination of the pelvis and both hips following a minor accident while playing. The clinical examination was reported to have been essentially negative but the roentgen study showed an abnormality of the capital epiphysis of the right femur (Fig. 1). The



CASE 38, FIG. 1. Roentgenogram at age of 4 years shows an abnormal right capital femoral epiphysis suggesting Legg-Perthe's disease. The epiphysis is smaller and less well developed than that on the left side. Its vertical dimension is markedly diminished. Bone density of the epiphysis and its articular surface is irregular. There is no widening of the epiphyseal line or evidence of metaphysitis.



CASE 38, FIG. 2. Original examination made at age 2 months shows acetabular dysplasia and dislocation of the right hip.



CASE 38, FIG. 3. Roentgenogram made at age of 2 years shows hypoplastic right capital femoral epiphysis with irregular mineralization. The dysplasia and dislocation have resolved.

vertical dimension of this epiphysis was diminished and this epiphysis was generally smaller and less well developed than that on the left side. Mineralization was irregular, some areas showing slightly increased density, and there was irregularity of the upper articular surface of the bone. The epiphyseal line was not widened and the position of the epiphysis in relation to the metaphysis was normal. There was no evidence of dislocation or of acetabular dysplasia. The bones of the pelvis and of the left hip were normal. Despite the fact that there were no metaphyseal changes, no widening of the epiphyseal line and no joint effusion, a tentative impression of Legg-Perthe's disease was entertained. A skeletal survey showed no other epiphyseal abnormalities. The patient was negative for sickling and there were no clinical nor laboratory findings to suggest Gaucher's disease.

When the patient returned for follow-up examination, interrogation of the mother revealed that the right hip had been x-rayed on several previous occasions. She was requested to obtain these previous films for comparison (Figs. 2, 3). When the films were examined, they showed dysplasia and congenital dislocation of the right hip.

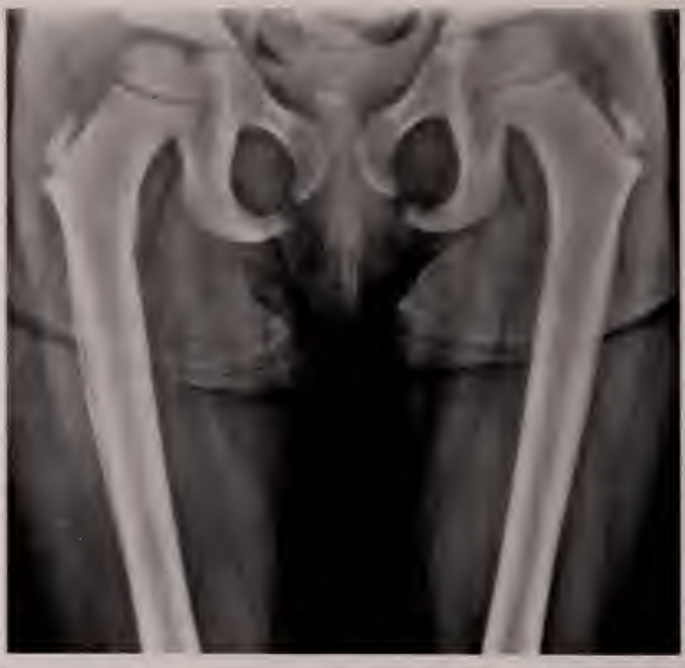
Final Diagnosis: LEGG-PERTHE'S DISEASE SIMULATED BY RETARDED DEVELOPMENT OF THE CAPITAL FEMORAL EPIPHYSIS FOLLOWING CONGENITAL DISLOCATION OF THE HIP.

CASE NO. 39

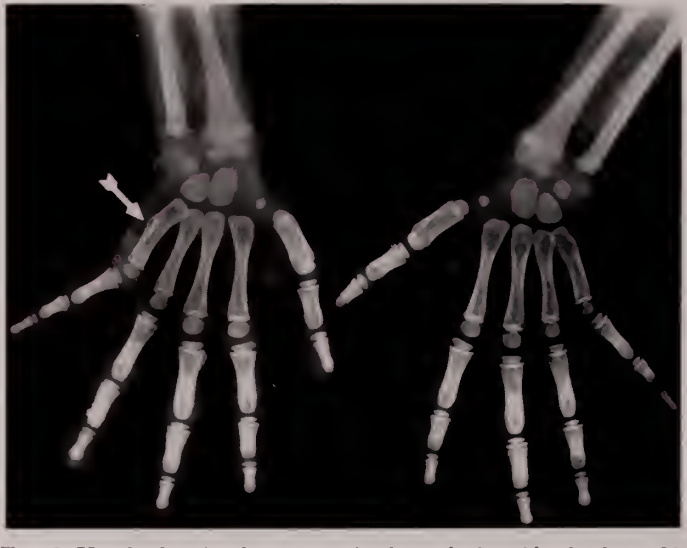
(Submitted by John E. Moseley, M.D.)

V. K., a 3 year old colored female, was admitted to the hospital for observation. She complained of tenderness in both thighs of 4 weeks duration. Her past history revealed an attack of measles two months prior to admission. She had recovered from this without complication. The history was otherwise negative. The physical examination was reported as negative except for marked tenderness on palpation of both upper thighs. The routine laboratory findings were all within normal limits. The temperature fluctuated between 98.2° and 100°. X-ray examination showed single layer periosteal elevation along the lateral aspects of the shafts of both femora (Fig. 1). There was periostitis along the lateral aspect of the shaft of the left fifth metacarpal and along the medial aspect of the shaft of the proximal phalanx of the third left finger (Fig. 2). Both ulnas were the site of a diffuse wavy periostitis. Single layer periosteal reactions were present at numerous ribs and involved both clavicles (Fig. 3). The mandibles were normal.

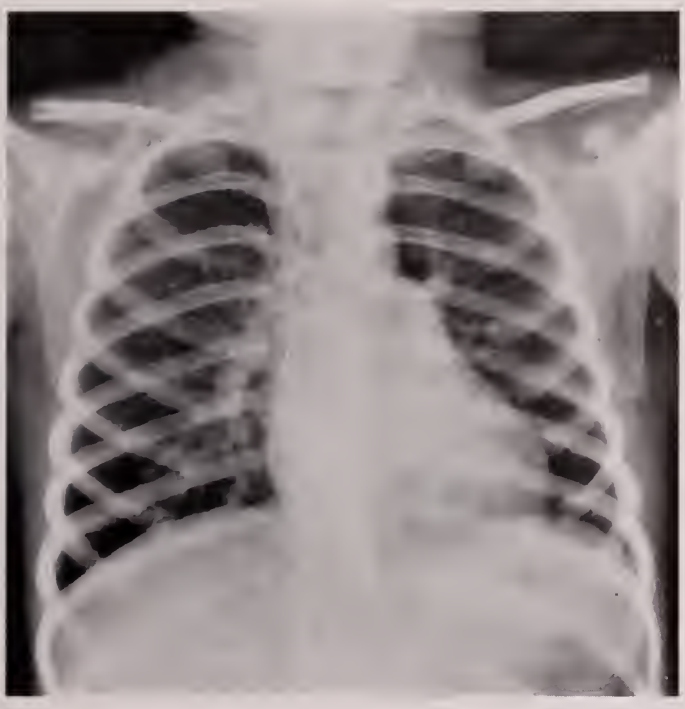
The radiographic differential diagnosis involved primarily Hypervitaminosis A and Caffey's disease. Aside from the cortical hyperostoses, there were no skeletal changes to suggest scurvy, rickets or lues. The involvement of the metacarpals and phalanges and the absence of fractures militated against trauma. The late onset of the condition and the absence of mandibular involvement made Infantile Cortical Hyperostosis (Caffey's disease) unlikely, while the wavy single layered involvement, particularly of the ulnar bones, was strongly suggestive of Hypervitaminosis A.



CASE 39, FIG. 1. Both femora show single layer periostitis on lateral aspects of shafts.



CASE 39, FIG. 2. Hands showing hyperostosis along shafts of both ulnas, fifth left metacarpal (arrow) and proximal phalanx of third left finger.



Case 39, Fig. 3. Chest showing cortical hyperostoses along numerous ribs and both clavicles.

Careful interrogation of the mother uncovered the fact that she had been giving the child excessive doses of oleum percomorphum. Withdrawal of Vitamin A from the diet resulted in the disappearance of all clinical symptoms within one week and skeletal survey two months later revealed marked but incomplete resolution of the bone changes.

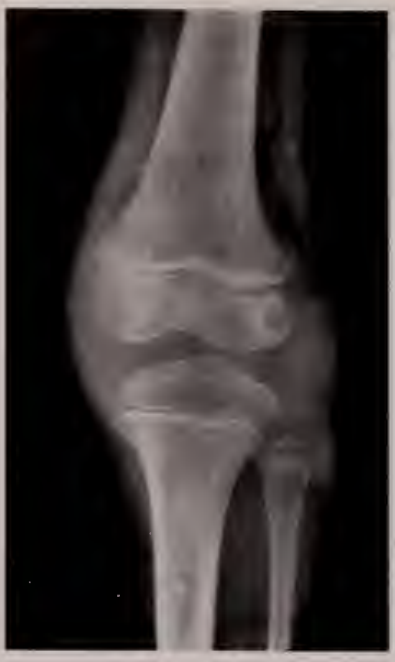
Final Diagnosis: Hypervitaminosis A.

CASE NO. 40

(Submitted by John E. Moseley, M.D.)

S. S., a 6 year old white male was admitted to the hospital because of painful swelling of the right knee. Two weeks prior to admission, the child had started complaining of pain in the knee and was noted to be limping slightly. About one week before admission, he fell on his right knee and thereafter the knee became swollen, tender and painful. One day before admission, the child appeared constitutionally sick, as evidenced by anorexia, malaise and fever.

Examination on admission revealed a temperature of 100.4 and findings limited to the right knee. There was a moderately large effusion into this joint which was tender and partially limited in motion. Laboratory findings: Hgb. 12.4; WBC 8,900 with a slight shift to the left. ESR 83. Urine: negative. X-rays of the right



Case 40, Fig. 1. AP view of right knee showing rounded lucent area of bone destruction with medial sclerotic border in lateral femoral condyle. There is a large collection of fluid within the joint space.

Case 40, Fig. 2. Oblique projection of right knee showing posterior position of area of bone involvement with partial destruction of posterior cortical wall.

knee (Figs. 1, 2) showed a rounded lucent area of bone destruction in the lateral aspect of the distal femoral epiphysis. The medial periphery of the area showed some diffuse reactive sclerosis. The cortex along the posterior aspect of the lesion was considerably demineralized and seemed to be destroyed in some places.

The knee was aspirated and 25 cc of thick, pinkish-yellow fluid obtained. Smear showed 99% polymorphonuclear leucocytes. Culture of the aspirate revealed streptobacillus moniliformis.

The child ran a moderately septic course with spikes as high as 104, then gradually returned to normal under treatment with penicillin and streptomycin. Follow-up x-ray studies before discharge showed some degree of healing evidenced by increased sclerosis about the lesion and beginning restitution of the cortical margin of the bone.

An effort to account for the source of the streptobacillus moniliformis led to the information that mice had often been seen in the patient's apartment building and on his floor. The patient admitted that he and his brother had found a dead rat while on their way to school sometime previous to his illness.

Final Diagnosis: PYOGENIC ARTHRITIC AND OSTEOMYELITIS DUE TO STREPTOBACILLUS MONILIFORMIS.

THE PULMONARY RADIOGRAPHIC CHANGES OF MITRAL DISEASE: MITRAL LUNG DISEASE

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The success of operations on the mitral valve for mitral stenosis has stimulated many new investigations, detailed analyses, and re-evaluations of older concepts. Problems relating to the effect of longstanding mitral disease upon the vascular (3), and respiratory (4) structures of the lung have been frequently discussed in the past.

We have been greatly interested by the frequency, severity and variety of lung changes, in their radiographic appearance, and feel their analysis to be of diagnostic and, possibly, prognostic significance. We also feel that emphasis as to their importance and, particularly, their frequency will stimulate the development of suitable techniques for the appraisal of the pulmonary complications of longstanding mitral disease.

MATERIALS AND METHODS

One hundred and five unselected patients with isolated or predominant mitral valvular disease have been reviewed for this study. All patients were either hospitalized at The Mount Sinai Hospital or were seen in consultation. Although all were ill with symptoms of mitral valvular disease, no effort of selection was made on any other basis. Any concomitant aortic or tricuspid valvular lesions were considered to be minimal and not contributory.

For the purpose of this study our cases were separated into three categories:

1. "Pure" mitral stenosis;
2. Combined mitral stenosis and insufficiency;
3. "Pure" mitral insufficiency.

Of the one hundred and five cases the diagnosis was confirmed in 68 either at surgery* or by post-mortem examination. The remaining patients were classified on the basis of clinical appraisal. In addition, right-sided cardiac catheterization was performed in 43 patients. In most patients operated upon, lung biopsies were obtained from two sites, the lingula and the left lower lobe. Three cases of aortic valvular disease were analyzed for one point of the discussion.

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* Most patients who underwent surgery in this series were operated on by Dr. Mark M. Ravitch; others by Drs. Robert Nabatoff and Irving A. Sarot. The cardiac catheterizations were performed by the Cardiac Catheterization Team under the direction of Dr. Alvin J. Gordon. Their cooperation in our studies is acknowledged with pleasure.

Method of Analysis

Pulmonary roentgenograms were analyzed with particular reference to the following findings:

1. A diffuse granular mottled appearance which gave rise to an increased background density of the lung fields; this will be referred to as "diffuse granular pattern".
2. Lines B of Kerley; referred to as "septal lines".
3. Nodular calcification and ossification.
4. Hemosiderosis.

RESULTS

Group I. "Pure" mitral stenosis; mitral stenosis without mitral insufficiency

This group was composed of 71 cases: confirmation was made at operation or post-mortem in 46. The diffuse granular pattern was seen 46 times. It was best seen bilaterally, extending to the peripheral lung fields and somewhat more prominent in the lower half. It produced a mottled appearance of the lung fields with a loss of the normal radiolucency of the lung to a varying degree. In 26 cases, the lines B of Kerley, or septal lines, were observed. Nodular calcification or ossification was seen in 10 and hemosiderosis in 9 (Table I).

Group II. Mitral stenosis in combination with varying degrees of mitral insufficiency (mild to moderate)

This group consisted of 23 patients in whom the diagnosis was confirmed fourteen times either by post-mortem examination or surgical exploration.

The diffuse granular pattern was seen in 17 cases and septal lines (Kerley) in 11, nodular ossification in 5 and hemosiderosis in 6 (Table I).

Group III. "Pure" mitral insufficiency; mitral insufficiency without mitral stenosis of significance

Eleven patients were in this group; the diagnosis was confirmed in three on post-mortem examination. All patients were "symptomatic", most of them in an advanced state of decompensation. None of the cases in this group demonstrated either a diffuse granular pattern, septal lines (Kerley), nodular ossification or hemosiderosis.

Three cases of rheumatic valvular disease of the aorta without associated

TABLE I

Roentgenographic findings in 105 unselected cases of mitral disease

	Number of cases	Diffuse granular pattern	Kerley lines	Nodular ossification, calcification	Hemosiderosis
"Pure" Mitral Stenosis	71	46	26	10	9
Mitral Stenosis and Insufficiency	23	17	11	5	6
"Pure" Mitral Insufficiency	11	0	0	0	0

mitral disease, calcified aortic stenosis in two (with post-mortem confirmation), and aortic insufficiency in one, have been seen who showed discrete but distinct septal lines of Kerley.

Summary of Results

The combined group of 94 cases of "pure" mitral stenosis and mitral stenosis in association with mild to moderate mitral insufficiency showed:

Diffuse granular pattern	63 (59%)*
Septal lines of Kerley	37 (34%)
Nodular ossification	15 (14%)
Hemosiderosis	15 (14%)

CORRELATIVE STUDIES

Because of the nature of the selection of cases in this series, which includes only patients with significant clinical symptoms, a correlative study between the severity of the clinical symptoms and the radiographic appearance of the lung fields was not made. None of our patients with mitral stenosis alone or mitral stenosis in association with varying degrees of mitral insufficiency ever showed normal pulmonary parenchyma. The diffuse granular pattern was observed associated with both normal as well as greatly elevated resting pulmonary artery pressures. The presence of septal lines (Kerley) was associated with elevated pulmonary artery and "pulmonary capillary" pressures in every instance in which cardiac catheterization had been performed, with the resting pulmonary artery pressure ranging from 60 to 150 mm Hg. The "pulmonary capillary" pressure was found to be between 20 to 25 mm Hg. in three of these with the remainder well above 25 mm Hg. In the cases with hemosiderosis the lowest systolic resting pulmonary artery pressure was 45 mm with the "pulmonary capillary" pressures above 25 mm Hg. Nodular ossification was found associated with low as well as high resting pulmonary arterial and/or "pulmonary capillary" pressure.

The diffuse granular pattern was present in patients with mild as well as severe clinical symptoms. Conversely, some severely ill patients failed to show this roentgen pattern. Septal lines (Kerley) were generally associated with advanced symptoms. Hemosiderosis was frequently but not consistently associated with a history of hemoptysis.

A significant number of patients with the diffuse granular pattern also showed septal lines. However, some cases with septal lines were not associated with the diffuse granular pattern. Nodular ossification and hemosiderosis were seen in the same case only occasionally. In five cases all four abnormalities were seen concomitantly, all being far advanced.

Although the eleven cases of "pure" mitral insufficiency were "symptomatic", aside from an increased prominence of the pulmonary arterial vasculature and

* These percentages are not meant to imply a statistically valid analysis but merely to illustrate the tendency of distribution.

occasional pulmonary edema, the diffuse granular pattern, septal lines (Kerley), nodular ossification and hemosiderosis were not seen.

THE RADIOGRAPHIC APPEARANCE OF THE PULMONARY CHANGES

The diffuse granular pattern which gives the fine mottled appearance and increased density to the lungs in the majority of cases of mitral stenosis (with or without mitral insufficiency) is produced by interstitial induration (2, 8, 18, 21, 22, 24, 28, 30, 31). Its differentiation from the vascular structures seem to offer few difficulties to the experienced observer. Although similarity between these two has occasionally been reported, angiocardiographic analysis has proven the non-vascular nature of the diffuse granular pattern beyond doubt (9). Its precise delineation from hemosiderosis is more difficult, perhaps not actually warranted in severe forms of the former and mild instances of the latter.

Although identical pathological changes of the pulmonary arteries and arterioles have been reported in mitral stenosis as well as mitral insufficiency, it has also been noted that interstitial fibrotic changes were not seen in mitral insufficiency (19). This conforms exactly with our observations of the lung in cases of "pure" or "essentially pure" cases of mitral insufficiency: the diffuse granular pattern, septal lines, nodular ossification and hemosiderosis are not seen in "pure" mitral insufficiency. Although atrial mean pressures in mitral insufficiency are similar to those found in mitral stenosis, the stimulus to interstitial pulmonary induration appears to be lacking. We have no ready explanation for this. Probably, the shorter duration of mitral insufficiency in its more severe form, and the rapid downhill course once left ventricular failure has occurred, may be significant factors. Vascular abnormalities and pulmonary edema as the result of left ventricular and left atrial failure are regarded as changes apart, and not as pulmonary parenchymal changes per se.

The septal lines B of Kerley (1, 10, 18, 33) are frequently seen in mitral stenosis and are in our opinion of considerable diagnostic importance. The linear shadows as seen radiographically are 0.5 to 1.5 mm in breadth and 5 to 15 mm in length. The margins are usually sharp and of relatively constant width, occasionally being slightly broader in the middle. Uncommonly, they are slightly heavier, somewhat more fuzzy in outline, often diminishing or disappearing if beneficial clinical results are obtained from surgical or medical treatment. They have a definite predeliction for the lung bases and are usually seen at the extreme periphery of the lung perpendicular to the pleura, i.e., they are almost parallel to each other. Their differentiation from blood vessels in the periphery shows them to be continuous with more central vascular structures and without tapering configuration. Focal and linear atelectasis offer no problem in differentiation as neither will show the thin line, regular shape, and peripheral parallel arrangement of the septal lines of Kerley. With practice, they can be easily identified (Figures 1–3).

When lung slices are examined by the technique of Goff and Wentworth, it is readily apparent that these lines correspond in size and distribution to the interlobular septa. Fleischner and Riener (18) have reported two cases of mitral

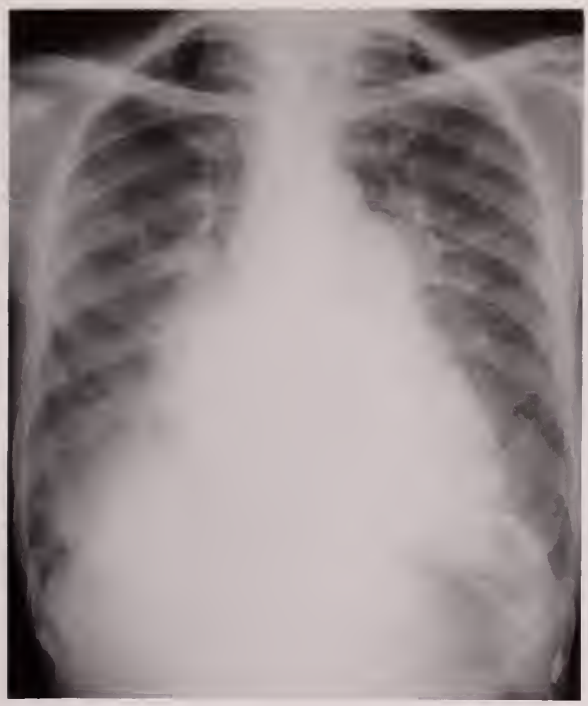

FIG. 1. Advanced mitral stenosis. Marked enlargement of the heart to the left, which is probably entirely due to right ventricular enlargement. Marked prominence of main pulmonary artery and secondary branches. Increased interstitial markings. Numerous parallel horizontal lines in right lower lung field. The Kerley lines were a constant finding, and therefore not due to transient septal edema.

stenosis with Kerley lines in which hemosiderosis was found in one instance and interlobular septal edema was regarded as responsible in the other. Although not histologically established, three stages of development may be assumed: (a) interlobular septal edema, if not relieved or of longstanding, giving way to (b) fibrosis, which in the course of time may be further altered by (c) hemosiderotic deposits. In our experience they are only occasionally of transient nature, i.e., giving way to otherwise successful surgical or medical management. Most often they are unaltered in appearance or number, even when most excellent therapeutic results are achieved.

It has been suggested that Kerley lines may appear radiographically when the pulmonary artery wedge pressure is greater than 30 mm Hg and will then exceed the normal plasma osmotic pressure (1). Although it is appreciated that this will affect pulmonary parenchymal lymph flow and pressure, precise knowledge of the relationship is wanting. The fact that we have observed instances in which pulmonary artery "wedge" pressure was below 25 mm Hg under essentially basal conditions does not preclude significantly higher level during effort and other non-basal states.

As stated above, Kerley lines may occasionally vary in number, size, or dis-

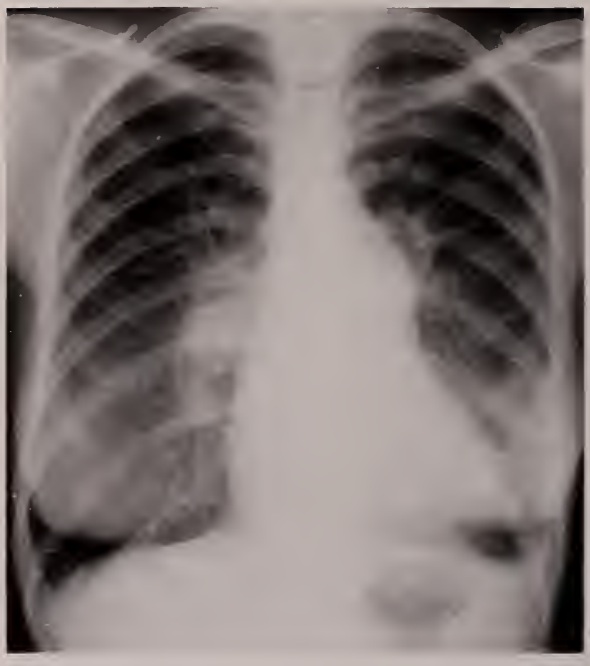

FIG. 2A. The patient has severe mitral stenosis. Pulmonary artery pressure 150 mm Hg. The pulmonary artery is markedly dilated as are the proximal secondary branches. The concavity between the pulmonary artery and lower left cardiac contour is due to the surgical removal of the left atrial appendage. Numerous parallel septal lines are seen in right lower lung field.

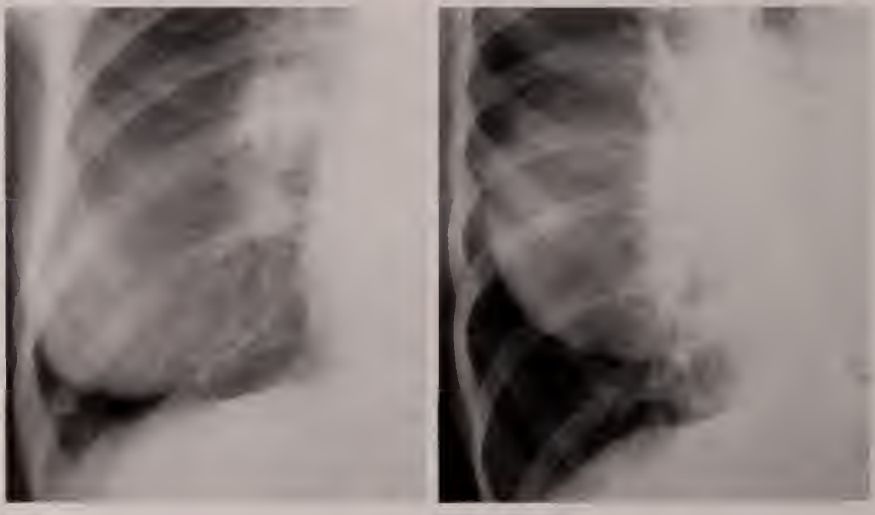

FIG. 2B. Same patient as in Figure 2A. The illustration on the left represents a higher magnification of the posterior-anterior view, showing the Kerley lines well. The illustration to the right shows the same section in a slight right anterior oblique. Often, the Kerley lines are seen to better advantage in moderately oblique views.

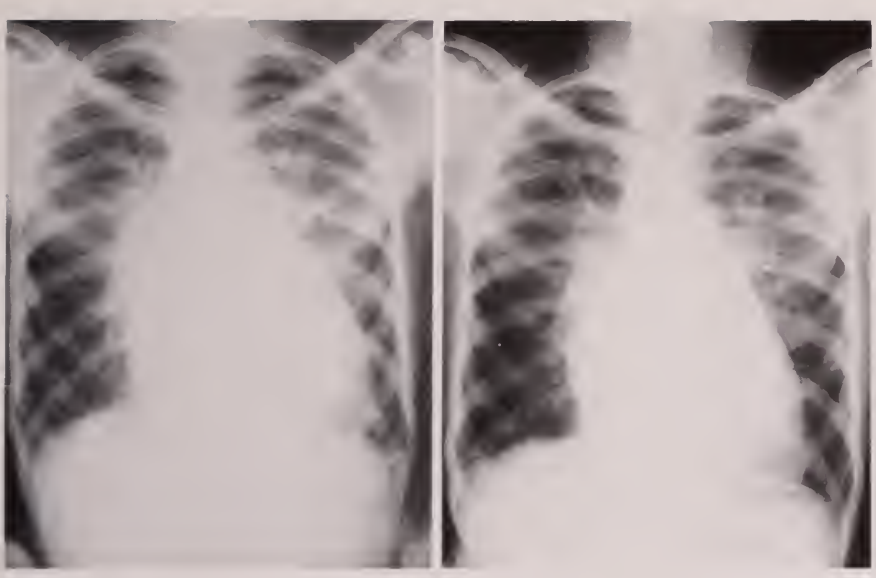

FIG. 3A. Severe, pure mitral stenosis with acute pulmonary edema in the illustration to the left and after medical therapy had been instituted to the right. Aside from hilar congestion and some pulmonary edema, broad Kerley lines are seen in the right lower lung field. Their outline is somewhat fuzzy. In the illustration to the right, the number of Kerley lines is fewer, their width has considerably diminished and their outline is more sharply defined. The Kerley lines, as shown on the right, remained thereafter. One can assume that septal thickening, as seen on the right, was associated with septal edema during the acute congestive period.

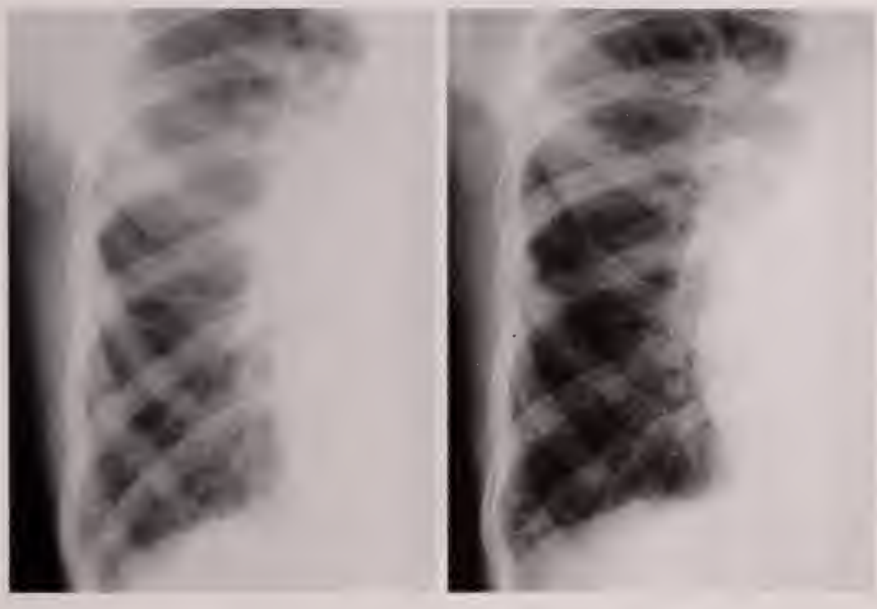

FIG. 3B. Same patient as in Figure 3A. Right lower lung field at higher magnification.

appear altogether. Usually, they are a permanent finding. Carmichael and his associates (1) noted Kerley lines in mitral stenosis as well as in mitral insufficiency; none of our cases of "pure" or predominant mitral insufficiency exhibited any.

The dynamic conditions suitable for the production of Kerley lines are apparently rarely reached in cardiac conditions other than mitral stenosis. We have not seen them in congestive heart failure from either coronary artery or hypertensive heart disease. We have seen one exception in an instance of idiopathic hypertrophy with very far advanced heart failure. They were poorly defined and few in number. Other exceptions showing septal lines of Kerley were occasionally encountered in aortic valvular disease of rheumatic origin with failure. One of these with calcified aortic stenosis of severe degree and incipient, as yet untreated, heart failure (paroxysmal nocturnal dyspnea only) showed a large number of Kerley lines, which readily disappeared under appropriate treatment (Figure 4). The patient succumbed to heart failure three months later. In the second patient with an extensively calcified aortic stenosis, a very few discrete Kerley lines were seen during a period of severe pulmonary congestion shortly before patient died. Another patient with severe aortic insufficiency and incipient congestive heart failure showed a few discrete Kerley lines bilaterally, which, incidentally, remained unaffected by therapeutic measures. None of these cases had any demonstrable mitral disease; by clinical evaluation in the first and third cases and by post-mortem examination in the second. The very fact that these cited exceptions have been observed underlines the diagnostic significance of Kerley lines for the presence of advanced mitral stenosis, by degree as well

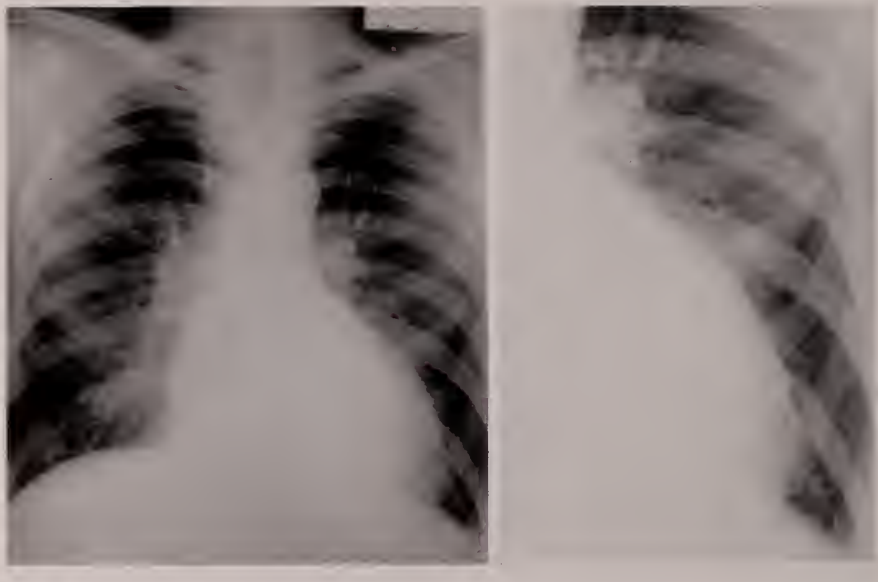

FIG. 4. Calcareous aortic stenosis. With the appearance of pulmonary edema, numerous Kerley lines were seen in both lower lung fields, particularly well in the left lower lung field.

as clinical cause. It furthermore should be limited to differential diagnostic considerations of cardiac diseases alone.

Until recently, pulmonary hemosiderosis has been thought to be rare (2, 8, 18, 21, 22, 24, 28, 30, 31). It may be found in association with mitral stenosis and only very occasionally in advanced longstanding congestive heart failure. Without association of any primary heart disease (secondary pulmonary hypertension has been recorded in one observed instance by us), it may occur in children as a disease entity of unknown etiology. Esposito (24) in a recent review of 100 autopsied cases of rheumatic heart disease, including all varieties of valvular involvement, found a 5 per cent incidence of hemosiderosis by radiographic examination, as contrasted with a 28 per cent incidence by post-mortem examination. Of the latter, all but four had mitral stenosis, and all five cases with radiographic evidence had mitral stenosis. This discrepancy between the incidence on radiographic and on pathological examination had been commented upon previously. Although collections of hemosiderin-laden macrophages occur in pulmonary congestion, regardless of etiology, their appearance is more discrete and their distribution diffuse. In cases of mitral stenosis, hemosiderotic changes are seen either grossly or microscopically in distinct nodular arrangement. Hemosiderin gives the appearance of being packed into the alveolar spaces, frequently with a fibrotic reaction in the adjoining alveolar spaces. The alveoli in the surrounding parenchyma are often uninvolved, and there may be no pathological evidence of chronic passive congestion. Hemosiderotic nodules smaller than one

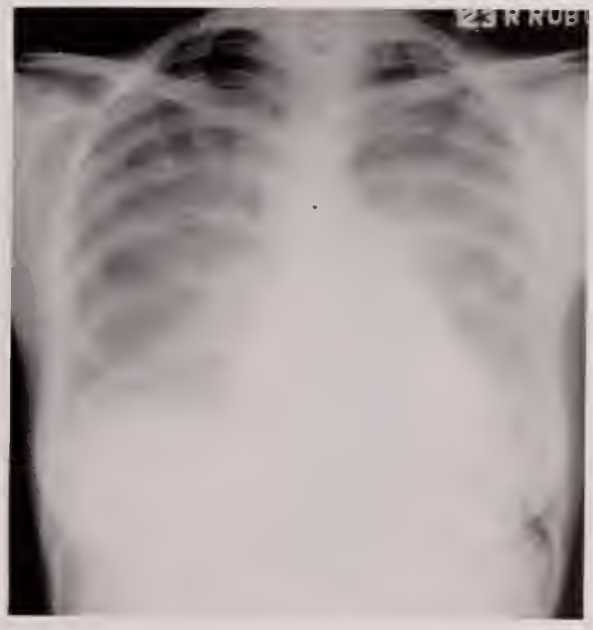

FIG. 5. Mitral stenosis, associated with mild mitral insufficiency. Marked increase of background density in both lung fields, with a distinct tendency to conglomeration. This form of rather diffuse hemosiderotic deposits throughout both lung fields is uncommon.

mm are usually not visible radiographically. The distinct nodular character will be noted when their diameter measures two to three mm or more (Figure 5). However, correlation between size of nodule and radiographic visibility depends on many variables, including roentgenographic technique and equipment, overlapping and superimposition of shadows.

Association of hemosiderosis with frequent episodes of hemoptysis has often been described, but such a history is not obtained in all cases. It is generally considered that repeated intrapulmonary hemorrhages constitute the pathogenetic basis of nodular hemosiderosis. Strassman (30) has shown that although erythrocytes introduced into the alveoli are usually removed by macrophages within 24 hours, their removal is delayed in the presence of pulmonary edema. Intra-pulmonary hemorrhages with accompanying venous congestion may interfere with the lymphatic drainage of phagocytosed erythrocytes, as proposed by Gumpert (21).

Nodular hemosiderosis usually occurs in advanced mitral stenosis, but in itself its prognostic significance should not be considered a contraindication to mitral surgery. In our series, hemosiderosis did not occur in any of the cases of pure mitral insufficiency. With evidence of mitral stenosis, apparent nodular hemosiderosis will rarely present difficulties in its differentiation from miliary tuberculosis, histoplasmosis, sarcoidosis and the pneumoconioses.

Nodular ossification in the lungs in association with mitral stenosis has previously been reported by one of us (11) with emphasis on its radiographic appearance, pathogenesis, histological appearance and clinical significance. Its association with mitral stenosis was first described by Salinger (29) in 1932. It is seen

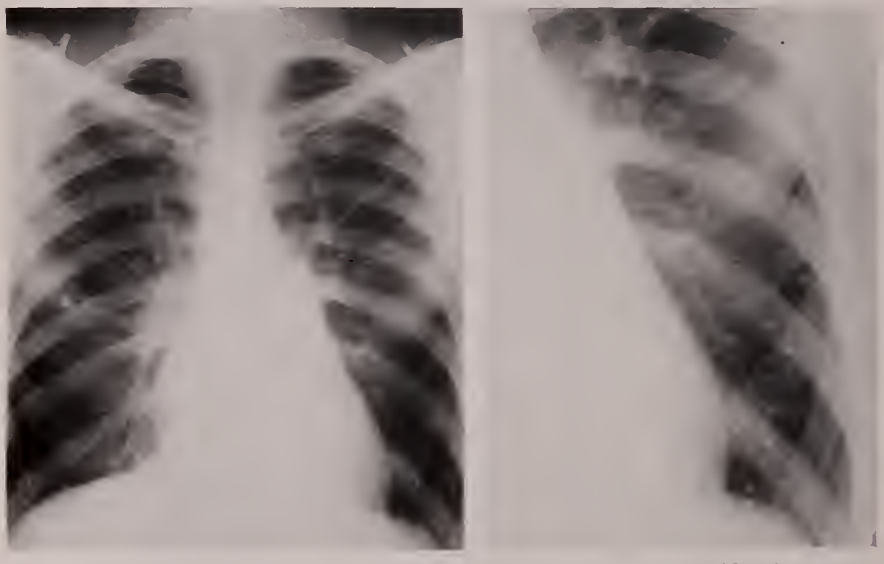

FIG. 6. Pure mitral stenosis of severe degree. Numerous nodular ossifications are seen in both lower lung fields. The illustration to the right shows the left lower lung field at a higher magnification. The variability of size and contour of the nodular ossifications is well shown.

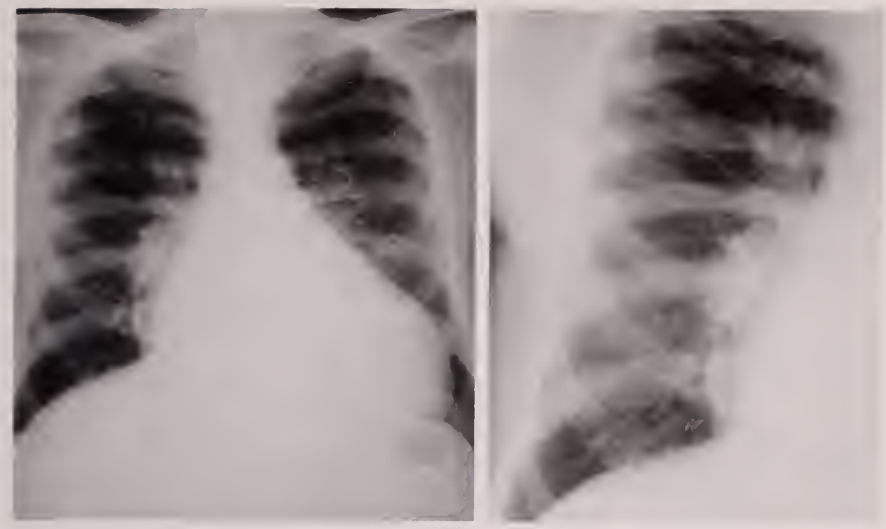

FIG. 7. Pure mitral insufficiency with advanced congestive heart failure. Note the absence of interstitial parenchymal infiltrates. Only the vascular structures are prominently seen.

bilaterally (Figure 6), with a basal distribution, having a rounded appearance of great density (11, 25, 26, 29). Histologically, the nodules consist of bony tissue, although early lesions have been seen with only central calcification. They most likely represent the end-result of an absorptive process of alveolar exudates or infiltrates. They have been observed in patients prior to the appearance of clinical congestive heart failure and even in some asymptomatic patients. The incidence of almost 15 per cent in our series indicates that this is not at all an infrequent finding. The observation that the resting pulmonary artery and wedge pressures may not be elevated appreciably in some cases, correlates with the finding that the presence of nodular ossifications may not always be directly correlated with the severity of the disease. Again, as with the diffuse granular pattern, Kerley lines, and hemosiderosis, nodular ossifications were not seen in "pure" mitral insufficiency (Figure 7). For that matter, they have never been observed in any other heart disease but mitral stenosis (without or with mild to moderate mitral insufficiency).

DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS

When the observer is obliged to analyze a chest roentgenogram without prior knowledge of the presence of valvular disease, or when the latter's existence does not become apparent from the cardiac silhouette, the differential diagnosis of mitral lung lesions may at times be quite difficult. Since, however, such an unsuspecting approach will only be practiced as an intellectual exercise and not in clinical practice, the problem will have shrunk to a minimum.

Interlobular septal lines may be seen in other diseases not involving the heart, as in lymphangitic carcinomatosis, Boeck's sarcoid, silicosis, anthracosis. We

have seen such a roentgenographic appearance in one case of Sickle cell disease (unpublished data). Still, in association with heart disease, they have only been seen distinctly with mitral stenosis and very occasionally with aortic valvular disease.

SUMMARY

The pulmonary roentgenographic findings in 105 unselected cases of mitral disease have been analyzed. All patients when seen were symptomatic. Furthermore, three patients with aortic valvular disease of rheumatic origin have also been reviewed, because of certain findings pertinent to this study.

The patients with mitral disease consisted of 71 cases of "pure" mitral stenosis, 23 cases with mitral stenosis and mild to moderate mitral insufficiency and 11 cases of "pure" mitral insufficiency.

Four varieties of pulmonary roentgenographic abnormalities were encountered: (a) a diffuse granular pattern; (b) interlobular septal lines B of Kerley; (c) nodular ossification and (d) hemosiderosis.

The cases with mitral stenosis with or without some mitral insufficiency, showed:

Diffuse granular pattern in about 60 per cent;

Septal lines in about 35 per cent;

Nodular ossification and hemosiderosis in about 15 per cent each.

None of these cases of mitral stenosis, with or without mitral insufficiency, was free of all radiographically demonstrable pulmonary abnormality. None of these pulmonary changes were seen in any of the cases of "pure" mitral insufficiency.

The fact that septal lines (Kerley) have been seen, although as an exception, in aortic valvular disease, has been mentioned.

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THE CONCEPT OF EXOCRINE SECRETION OF ELECTROLYTES AS VIEWED BY A GASTROINTESTINAL PHYSIOLOGIST[1]

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As a student, I was greatly intrigued by the ability of the body to produce a strong inorganic acid like HCl at concentrations of 0.1 N and higher. I felt confident that this synthesis must rest on a physico-chemical foundation—probably very simple in its essence, but certainly one which might be investigated with much profit and pleasure by means of the precise concepts and methods of the physical chemists. Subsequently, I learned that the pancreas can produce bicarbonate in equally high concentrations, and that the salivary glands and the kidneys also produce fluids with unusual and not easily explained electrolyte patterns. In this way, I was led to wonder about exocrine secretions in general, and about the intracellular mechanisms by which these highly specialized fluids are produced, and whether these various exocrine electrolyte processes function according to certain common designs. There exists today a strong tendency among investigators in this broad area to formulate working hypotheses and to design their experiments in accordance with some generalized pattern. I am mindful of one of my erstwhile associates who immigrated to our laboratory from a group in which acid formation in the kidney was the current problem, and who set out to convince me by our own experiments of the essential similarity of renal and gastric acid formation. It is generalized thinking of this kind which has led me to entitle my presentation "The Concept of Exocrine Secretion".

Gastrointestinal physiologists apply the term "exocrine" to all the electrolyte, enzyme, and mucous secretions of the alimentary canal. Except for bile salts, the discharge of most other organic substances into the lumen of this tract is considered as excretory, and the mechanics of such excretions are not usually thought of in the present context. Included in the general category of exocrine secretions, we find also various fluids formed by other organs, including the renal tubule, the sweat glands, and sometimes also the frog skin. This is in keeping with the definitions given by the New Gould Medical Dictionary: a *secretion*, in general, is defined as "a certain substance [formed] from materials furnished by the blood" and "is either eliminated from the body (excretion) or used in carrying on special functions". Then, an *exocrine secretion* is one which is delivered "to an epithelial surface, either directly or by means of ducts", in contradistinction to an *endocrine secretion*, which moves internally or into the blood stream. At this point, it is interesting to recall the current notion that the zymogen cells of the stomach and pancreas are both exocrine and endocrine, and the evidence reported by

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[1] This paper is an abridgment of an address to the gastrointestinal group at the annual meeting of the Federation of American Societies for Experimental Biology, Atlantic City, New Jersey, April 18, 1956.

Dr. Henry Janowitz and myself that intracellular pepsinogen appears to be secreted in two directions simultaneously in accordance with a coefficient of exocrine-endocrine partition which is fairly uniform under *fixed* physiological conditions and independent of the rate of secretion. In spite of this dual role of at least two of the enzyme-forming glands, the meaning of exocrine secretion is unequivocal, and applies equally well regardless of whether the secretion be merocrine, as in the case of the parietal cells; holocrine, as in the case of the sebaceous glands; or apocrine, as in the mammary glands.

Thus, exocrine secretions are characterized predominantly by their being delivered at epithelial surfaces. But what of the mechanisms by which different exocrine cells effect their specific syntheses? Dare we expect that different glands of electrolyte secretion, from different organs, possess essentially the same mechanisms of formation? Obviously, the chemical processes for generating zymogen and mucous secretions must be different from those for the electrolyte secretions, even though the former may contain inorganic solutes along with organic substances. On the other hand, Dr. Earl Thomas has presented the thought that the HCl-forming cell of the stomach and the bicarbonate-forming cell of the pancreas may operate in the same way but with reversed polarity, because the parietal cell ejects bicarbonate into the interstitial spaces as a by-product of HCl formation, and the pancreatic cell ejects HCl, though in neutralized form, as a by-product of its bicarbonate secretion. Other gastrointestinal physiologists treat the entire epithelial layer of the stomach as a unitary agent responsible for the process of gastric secretion of all the electrolytes, much as the renal physiologists do with the tubular epithelium and the general physiologists do with the frog skin membrane. This search for unity has come about very naturally, because of the ease of transition from dealing with the "mucous membrane" as a convenient *morphological expression*, to using it as a single *physiological entity*, analogous to membranes employed in studying purely physico-chemical phenomena.

How valid for the purposes of hypothesis formulation is this treatment of the "mucous membrane" as a unitary structure, and the concept of exocrine secretion as a unified process? These questions were uppermost in my mind when I first started to study gastric HCl formation, and subsequent extensions of my inquiries to mucus and pancreatic secretion were in great measure extensions of my concern with these more general questions. As a result, I have been able to form for myself, at least, a clear view about the inadequacy of such unitary treatments of the gastric mucosa and the liquid we call gastric juice; and I propose now to take you over the course of the investigations which have brought me to this conclusion.

The literature of gastric secretory physiology prior to 1925 gave few indications of efforts to formulate research objectives in precise quantitative terms, and to employ experimental procedures consonant with the demands of a physicochemical attack. The chief tools which I found available to me were first and foremost, the isolated stomach pouch technique for the continuous collection of "pure" gastric juice; and, *secondly*, histamine and food as very potent stimuli

for evoking gastric secretory activity. Starting with these tools, but with no preconceived hypothesis, Dr. Cowgill and I set out to repeat an exceedingly simple experiment which had been done by many investigators before us. This consisted of suspending a Pavlov pouch dog in a stand, with a funnel-shaped device for collecting the secretion as it dripped out of the pouch, collecting the basal secretion for two to four quarter-hour periods, injecting histamine at moderate dosage, and collecting successive quarter-hour samples thereafter. On these specimens we measured the rate of secretion as volume per 15-minute sample, and free and total acidities.

I hope you will forgive this narration of elementary procedural details; I state them in order to define clearly certain changes which I subsequently found to be necessary and still consider of great importance. Actually, it required only a few such experiments to demonstrate their weaknesses.

In the first place, the pouch mouths were surrounded by extensive excavations of eroded skin and subcutaneous tissues—a difficulty which we shared with most other workers. This condition resulted not only in great discomfort to the animal, but in considerable contamination of the specimens because of the funnel shape of the juice collectors. Some investigators were using metal or hard rubber cannulae in place of such a natural stoma, but this device would also stimulate mucus secretion, traumatize the mucosa and contaminate the specimen with exudate. Consequently, we continued to use the natural stoma, but introduced the following changes in technique. Each pouch mouth was made small, and in such a way as to provide a rosette of extruding mucosa on the abdominal surface. Then, in order to minimize the opportunity for erosion of the skin, the animals were dressed twice and sometimes three times a day, using a more efficient type of dressing than before; also the nocturnal secretion was reduced to a minimum by allowing the dogs to feed only during the morning hours. Sometimes the mucosal rosette retracted, leaving a simple small opening through the skin. In any case, skin erosion was eliminated, practically entirely.

In addition to these surgical and post-operative procedures, I devised a more efficient type of collecting device, whereby quantitative collections of secretion were virtually assured, and even traces of external contaminants were excluded. This contraption is still in use in our laboratory without any essential change.

A second change, this time in analytical technique, also had to be made, though this was not done until later. In place of electrometric pH determinations, a suitable semi-micro acid-titration technique, reliable to about 1 per cent, had to be devised, because the titrimetric method is more sensitive in the free acidity range than is the pH method, and because important specimens were often very small and the determination of other ions as well as acidity was anticipated. Free and total acidities were defined in terms of precise pH end-points: 3.5 for free acidity, because it corresponds to an HCl concentration of less than 1 meq/L, and 7.0 for total acidity, because it is the neutral point of pure water. To insure these end-points precisely, pairs of buffer standards, 0.1 of a unit above and below each limiting pH, were used, with brom-phenol blue and phenol red as indicators.

One other serious defect in the experimental design must be mentioned. This derived from an error in the volume-rate of secretion data, resulting from persistence of and variations in basal (i.e., unstimulated) secretion of HCl throughout the experiment. This error was never remedied until recently, when we found that the basal secretion of a fasting dog can be eliminated completely by means of an adequate resection of the antrum.

With these several improvements in effect, we set out to study the relation between the acidity of pure gastric juice and its volume-rate of secretion. Using this *continuous collection procedure* and food as stimulus, we observed a good correlation between pH and flow-rate, expressed as the volume of each 15-minute sample. Results following a subcutaneous injection of histamine were essentially the same, when the dosage was around 0.05 mg/kg body weight.

What do such experiments tell us about the nature of the parietal secretion and how it is made? Evidently, they are wholly in accord with the theory which Rosemann proposed in 1907, namely, that the concentration of HCl in this primary secretion varies with the rate of its cellular formation. This theory has led many investigators to the corollary, that the original parietal secretion contains a neutral chloride—organic or inorganic—which subsequent to leaving the cell, undergoes hydrolysis with reabsorption of the non-acid product. Modern counterparts of this premise, from the laboratories of Conway in Dublin, the Scandinavian schools, and some of our American colleagues, are expressed in terms of ion-transport and -exchange processes.

But this wasn't the only possible interpretation of such experiments. In 1910 (or probably before), Pavlov claimed "that the gastric juice as it flows from the glands possesses a *constant acidity.*" This generalization was essentially hypothetical, as indicated by his further statement that "It is a rule almost without exception, that the acidity of the juice is closely dependent upon the rate of secretion; the more rapid the latter, the more acid the juice and vice versa." Quantitative evidence to support this concept of constant acidity was not given, except for the additional comment that "if the stomach had been washed, so to speak, in this manner several times in succession" [in order to remove acid-neutralizing mucus by discarding the portions of the juice first to flow over the mucus-covered surface] "not infrequently all connection between rate of secretion and degree of acidity can be removed." Such a constant acidity theory had been formulated in 1883 by Heidenhain, but the supporting evidence at that time also derived only from some casually collected specimens of dog juice. A survey of the physiological literature up to 1930 revealed many proponents of both the Rosemann and the Heidenhain-Pavlov theories, but no conclusive evidence to resolve the conflict between them. It was this lack that determined my subsequent experiments.

Let us first examine the correlation between acidity and rate. A repetition of the earlier food and histamine experiments, using the micro-titration instead of the pH technique, yielded the same kind of qualitative parallelism of acidity and rate curves as before, except for this: When we compared the two acidity values corresponding to a pair of identical rate-values at the beginning and end

of these curves, we found a considerable discrepancy. For example, in an illustrative experiment, the acidity near the beginning of the experiment was about 70 meq/L, whereas its paired value at the end was about 135 meq/L—almost twice as large. Even this graphic method of analysis, crude as it may be, indicated that all was not well with the Rosemann theory.

Returning to Pavlov, it was evident that if the hypothetical primary acidity is constant, and the variations observed in pouch juice result from admixture of mucus, then one must strive to eliminate this and other acid-neutralizing fluids during the course of each experiment. This called for the following changes in experimental design: First, the dogs must have been dressed with special care for days prior to the experiment, so as to insure the absence of inflammatory exudate and blood. Secondly, the collecting catheter must be as narrow and smooth as possible, to reduce stimulation of mucus by rubbing. Thirdly, histamine must be used at tolerable dosage, in order to get a vigorous flow of juice to lubricate the surface between catheter and mucosa, and so reduce mechanical stimulation of the mucus cells still further. And finally, the first one or two 15-minute specimens ought to be discarded because of contamination of mucus normally accumulated on the mucosal surface. With these special precautions, the results entirely justified the efforts. With a histamine dosage around 0.15 mg of base/kg body weight, the rate curve rose to a maximum in the third or fourth quarter-hour, usually, and then fell off slowing to practically zero by the end of 2.5 hours. The acidity curve, on the contrary, rose to a high maximum value in the third quarter-hour and remained constant for seven such specimens—$1\frac{3}{4}$ hours duration—while the rate was falling off. Here, for the first time was decisive evidence; not only is the acidity of pure gastric secretion basically independent of the rate, but it can be surprisingly constant when precautions are taken to minimize its content of mucus and other non-acid fluids. Each of eight such histamine experiments yielded a constancy of ± 0.01 of a pH unit, and for all eight the level was 0.91 ± 0.02—corresponding to a titrimetric free acidity around 151 meq/L.

Does such constancy obtain also when food is used as a stimulus? It was never possible to demonstrate this by *continuous collection* experiments like those with histamine, because the rate of secretion with food was never high enough to give adequate lubrication to the surface between catheter and mucosa. Also, the motility of the Pavlov pouch may increase following a meat meal, and this would augment mucus output by rubbing of mucosa against mucosa as well as against the catheter. To meet this contingency, Dr. Cowgill and I devised a new kind of collection technique. This procedure depended upon delivering the neck of the pouch at surgery between the split abdominal muscles, in such a way as to develop sphincteric action at the stoma. When such a dog was left in its cage post-prandially, the secretion was retained in the pouch until it was withdrawn by gentle aspiration through a fine catheter, or until the pouch pressure became great enough to force the sphincter to permit escape of the fluid into the dressing. Thus, post-prandial secretion could be collected intermittently with absence of the catheter during the period of accumulation. It seems likely,

also, that distention of the pouch by the retained fluid prevented the rubbing of mucosal surfaces against each other and thus the augmentation of mucus secretion by such mechanical stimulation.

In each experiment by this *discontinuous or retained juice technique* the first portion of retained juice was discarded in order to wash out whatever mucus had accumulated prior to feeding. With this precaution, the pH values again reflected the constancy shown by the high-dosage histamine experiments, even though the average rate of secretion of the latter was about three times that of the food experiments. Hence, it is evident that this constant acidity phenomenon obtains with the composite vagal and humoral stimulation following the ingestion of food, as well as with purely humoral stimulation by histamine.

Further support for this point was made possible by a most happy accident in the Biological Laboratory at Cold Spring Harbor one summer. Five weeks after operation, one of our sphincter pouch dogs presented us with a beautiful litter of pups. And then came our surprises. Instead of the relatively low rates of basal and post-prandial secretion which had been observed during last weeks of pregnancy, the dog immediately began to hypersecrete at a terrific rate, incessantly, day and night. This phenomenon has since been reported by several other investigators, but its causation is not yet clear. The hypersecretion started on the first night following parturition and persisted throughout the entire period of lactation, but not beyond. Thanks to the sphincter, we were able to collect a large number of specimens of the retained juice, very few of which contained any significant quantity of visible mucus. On some days, the 24-hour collection went as high as 250 cc, and the average for the first three weeks postpartum was about 150 cc, exclusive of the juice lost by forced evacuation of the pouch at night. This maximum daily volume was five to ten times that recorded prior to parturition and after cessation of lactation. Sixty-six post-prandial hypersecretion specimens had an average total acidity of 157 $\pm$ 7 meq/L, with a negligible combined acidity. The mean for a large series of post-prandial specimens, similarly collected from 4 non-lactating animals, was likewise 157 $\pm$ 3 meq/L. Thus, we have here a third kind of evidence of constancy, observed under conditions of unequivocal hypersecretion.

A fourth variety of such evidence became available in a study with Dr. Janowitz on the inhibition of histamine-stimulated secretion by atropine. This work disclosed that gastric secretion evoked by the subcutaneous injection of 2.5 μg of histamine base every ten minutes, can be prevented completely by a single injection of atropine sulphate at a dosage of 0.4 mg/kg. Although the rate fell practically to zero, the acidity in some of the experiments remained constant for about three hours.

Consequently, regardless of the mode of stimulation, the acid level can be constant for considerable periods while the volume-rate of secretion is undergoing drastic variations. These observations constitute incontrovertible proof of the validity of the Heidenhain-Pavlov theory—to the detriment of Rosemann's view that acidity and rate correlate well. Significant irregular deviations below this constant acidity must be ascribed to variable admixture of mucus and other

fluids. As for the parallelism between acidity and rate which invariably occurs in these experiments unless special precautions are taken to minimize the flow of non-acid fluids, this can be explained by their having a relatively constant rate of secretion while the rate for the parietal fluid is varying.

Formulation of a quantitative hypothesis at this stage would have been much too premature, because I lacked insight into the variations in concentration of chloride, cations, and other solutes of mixed gastric juice. Therefore, I next set out to study the behavior of the chloride concentration in relation to the acidity. Using the continuous collection technique, numerous experiments were performed with either histamine or food, to obtain relatively low rates of flow. The resulting graphs for the variations in total chloride and total acidity with collection time sometimes appeared to be parallel, whereas on other occasions the chloride values varied so little as to appear to be practically constant. Is the chloride concentration correlated with the acidity—as suggested by data of the first variety—or is it not? A review of the literature up to 1932 again revealed a dualism of opinion, with just as little decisive evidence.

Now, if these two variables are really correlated, in spite of very small ranges for the chloride values, this would be manifested by plotting them directly against each other with exclusion of the time variable. Many of our experiments seemed to support this view, but the absence of points with really low acidities left some doubt in one's mind. To relieve this uncertainty, I pooled the data for 121 samples from many such continuous collection experiments, regrouped them according to successive decades of acidity, and plotted the mean total chloride for each such group against its mean acidity. The resulting graph left no doubt of the existence of a linear correlation of the two variables, with a small slope. Similar data from a group of post-prandial samples collected by the retention technique, and a set of data reported by a group of English investigators (MacLean, Griffiths, and Williams; 1928) indicating the constancy of chloride concentration, were found to conform to the same kind of rectilinear relations when analyzed in this way. Several years later, I subjected these and several other groups of such data to statistical analysis, and found coefficients of linear correlation so high as to afford conclusive proof that the total chloride concentration of pure gastric juice is not constant but is positively correlated with the total acidity. The seeming constancy of total chloride concentration, argued by other investigators, derives only from the small slope of these regression lines—coupled, perhaps, with analytical data of low precision.

What about the cations? Twenty-five years ago flame photometers were unknown, and the time required for chemical determinations of sodium and potassium was so great as to preclude such measurements on the great number of specimens required for statistical purposes. Consequently, I had to resort to the technique employed by my predecessors in this field, that is, to use neutral chloride instead of the sum of the individual cation concentrations, and to measure this as the difference between total chloride and free acidity. Employing these procedures, it was found that neutral chloride also varies linearly and inversely with total acidity. The correlation coefficients were of a very high order,

the regression coefficients—that is, slopes—were essentially the same for data from different sources, and the lines all extended down fairly close to the acidity axis. Furthermore, extrapolation of these lines to determine their intercepts with the acidity axis, yielded values in the range 157 to 176 meq/L with a weighted arithmetical mean of 165 meq/L. This means that if we could get a specimen of gastric secretion of this high acidity, it would be entirely free of neutral chloride, and its total chloride would likewise equal 165 meq/L. By the same token, it may be inferred that acidities greater than this value are not attainable—at least under normal physiological conditions.

Our next concern must logically be with the variations in other constituents of pure gastric juice. The analytical work necessary to determine these factors on the large number of specimens requisite for statistical study was beyond my scope at that time. Hence, to compensate for the biological variations in each component, I used pooled specimens of pouch juice, collected by stimulation with food or histamine, of various dosages, and mixed according to decades of total acidity. Analyses of a series of large specimens obtained in this way yielded data which likewise showed significant trends toward a limiting value around 165 meq/L. Free acidity and total chloride approached this same limiting value as before, while combined acidity and neutral chloride both grew vanishingly small. The lowest value for neutral chloride actually observed in some of the individual specimens that made up this pool had values as low as 3 meq/L. Organic and inorganic phosphorus could not be detected at all, and several color tests for protein and carbohydrate were negative in the specimens of highest acidity. Independent evidence regarding protein was derived from data published by Dienst in 1931, from which I was able to establish that the relation between the total nitrogen content of human gastric juice and the acidity is similar to the rectilinear correlation for neutral chloride, with an acidity intercept (corresponding to zero nitrogen) of 163 meq/L. Total inorganic and organic solids likewise decreased with decreasing acidity, but these appeared to approach values slightly above zero—probably indicative of contamination of this "pure" gastric secretion by minute amounts of epithelial detritus. The specific gravity behaved consistently, but the freezing point depression was greater than expectation by about 0.02°C, according to the International Critical Tables. The meaning of this small difference remains to be determined.

From all these findings, it was inferred with a high degree of probability that this hypothetical limiting specimen of gastric secretion is practically pure HCl at a concentration about 165 meq/L, that it corresponds to pure parietal secretion, and that the other constituents of mixed gastric juice as ordinarily collected derive from mucus and other non-acid secretions. Does this limiting concentration have any special physiological significance? Clearly, it is greater than the mean total ionic concentration of human blood plasma, which is given by Homer Smith as 154 meq/L. This volume concentration, however, corresponds to a thermodynamic (weight) concentration of 167 meq/kg water. The weight concentration for pure 165 meq/L HCl is 165 meq/kg water. It is evident, therefore, that in terms of this latter, thermodynamically significant unit, the hypo-

thetical parietal secretion and blood serum possess identical concentrations and are therefore isosmotic—a deduction which is essentially in keeping with the freezing point depression data already cited as well as inferences and observations of other investigators. In short, the concentration of HCl in pure parietal secretion seems to be determined solely by osmotic forces.

Now, at last, I had enough data to warrant the synthesis of a working hypothesis to explain the variable composition of mixed gastric juice, and the interrelations among its several ionic constituents; also to serve as a basis for further researches in this area. Accordingly, I formulated a set of premises, and then proceeded to examine certain inferences from them in the light of the facts already established. As you will see, this hypothesis was an extension of Pavlov's very primitive theory, going far beyond Pavlov in that it was designed in quantitative terms and embraced the variations in concentrations of all the major inorganic ions of mixed gastric juice collected under various conditions of stimulation.

The premises are as follows:

1) "Pure gastric secretion" is a mixture of several exocrine secretions formed in the mucous membrane.

2) One of these, derived from the parietal cell, and designated the acid-component, is essentially a solution of pure HCl at a relatively invariant composition.

3) Under normal osmotic and acid-base conditions, the concentration of HCl in the acid component is 165 ± 10 meq/L; this value is independent of the mode of stimulation, and of the secretory rate, but is precisely dependent on the osmotic activity of the mucosal interstitial fluid. Hence, this concentration is a physiological parameter in the sense that body temperature and pulse rate are such parameters.

4) The parietal secretion is formed by a "steady state" process. Such a mechanism stands in direct contrast to one in which solvent and solutes move out of one or more varieties of cell independently of each other, after which movements the secreted solution undergoes changes in chemical composition until it reaches a "state of equilibrium".

5) The other exocrine secretions composing mixed gastric juice are mucus, the hypothetical mucoid secretion, and pepsin; desquamated epithelial cells and a transudate of interstitial fluid may also be present as contaminants. For convenience, these exocrine secretions are treated as a unit, designated the "alkaline component"—to differentiate it from the "acid component."

6) The chemical composition of the alkaline component is highly variable, being dependent on the proportions of its constituent secretions. At this stage of formulation, the mixture is presumed to be a dispersion of mucin and other organic substances in a menstruum with an inorganic composition similar to that of extracellular fluid; that is, its pH is above 7.0 and it contains the usual buffer anions—bicarbonate, primary and secondary phosphate, and proteinate—as well as chloride and all the common cations. The concentration of total anions and total cations is about 165 meq/kg water.

7) As a corollary to these premises, the composition of mixed gastric juice is the resultant of dilution and neutralization which occur on admixture of the acid and alkaline components, and all concentration values must fall between limits set by these two extremes.

8) This hypothesis is only a *first approximation* and is designed for modification and further amplification as new facts are brought to light, especially such as concern the chemistry of the mucus and mucoid secretions in the alkaline component.

A comparison of the observed facts with this hypothesis and its logical consequences, reveals a great deal of agreement between them. For the upper limit of the acidity range, I have already described specimens in which free and total acidities, and total chlorides differ from 165 meq/L by no more than 10 units; also combined acidity and phosphate are zero, and neutral chloride differs from zero by no more than 3 to 5 meq/L. The essential constancy of these limiting values, regardless of mode of stimulation and rate of secretion, constitute points of complete agreement between hypothesis and observation.

Concerning the lower limit of the acidity range, I have some data to be published shortly, on the inorganic constituents of several different mucous secretions which are suitable for this test of agreement. The chemical anatomy of viscous mucus, obtained by topical stimulation of the mucosa with acetylcholine, closely conforms with expectation statistically. The mucinous fluid evoked by topical application of the enzyme inhibitor, N-ethyl maleimide, possesses a similar but not identical chemical anatomy, as does the highly viscous opaque mucus stimulated by eugenol and other irritants. All these quantitative descriptions show wide ranges of variation in the individual concentrations, generally ascribable to contamination by desquamated mucus cells and transudate. The physiological character of the maleimide fluid has not yet been defined, but data on its content of hexosamine, other reducing sugars, and protein leave no doubt that it also contains glyco-protein in significant quantities. Of course, all these mucinous secretions have pH's which never are below 7.0 unless they are contaminated by some parietal secretion.

According to the hypothesis, the lowest titrimetric acidity attainable in gastric juice is not zero, but a negative number, corresponding to the buffer values of the alkaline component. Clinical gastroenterologists call this negative acidity "acid deficit." Since the alkaline component is tentatively postulated to have a composition resembling that of blood plasma or interstitial fluid, we may expect a buffer value of the same order of magnitude as the concentration of the combined buffer anions in the extracellular fluids. The latter is about 40 or 45 meq/L, whereas the observed buffer values here are 12–48 meq/L. The ranges for the other constituents of mucus also agree grossly with the corresponding data for extracellular fluid, whereas for the total anion and cation concentrations, the agreement between theory and observation is most satisfactory.

So much for the upper and lower limits of these concentration variables; What about the variations between these limits? When the acid and alkaline components are mixed in any particular proportion, their constituent concentra-

tions obviously change as a result of dilution and—in the case of acidity—neutralization. Time does not permit of a detailed description of the chemical anatomies corresponding to mixtures with different ratios of the acid and alkaline components, but I must call attention to a decrease, with decreasing acidities, of total anion and cation concentrations resulting from the loss of carbonic acid formed by interaction of HCl and sodium bicarbonate. However, on the basis of the hypothesis, it was possible to develop a pair of algebraic equations to define be varying concentrations of total and neutral chlorides as functions of total acidity. These theoretical equations both proved to be rectilinear, and a comparison of their parameters with those of the straight line graphs observed empirically revealed their corresponding intercepts and slopes to be in essential agreement. It follows, therefore, that the total and neutral chlorides of any specimen of gastric juice of specified acidity may be expected to conform within statistical limits to the values inferred from our hypothesis—at least within the acidity range of the early experiments. This range must be extended to include very low acidities and I hope to be able to accomplish this in the near future.* The mathematical analysis of this problem can be found in a paper in the Journal of Biological Chemistry of August, 1932.

Throughout the foregoing, I have discussed the metallic cations in gastric juice only in terms of neutral chloride. Although I think I have never specified this, I confess that I always thought of sodium and potassium as being present in the same proportion as in blood plasma. Subsequent studies, however, have shown this to be wrong.

In a systematic investigation of these ions, in canine gastric secretion, published in 1941, Gray and Bucher reported that the total and neutral chloride concentrations varied with the acidity in accordance with the pattern which I had described. Sodium, measured as such, behaved like the neutral chloride, but potassium remained statistically constant at 7.4 meq/L, regardless of variations in acidity, rate of secretion, or sodium value. In consequence, these investigators were led to state that (a) pure parietal secretion contains no Na, in agreement with my hypothesis, but it does contain potassium at this fixed concentration; and (b) the concentration of potassium in the alkaline component is likewise constant about 7.4 meq/L. Subsequent reports by Fisher and Hunt, Linde and Obrink, by Martin, and by Gudiksen, all seemed to support this conclusion of Gray and Bucher.

However, the literature contains many references to indicate that the potassium concentration of gastric juice can vary considerably, both above and below the level of 7.4 meq/L. For dogs, published data range as high as 24 meq/L, and for man, with or without gastrointestinal disorders, as high as 65. In spite of these high valued observations, the evidence of Gray and Bucher was so contrary to my own hypothesis, that I had to face the issue. Now, careful scrutiny of Gray

* Since writing this paragraph, I have received a reprint from Dr. A. Lambling (Paris) of a series of papers in which he and several associates confirmed this rectilinear relation between total chloride and acidity in man over the entire acidity range, from less than zero (acid deficits) to over 140 meq/L.

and Bucher's experiments with histamine-stimulated juice from stomach pouch dogs revealed two defects in their design—defects of such a nature that even if significant variations in potassium concentration had occurred, they would not have been detected. These faults arose out of their discarding all specimens collected during the first hour of the experiment, and their use of large pools of the subsequent ones. Accordingly, Drs. Colcher and Janowitz and I performed a series of experiments with canine Heidenhain pouches and a single injection of histamine as stimulus, in which we collected as many individual samples as possible in the course of any one experiment, keeping the volumes just large enough to permit measurement of all the factors with which we were concerned. To my delight, the potassium concentration curve (determined by flame photometry) began to rise immediately after the injection, attained a peak value within 45 minutes, and then fell off gradually to a level which it maintained until the experiment was terminated. The peak of this potassium curve usually appeared just in advance of the peak of the acidity curve, and in general, there was no correlation between these two variables. The curves for sodium, on the contrary, varied inversely with the acidity, and had the same form as all the neutral chloride curves and the sodium-acidity curves of Gray and Bucher. A similar study on man has been started by Dr. Werther in our laboratory, and a limited series of experiments already completed appear to be in agreement with these dog experiments. The overall range of potassium concentration in all our dog experiments was 0.4–12.8 meq/L, which clearly refutes the conclusion of Gray and Bucher, and others, about its constancy in mixed juice and therefore in the parietal and alkaline components. Likewise, the characteristic pattern of the curve for potassium concentration against time; the lack of correlation of potassium with acidity, sodium, and volume-rate of secretion; and the fact that we sometimes observed terminal potassium values of 1 meq/L and less—all these clearly controvert the argument of Gray and Bucher, and still allow for the possibility that the output of potassium is not linked to that of the hydrogen ion but comes about through some other mechanism.

If this be so, where does this potassium come from? Studies on the content of this element in the several kinds of mucinous secretions excluded these as possible sources. The intracellular contents of desquamated mucus epithelium also suggested itself, but this was ruled out by the potassium content of eugenol mucus which contains such cells. A third possibility is that this element derives from cell leakage, following the act of stimulation with histamine, and the evidence in support of this explanation is already considerable.

Whatever the meaning of these potassium curves may be, it is evident that they will necessitate some modification in the original hypothesis. Also, the next step in expansion of the concept of pure gastric secretion as a mixture of several well-defined exocrine secretions must take cognizance of the mucopolysaccharides and proteins contained in the non-acid secretions, as well as the inorganic salts. Above all, however, the mathematical formulation of a second approximation hypothesis ought to include measures of the random variations in all the concentration values for primary exocrine secretions, whether the cause

of variation be physiological or analytical. Our work on the glycoprotein-containing secretions is now at a stage where such an extension of the original hypothesis is possible.

Before closing, I wish to mention my analogous, though primitive, working hypothesis to explain the variable components of pancreatic secretion. The direction which this is taking is indicated by the following observations, reported by Dr. Earl Thomas and his associates, and confirmed and extended by the work of Dr. Birnbaum and of Dr. Tankel in our laboratory. Superficially, pancreatic secretion resembles gastric secretion in that the concentration of bicarbonate increases with increasing rate of secretion, and approaches a plateau in the neighborhood of 160 meq/L. The concentration of chloride varies inversely with the bicarbonate concentration, and the sum of the two is nearly constant, independently of the secretory rate. We have already obtained a few chloride values as low as 9 or 10 meq/L, in specimens with very high bicarbonate values, and I suspect it may be possible to obtain specimens with wholly negligible chloride concentrations by suitable improvement in experimental design. These facts present the possibility that pure pancreatic secretion is a mixture of at least three distinct exocrine secretions, and that the formation of the bicarbonate-containing secretion may also constitute a steady-rate phenomenon, but as yet this is far from a certainty.

And now to conclude; it has been my intention to explore the concept of exocrine electrolyte secretion—more particularly, to determine whether we may expect different electrolyte-containing secretions to resemble each other in regard to their intracellular mechanisms of formation. The evidence indicates the danger of any such presumption. Even if secretion of pancreatic bicarbonate resembles that of gastric HCl in being a steady state process in which osmotic forces play a major role, none of the others share this characteristic. The mucinous secretions may prove to have a uniform chemical anatomy related to interstitial fluid and isosmotic with it, but I doubt whether the electrolyte patterns of saliva, sweat, or urine will ever be found to fit into such a pattern.*

As for gastric secretion, there can be little doubt that this is a mixture of three or more independently formed exocrine secretions, and not a physiological unit; nor that the gastric mucous membrane is a mosaic of different kinds of cells which cannot be treated as a single entity for physiological purposes. Hence, any hypothesis concerning the cellular formation of one of these exocrine secretions must be formulated in reference to a specific cell, rather than the morphological conglomerate designated gastric mucosa. Likewise, any experiment designed for quantitative study of the energetics—chemical or electrical—of such a secretory process in terms of changes in ion concentrations in the mixed gastric juice and concentration gradients across the mucous membrane, is likely to prove abortive—because each such ion derives from two or more fluids which are secreted or transuded independently of each other. As a result of the dilution and

* Since writing this paper, evidence regarding the essential differences between renal and gastric acid secretion has been presented in a paper by Janowitz, Dreiling, Rolbin, and myself, in *Gastroenterology*.

neutralization attending such admixture, the ion concentrations of the primary secretions are changed significantly, according to their relative volumes in the mixture. Such an experiment can be valid only if the "mixed" gastric secretion being poured out at the mucosal surface is more-or-less pure parietal secretion, or mucus, or other component. This calls for devices for the complete inhibition or absence of stimulation of each of these exocrine secretions separately, at the same time that a single one of them is stimulated to secretory activity. Two such devices are already in use in our laboratory, and they are proving of great value in this connection.

I wish to express my obligations to my animal caretakers and my various technicians, as well as to my several associates whose names I have already mentioned. Without the faithful service and close cooperation of all these members of my laboratory family, much of the work I have described this evening would not have been possible.

EXPERIENCES WITH THE PUMP OXYGENATOR

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INTRODUCTION

This is a report of the experiences of the Surgical Research Laboratory of The Mount Sinai Hospital in the use of extracorporeal circulation. As the field of intracardiac surgery develops, new techniques and procedures utilizing the pump oxygenator as a tool will be tried in the experimental laboratory. Before any new procedure is performed on a human, one is first obliged to succeed with the laboratory animal. The factors that determine whether an animal will survive the cardiopulmonary bypass are multiple, and this itself makes evaluation of a new open heart technique extremely difficult. This paper is an attempt to point out and discuss some of the problems in the development and use of the pump oxygenator.

HISTORY

The development of reliable machines and methods to permit safe intracardiac surgery to be carried out has been the subject of intensive research for the past twenty years. One of the pioneers has been Gibbon who first repaired a congenital defect with total cardiopulmonary bypass in 1953. The Gibbon type apparatus oxygenates blood by filming it on screens in an atmosphere of oxygen (1). Other methods of filming blood have been on rotating discs and drums (2). The membrane type of oxygenator allows exchange of gases through a semi-permeable membrane (3).

A most significant advance was made by the University of Minnesota group in the clinical use of the bubble oxygenator (4). In their hands this method of oxygenation has yielded excellent results. The large number of successful cases now being reported with various pump oxygenators indicates that there is some merit in all of them and that the final answer as to which method, if any, is best is not now apparent.

Certainly as one's experience increases with a particular type of pump oxygenator, the results improve. The perfection of techniques and the learning of many details requires a substantial period of intensive work in the laboratory.

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Most important for success is the development of a team accustomed to working together.

Because of its simplicity and inexpensiveness, we have utilized the bubble oxygenator of DeWall-Lillehei for our initial work (5). In our hands it is now a useful laboratory tool and a successful system for total cardiopulmonary bypass in the human. Early in our experience the mortality rate in animals was high, but now one can almost always expect a survivor following a simple perfusion through a right thoracotomy.

TECHNIQUES

The bubble oxygenator consists of a venous reservoir into which caval blood is drained by gravity, a mixing tube in which the venous blood comes into contact with bubbles of oxygen, a debubbling chamber which is lightly coated with antifoam to disperse bubbles and a helix which functions as a reservoir for arterialized blood. As blood flows down the helix it laminates, thus allowing any small bubbles present to rise to the top and be removed (5). All tubing is made of polyvinyl plastic which can be autoclaved. Blood is propelled through the system by a Sigmamotor pump. The pump's metal fingers propel the blood along through rubber latex tubing. All connections between the tubing are made of stainless steel, which is tapered and highly polished to avoid turbulence, hemolysis and formation of fibrin emboli (6). A double-barreled mesh filter (Abbott) is inserted in the arterial line just after the blood leaves the helix.

Rigid attention to details from start to finish is of utmost importance in any perfusion experiment. The polyvinyl tubing making up the components of this system must be carefully washed and packed for autoclaving. The helix is marked off in gradations of one-hundred cubic centimeters for purposes of blood balancing. Polyvinyl becomes quite flexible upon warming and must, therefore, be packed in gentle loops. This avoids kinking and distortion of tubing which results in increased turbulence of blood flow. The output of an occlusive pump of this type depends on the size and physical characteristics of the rubber latex tubing which passes through it. We have learned that it is unwise to reuse this rubber tubing since autoclaving alters the elasticity and, therefore, may markedly diminish the output of the pump.

On the morning of the run the pump oxygenator is set up under sterile conditions. Where there are high pressures, connections are either wired or secured with hose clamps. At this time a careful inspection of all tubing is made for the presence of defects. An occlusive pump has a negative phase in which air can be sucked in and transmitted to the patient on the arterial side. One animal was lost from just such a defect—a small amount of air was aspirated in without any visible blood leakage.

Sterile five per cent dextrose in water is then added to the helix for debubbling and calibrating. The dextrose and water is first warmed to eliminate any excess air. Calibration is for a flow rate of 40–50 cubic centimeters per kilogram. As knowledge has been gained higher flow rates have been safely used. We now realize that there can be no predetermined flow rate. At the beginning of per-

fusion, the flow rate must be adjusted to give an adequate arterial pressure and a satisfactory EEG. (In some humans the perfusion rate was over 5000 cc per minute.) For priming the pump, fresh blood was collected into siliconized heparinized bottles from a donor dog under procaine and anectine anesthesia. As has been pointed out, barbiturates are to be avoided since they are transferred to the recipient dog, with resultant failure of the animal to wake up following perfusion. Blood is kept at thirty-seven degrees until the pump is ready to be primed. As this blood stands, there is a gradual drop in the pH (7).

When preparation of the pump is complete and the operative procedure is sufficiently far along, the priming volume of blood is slowly added to the helix, which is immersed in a constant temperature water bath at 41–42 degrees centrigrade. If possible the priming volume of blood is made equal to one-and-a-half to two minute's flow. Thus the helix has a high starting volume and an attempt is made to maintain this level in the helix during the perfusion. We believe the maintenance of a high level in the helix to be extremely important for survival following perfusion. The longer the period of time allowed for lamination of blood, the less the possibility of embolic phenomena. With high levels no secondary reservoir beyond the helix is necessary.

Anesthesia is induced and maintained with very small doses of pentothal and an attempt is made to keep the animals extremely light. No further anesthesia is given once the perfusion begins. It has been noticed on several occasions that even minimal doses of pentothal, ineffective before perfusion, will cause profound depression following perfusion.

The usual incision for simple cardiopulmonary bypass was a right thoracotomy through the fifth interspace. Attempts to routinely use a transsternal approach will result in an extremely high mortality rate. This incision gives poor chest stability in the dog. Before perfusion begins all blood losses are replaced with citrated blood so that the animal is placed on the pump with a normal blood volume.

Just prior to insertion of the catheters the animal receives 1.5 milligrams of heparin per kilogram. After ligation of the azygos vein the caval catheters are inserted rapidly through the right atrial appendage. Insertion of the catheters is facilitated by the use of a metal stylet the length of the catheter. In an occasional animal a large azygos vein has been ligated with a resultant fall in arterial pressure and rise in venous pressure. Upon removal of this ligature the pressure returns to normal. The position of the superior catheter is then adjusted to include drainage from the azygos vein. Delivery of oxygenated blood is through a catheter threaded through the femoral artery into the abdominal aorta. The largest possible catheter is used to avoid turbulence. Use of the femoral artery is convenient, means one less tube coming out of the chest and in addition it has the possible advantage that any small emboli which might be present would tend to pass into the abdominal viscera rather than to the brain. Arterial and venous pressures were constantly monitored via strain gauges. The usual run is thirty minutes. Oxygen enters the mixing tube at a rate of four to five times the blood flow.

If cardiac arrest was desired either potassium citrate or acetyl choline was used. The difficulty in restarting the dog heart arrested with potassium citrate has therefore led to the exclusive use of acetyl choline for cardioplegia in the laboratory. After bypass the blood volumes are balanced. All losses due to suction are measured and the final level in the helix is noted. If a large transfusion is needed it is given through the pump. Smaller amounts are replaced with citrated blood.

Following the run protamine equal to twice the amount of heparin is given in a slow intravenous drip. This not only avoids the hypotension associated with rapid injection of protamine, but also apparently the rebound effect of heparin.

Postoperatively chest tubes are left in place and the night of surgery these animals are checked at frequent intervals until all air and blood is evacuated. Each animal received combiotic for five days.

RESULTS AND COMPLICATIONS

Over one-hundred and twenty animals have had simple perfusion through the right chest for various lengths of time (average thirty minutes) with gradually decreasing mortality. In the most recent experiments there have been no deaths due to perfusion.

Five animals were lost due to a peculiar type of "atelectasis" which occurred on the unoperated side following perfusion. Grossly the lung appeared beefy red. There was no bronchial tree obstruction. Microscopic examination of these areas has revealed the alveolar spaces to be filled with fresh red blood cells. During total bypass the lung receives its blood supply only from the bronchial arteries and the recirculation of coronary sinus blood. State has shown that the bronchial blood flow is markedly decreased by collapse of the lungs (8). If the lungs do not remain well expanded during all phases of the perfusion, it is entirely possible that the alveolae and capillaries of the lung parenchyma will become anoxic. When the animal is then abruptly removed from the bypass there is sudden restoration of a large blood flow through the lung. Under these circumstances diapedesis of red blood cells through anoxic alveolar and capillary walls might easily occur. These lungs are not like the usual atelectatic lungs. They cannot be re-expanded by cleaning out the tracheobronchial tree or blowing up the lungs. The changes are irreversible. Since cognizance was taken of this situation every effort has been made to keep the lungs completely expanded during the perfusion and therby preserve bronchial blood flow. With this method this complication has never occurred. Further studies are under way to substantiate these observations.

Two animals died in acute pulmonary edema which resulted from over transfusion. To overcome the problem of blood balance animals are carefully weighed before and after perfusion, sponges are weighed and blood which is suctioned is collected into calibrated graduates and replaced cubic centimeter for cubic centimeter.

Generalized bleeding into the chest was the cause of death in only one animal. However, oozing into the wound and chest has at times been troublesome. This difficulty can largely be avoided by meticulous hemostasis and an adequate dose of protamine. Twice the number of milligrams of protamine as of heparin is

diluted in five per cent dextrose in water and given slowly. Any attempt at rapid direct injection of protamine will result in a marked drop in blood pressure.

LABORATORY STUDIES

As others have pointed out, there is a definite metabolic acidosis following cardiopulmonary bypass (9). The acidosis is less severe with higher perfusion rates (10). There is usually a slight fall in potassium and variable change in sodium (7). Hemolysis has been between forty and fifty milligrams per cent in the dog.

CONCLUSIONS

1. Before any pump oxygenator is used in the operating room success must be achieved in the laboratory. The most important factor in determining success is the development of a team intimately familiar with all the principles and techniques of perfusion.
2. Increasing experience with the bubble oxygenator has led to the gradual increase of flow rates.
3. Maintenance of a high level of blood in the helix eliminates the possibility of emboli even at high flows.
4. Anesthesia should be minimal on all bypass procedures.
5. An attempt is made to maintain a constant blood volume.
6. During perfusion the lungs should remain well expanded to avoid diapedesis of red blood cells into the alveolae.
7. Our studies verify the presence of a metabolic acidosis during perfusion.

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UNUSUAL SPECIFICITY OF AUTO-ANTIBODY IN AUTO-IMMUNE HEMOLYTIC DISEASE*

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The antibodies demonstrable on the red cells of patients with auto-immune hemolytic anemia have usually been considered to be "non-specific" because they react with all human erythrocytes irrespective of blood type. Recent studies however, have indicated that some of these apparently panagglutinating antibodies are specific for a blood factor present on the patient's own erythrocytes. Weiner and co-workers described a case of acquired hemolytic anemia in which an antibody of anti-e specificity was eluted from the patient's red cells (1). Sanger (2) observed an additional case with anti-e specificity, and an antibody with anti-e specificity was reported by Hollander (3). Dacie and Cutbush (4) found similar "specific auto-antibody" in five of ten cases of acquired hemolytic anemia and van Loghem and van der Hart demonstrated specific auto-antibodies in 10 of 18 cases of auto-immune hemolytic disease (5). In all but one of these reported cases, the specific antibody was so obscured that it could be demonstrated only after differential absorption which removed concomitant non-specific auto-antibody. In each case investigated, the blood factor corresponding to the specific antibody was present on the patient's own red cells and this antigen-antibody relationship was presumed to account for the hemolytic process. Furthermore, observations on red cell suvrival time in several cases have demonstrated relatively good survival of transfused cells lacking the specific blood factor in contrast to the markedly decreased survival of autologous red cells (6) or of other red cells containing the specific blood factor (7).

A number of cases of acquired hemolytic anemia have been studied in our laboratories, in which specificity could be detected in the auto-antibodies. In two instances, however, the corresponding blood factor was not present on the patient's erythrocytes. Certain observations in these two cases may cast additional light upon the significance of auto-antibody specificity.

EXPERIMENTAL STUDIES

The sera and eluates studied were absorbed primarily to disclose Rh-Hr specificity. Absorptions were performed at 37°C. for one hour, using small (usually $\frac{1}{10}$) volumes of washed packed red cells, until the serum or eluate no longer reacted with the absorbing blood. The absorbed and unabsorbed ma-

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terials were then retested against a series of bloods of known types. For Rh-Hr specificity, absorptions of aliquots were performed with red cells of phenotype* Rh_0, rh, Rh_1Rh_1 and Rh_2Rh_2. In selected cases studies for K-k, S-s, M-N, Fy^a-Fy^b and Jk^a-Jk^b specificity were also performed by the same technic, using appropriate absorbing bloods.

Case # 1

Mr. M. S., age 78 years. Chronic lymphatic leukemia with thrombocytopenia and a mild compensated hemolytic process; blood transfusions required only for hemorrhage.

Blood type: A_1 Rh_1rh kk

Direct antiglobulin test: +++ to ++++ at 37°C., + to ++ at 4° to 25°C.

Serum antibodies due to iso-immunization from blood transfusions and repeated stimulation with 0.25 ml of E positive K negative blood to maintain titer of anti-E*.

	Titer			
Specificity	Saline	Trypsin	Ficin	Indirect Antiglobulin
anti-E	1:16	1:32	1:32	1:8
anti-K	0	0	0	1:8

Native serum. Use of a panel of bloods from which E and K positive cells had been excluded demonstrated the presence of anti-D by the trypsin technic at 37°C. Ficin technic revealed the presence of both anti-D and of non-specific antibody, presumably because of the greater sensitivity of this method. No reactions were obtained at temperatures below 37°C. Thirty-one D positive (E negative, K negative) trypsin treated bloods were agglutinated by this serum, whereas 35 D negative (E negative, K negative) trypsin treated bloods were not agglutinated (Table I).

The D specificity of this serum appeared to be a cross-reaction of the iso-immune anti-E in that all D antibody activity could be removed from the patient's serum by absorption with type rh″ (D−E+) red cells. The anti-D specificity could also be removed upon absorption with Rh_0 or Rh_1 (D+E−) red cells with minimal or no reduction in the anti-E titer. However, eight absorptions with equal volumes of rh (D−E−) red cells failed to remove the D antibody activity.

Eluate. The reactions of the unabsorbed eluates prepared from the patient's red cells were those of a pan-antibody active only at 37°C. Specificity was not demonstrable by any technic, although cells containing the known blood factors in various combination were used for testing.

Aliquots of the native eluate were absorbed with red cells of phenotypes Rh_0, Rh_1Rh_1, × Rh_2Rh_2, and rh, and the absorbed fluids retested against selected bloods. A single absorption with 0.1 volume of packed ficin-treated rh″ (D−E+) red cells produced an absorbed fluid with anti-D specificity (Table II).

* Rh phenotype notations are those of A. S. Wiener (8). Rh specificity or "blood factor" notations are those of R.R. Race (9).

TABLE I

*Demonstration of Anti-D Specificity in Native Serum, Case I**

Test Red Cells	Method†			
	Saline	Trypsin	Ficin	Indirect Antiglobulin
31 D positive‡	0	+++	++++	+++
35 D negative‡	0	0	+§	0

* Rh_1rh kk patient with acquired hemolytic anemia.
† At 37°C. All reactions negative at 4° and 22°C.
‡ Selected as negative for the B, K, and E blood factors.
§ Positive reaction of equal intensity with all 35 bloods tested.

TABLE II

Demonstration of Anti-D Specificity in Eluate, Case I, after Absorption with Type rh″ Red Cells

Test Red Cells	Method*			
	Saline	Trypsin	Ficin	Indirect Antiglobulin
10 D positive†	0	0	++	+
6 D negative‡	0	0	0	0

* 37°C. Reactions negative at 4° and 22°C.
† Included phenotypes Rh_0, Rh_1rh, Rh_1Rh_1, Rh_2Rh_2, and Rh_1Rh_2.
‡ Included phenotypes rh′, rh″, and rh.

Since anti-D was present in the patient's serum and could presumably react with the patient's own D positive red cells, it is not surprising that anti-D could be eluted from the patient's erythrocytes; however, similar absorption with 0.1 volume of Rh_1 or Rh_0 (D+E−) red cells left an antibody with anti-E specificity (Table III).

This finding was unexpected, since the erythrocytes from which the eluate had been prepared lacked the E blood factor*. The possibility of contamination with some of the anti-E present in the patient's serum was excluded by the absence of demonstrable antibody in the erythrocyte washings prior to elution, and by the exhaustive washing of both the red cells and of the red cell stromata prior to elution. A further control was the simultaneous and repeated preparation of eluates from the red cells of an Rh negative (rh) patient with acquired hemolytic anemia who was strongly iso-immunized to D (titer 1:256). These eluates contained no evidence of anti-D, although anti-e could be demonstrated without difficulty after suitable absorption.

Although anti-E specificity was obtained in an eluate from E negative red cells it could be considered to be a cross-reaction of anti-D; i.e,. anti DE reacting

* In this patient, as well as in the subsequent case, careful red cell typings had been performed many months prior to the time that a positive direct antiglobulin reaction first appeared and the absence of the blood factor in question was noted with more than one reagent.

TABLE III

Demonstration of Anti-E Specificity in Eluate, Case I, after Absorption with Rh_0 or Rh_1 Red Cells

Test Red Cells	Method*			
	Saline	Trypsin	Ficin	Indirect Antiglobulin
6 E positive†	0	++	++++	+
10 E negative‡	0	0	++	0

* 37°C. Reactions negative at 4° and 22°C.

† Included phenotypes Rh_1Rh_2, Rh_2Rh_2, and rh″.

‡ Included phenotypes Rh_0, Rh_1^wrh, Rh_1Rh_1, rh′ and rh.

with the patient's D positive cells. Anti-D specificity was present in the same eluate, (i.e., anti-DE), and the serum anti-D activity appeared to be anti-E cross-reacting with D, so that the red cell eluate (or an appreciable portion of it) might be the same cross-reacting anti-DE. Unfortunately, this hypothesis could not be tested by repeated absorption of the eluate with type Rh_0 (D+E−) cells. We have found that eluates are subject to non-specific loss by simple absorption upon repeated exposure to apparently compatible red cells or upon Seitz filtration.

Case #2

Mr. I. T., age 67 years. Subacute myelocytic leukemia with thrombocytopenia and mild compensated hemolytic process; blood transfusions required only for hemorrhage.

Blood type: O rh kk

Direct antiglobulin test: Negative prior to development of Rh antibodies; ++++ at 37°, 25°, and 4°C. after Rh iso-immunization.

Serum antibodies due to iso-immunization by two units of Rh positive blood and later by purposeful stimulation with 0.25 ml of Rh positive blood:

	Titer of Rh Antibodies*					
	Rh_0	rh′	rh″	rh	D.A.R.†	A.F.R.‡
Prior to transfusion	0	0	0	0	0	0
Following 2 units of Rh positive blood	32	1	0	0	0	0
Following successive stimuli (1)	512	8	1	1	0	0
with 0.25 ml of Rh positive (2)	1280	16	4	1	0	±
blood at approximately 2 (3)	5120	320	64	1	0	+
week intervals (4)	5120	320	n.t.	4	++++	++++

* Using ficin treated red cells.

† Direct antiglobulin reaction.

‡ Auto-ficin reaction: auto-antibody demonstrable at 37°C. when serum of patient was tested with patient's red cells treated with ficin.

TABLE IV

Eluate Specificity, Case II

Test Material	Test Red Cells 37°C.*		Test Red Cells 4°–25°C.*	
	10 D positive	7 D negative	10 D positive	7 D negative
1. Native eluate	++++	++++	++	++
2. Eluate post-absorption with D positive bloods†	0	0	0	0
3. Eluate post-absorption with D negative bloods‡	+++	0	+	0

* Ficin method. Identical but slightly weaker reactions obtained with indirect antiglobulin method.

† Identical results obtained with eluate aliquots absorbed with Rh_1Rh_1, Rh_2Rh_2, Rh_1Rh_2 and Rh_0 bloods.

‡ Identical results obtained with eluate aliquots absorbed with rh, rh′, and rh″ bloods.

The native eluate contained antibody which reacted with bloods of all types by the indirect antiglobulin technic and strongly agglutinated all enzyme-treated red cells regardless of antigenic composition. The reactions were maximal at 37°C., and were much weaker at lower temperatures. After absorption at 37°C. with D negative bloods (types rh, rh′, or rh″) the eluates gave positive reactions with 10 D positive bloods but failed to react with 7 D negative bloods. Similar absorptions with Rh_1Rh_1, Rh_2Rh_2 or Rh_0 cells resulted in complete loss of activity (Table IV).

Over a two year period the eluates became progressively weaker, and appeared to contain a progressively increasing proportion of anti-D antibody relative to the pan-antibody.

DISCUSSION

Previous studies of the specificity of auto-antibodies in acquired hemolytic anemia, have demonstrated antibodies with specificity for antigens present in the red cells of the patients selected for study. This report reveals two instances in which antibody eluted from the patient's own red cells (auto-antibody) had specificity for a blood factor not present in the patient's red cells.

One explanation for this unusual finding is lack of control over antibody production which is always taking place. Thus it might be assumed that all individuals are subject to auto-erythrocytic antibody production, but that hemolytic anemia results only when this "horror auto-toxicus" outruns normal curbs. This explanation would allow for the production of auto-antibody through previously established auto- and iso-immune mechanisms.

Another possible explanation is that of immunization to an Rh structure common to all Rh antigens, yielding results suggestive of complete non-specificity. Such immunization could arise either de novo as the initial sensitization, or as a result of initial iso-immunization to a blood factor in the Rh system, with subsequent widening of the "spectrum of specificity" as further stimulation oc-

curred. Such an antibody, although capable of reacting with all antigens containing the basic Rh structure might nevertheless react preferentially with one or more specific Rh blood factors. Thus an eluate containing such an antibody might in its native state react with all human red cells containing antigens in the Rh system and appear non-specific, but after suitable absorption react with only the preferred antigen.

The first explanation would appear to be more generally applicable but in selected individuals the second explanation may be contributory.

SUMMARY

Studies pertaining to the Rh specificity of antibodies in the red cell eluates obtained from two cases of auto-immune acquired hemolytic anemia, disclosed in each a specificity for an Rh factor not demonstrable in the red cells of the patient. In both instances the patient had been iso-immunized first by blood transfusion and later by purposeful stimulation for the unusual specificity. Both patients required occasional blood transfusion for hemorrhage due to the thrombocytopenia, but not, apparently, for hemolytic anemia.

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VERTEBRAL ANGIOGRAPHY

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The main purpose of this study on vertebral angiography is to determine its importance in clinical neurology. The following questions which are vital in evaluating a neuro-radiologic procedure will be answered: (a) difficulty of the procedure and incidence of failure; (b) complications inherent in the procedure including discomfort to the patient, morbidity, and mortality; (c) the correlation between pathological processes and x-ray findings. These questions will be partially answered from experience of the past year at The Mount Sinai Hospital.

There are, to my knowledge, at least nine different methods of vertebral angiography. As early as 1933, Moniz noted retrograde filling of the basilar artery in five of six hundred cases of carotid angiography. Seeing no apparent complication in these patients, he proceeded to the first vertebral study by inserting a needle into the right subclavian artery. In 1937, Shimidzu described a percutaneous method of catheterization of the subclavian artery and showed filling of the vertebral system. In 1938, Sjöquist, and in this country King (1), described a method of cutting down to the vertebral artery in the neck for a direct approach. Takahashi, in 1940, developed a direct percutaneous approach to the vertebral below its entrance into the transverse foramen. The above methods were all found to be impractical for routine work because of the necessity for anaesthesia in some and the need for a surgical procedure in others. The first practical method which now has become a routine in many centers was originally described by Lindgren of Sweden in 1947 (2). This entails a direct approach, without anaesthesia or surgery, to the vertebral artery as it runs through the transverse foramen. This method, which is essentially the one we use at The Mount Sinai Hospital, was used by Sjögren (3), who reported a series of two hundred cases in which there were no permanent complications. He was successful in 148 of the last 150 cases.

Ameli in 1952, published a large series of cases done by the retrograde method (4). With a needle in the proximal right carotid artery, the right brachial artery is occluded with a pressure cuff. The distal carotid is then occluded. At this point the opaque material is injected into the carotid artery and is forced down to the innominate artery and eventually up to the vertebral from below. In most hands, this method does not give a high percentage of successful procedures. However, a group in Syracuse claims success in forty-four of fifty-two attempts (5).

Namin, in France, enters the vertebral percutaneously between the occiput and the atlas in a posterior approach (6). He claims good results in 162 cases.

Recently in Sweden, Ollson and Radner have developed a method in which they enter the radial artery and thread a catheter into either vertebral artery.

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Radner reported a series of 221 cases (7). The fact that the radial artery was sacrificed after the procedure, the higher incidence of complications, and the intrinsic complexity of the catheter method, including the need for fluoroscopy makes Radner's method unsuitable for general use.

A method suited for infants and children was noted by Gould (8) in 1955. A cut down is done on the brachial artery and a large amount of opaque fluid is injected in the retrograde manner. Seven out of seven children had successful vertebral angiography in this report.

The latest method in the literature was devised in Sweden and is a catheterization method in which the catheter is inserted into the femoral artery and threaded up to the vertebral (9).

METHODS

At The Mount Sinai Hospital we have used only two methods; the direct percutaneous procedure and the retrograde filling technique via the right carotid artery. We use the same general method as described by Sjögren (3). The patient is usually given Demerol 75 mg. and Atropine 0.4 mg. before going to the x-ray department. Procaine is used to anaesthetize the skin and deep tissues of the neck. We have found that if procaine is injected close to the fascia overlying the transverse processes of the cervical vertebrae, severe pain is usually avoided. Either a long Cournand needle or a short bevel 17 gauge spinal needle is introduced near the midline, low in the neck, and angled upward for the distance of two or three vertebrae. When the trachea is moved laterally, the vertebral body is met. The needle is then moved laterally, off the body and onto the fascia overlying the processes of the vertebrae. The needle is next inserted between two processes into the transverse foramen. It is usually not difficult to enter the artery which runs through the foramen along with the vertebral veins and the cervical roots. Once the needle enters the artery, blood spurts back, though with less vigor than in carotid artery puncture. The needle is always kept pointing laterally during this maneuver to preclude the possibility of entering the subarachnoid space. The greatest problem is to keep the needle in the artery while the patient is being positioned for the x-ray. We have found that the needle stays in longer if the angle upwards is so great that the needle approaches a parallel with the artery. Hypaque® has been used as the contrast substance in all of our studies.

RESULTS

There were only twenty-three successful vertebral angiograms done before January 1957. A successful study may be defined as one in which either a lateral or anterior-posterior view shows complete filling of the basilar and vertebral arteries and some filling of the posterior cerebral arteries. Most of the recent films, done by the direct method, show many more branches, as will be shown later in this paper. From January to August 1 of 1957 twenty-eight vertebral angiograms have been done giving us fifty-one cases in this modest series. Most of the vertebral studies before 1957 were accidentally obtained while attempt-

TABLE I

Summary of Vertebral Angiography at The Mount Sinai Hospital

1953–1956		
Purposeful direct study	7	
Accidental direct study	6	
Retrograde study	10	
Total	23	
January–July 1957		
Attempts at retrograde study	15	
Successful retrograde study	6	
Accidental retrograde study	1	
Attempts at direct study	26	
Successful direct study	19	
Accidental direct study	3	
Total Successful cases	28	
(one case had successful retrograde and direct angiograms)		
Complications		
Retrograde studies	none	
Direct	1	(weakness of shoulder for at least one week)
Accidental Direct cannulation without injection of Hypaque	1	(severe brain stem dysfunction) (?related to procedure)

ing to do routine carotid angiography, or were retrograde visualizations which are usually incomplete.

The figures after January 1957 give some indication as to the difficulty of the procedure. I have listed all the attempts with a notation as to the success and failure. The patients who had only one view; either lateral or anterior-posterior are considered satisfactory studies (Table I).

From January to August 1, 1957 there have been thirty-eight cases in which either a retrograde or direct vertebral study was attempted. Of fifteen attempts at retrograde filling, six were of value in that some information was elicited. In general, retrograde filling is poor, although there have been some excellent retrograde studies. Anatomic variation may contribute to the variable results. Of twenty-six attempts at direct vertebral angiography, nineteen were successful. An additional three direct vertebral were done accidentally in this period.

In summary, direct percutaneous angiography of the vertebral artery is a simple procedure, not much different from carotid angiography. With experience, success should probably occur in more than eighty-five percent of the cases. On the other hand, retrograde filling technique gave information in less than one-half of the attempts, and these tended to be less complete studies.

The incidence and degree of morbidity and discomfort is important in evaluation of special x-ray procedures. The retrograde method is no more difficult than carotid angiography and does not cause significantly greater discomfort to the patient. The occlusion of one carotid during the retrograde procedure has not been associated with any morbidity. Direct vertebral angiography is usually more difficult than carotid studies; however there have been many comparatively

painless direct procedures. Patients frequently complain of pain in the shoulder, arm and posterior neck during and after the procedure. The cervical root is posterior to the vertebral artery and is frequently irritated when the needle is inserted. Once sufficient familiarity with the procedure is acquired, the attendant discomfort to the patient is not much greater than one sees in carotid studies.

The length of time and number of attempts at cannulation is variable. It usually takes more attempts to enter a vertebral artery than a carotid, although some vertebral arteries have been entered on the first attempt. Many patients complain of dizziness, falling, or peculiar sensations during the injection. Aside from pain and stiffness of the neck which lasts for one to three days, and a few instances of transient dysarthria, we have only one definite complication from vertebral angiography. This patient had weakness of his shoulder muscles on the side injected for at least one week after the study. This was presumably due to local nerve trauma in the transverse canal. Two patients died within forty-eight hours of the vertebral study. Both of these patients were moribund before the procedure, and their clinical states did not change perceptibly. Postmortem examination did not show any acute changes in the brain stem. One patient developed symptoms of brain stem dysfunction a few minutes after a vertebral artery was cannulated by error during an attempt at carotid artery angiography. The needle was withdrawn within one minute, and no opaque fluid was injected. It is not clear what caused this complication.

In summary, there was no mortality associated with the procedure. Two patients of a total of thirty-eight attempts suffered permanent morbidity (Table I).

DISCUSSION

Interpretation of vertebral angiograms remains difficult. It seems reasonable to assume that as the present limited experience increases the clinical value of the procedure will grow. Because of the frequent normal variations of vessels in a comparatively small space, evaluation of these studies is more difficult than that of carotid angiograms. In certain types of vascular disease such as aneurysms, arterio-venous anomalies, and obvious stains from tumor masses, the interpretation is simple. The displacement of veins and arteries associated with tumors of the posterior fossa is more difficult to judge.

Olsson reported fourteen verified angle tumors in which vertebral angiography was claimed to show significant changes in thirteen (10). He states that small changes in the superior cerebellar artery are indicative of tumors. Radner had ten cases of angle tumors and only two showed significant abnormalities in his opinion (7). Decker noted changes in the posterior cerebral artery in posterior fossa lesions. In twenty-six cases of cerebellar tumor he noted that one-fifth of the cases had a raised posterior cerebral artery (11).

Columella (12) studied supratentorial lesions and noted many changes in the posterior cerebral branches in posterior cerebral tumors. Lofgren attempted to correlate the vertebral angiogram and the etiology of hydrocephalus (13). He feels that if there is no shift in the cerebellar vessels, then a diagnosis of stenosis of the aqueduct is likely. Radner (7) in reviewing his 221 cases noted that in

four cases of cerebellar astrocytomas and four cases of medulloblastomas, the only finding was evidence of hydrocephalus. In five cases of cerebellar hemangioma four showed abnormal vascularity. One of four posterior fossa meningeomas showed a stain on vertebral angiography. Other authors have stressed the course of the posterior inferior cerebellar artery (2). This artery, when seen running well below the foramen magnum is thought to give evidence of a mass in the posterior fossa (Figure 6).

In general the world literature agrees that tumors of the posterior fossa do not show diagnostic staining as frequently as masses in the supratentorial regions. Small movements of the arteries and veins are usually subtle for interpretation, although obvious deformities of the vessels can be seen with some tumors (Figure 5).

Frequently, the posterior cerebral artery will fill only from the basilar artery and therefore tumors or vascular malformations of the occipital and posterior temporal regions can only be diagnosed by vertebral angiography (and air studies). When an aneurysm is suspected the need for vertebral angiogram is obvious. In many centers a vertebral angiogram is routine in the search for an aneurysm after an episode of subarachnoid hemorrhage. Spatz (14) reported sixty cases of subarachnoid hemorrhage with vertebral studies. Sixteen patients showed pathology related to the subarachnoid hemorrhage. There were eight cases of posterior fossa aneurysms and eight cases of arterio-venous anomalies of the posterior circulation.

The information gained from vertebral angiography at The Mount Sinai Hospital was reviewed. Of the fifty-one known cases three had definite evidence of tumor staining on the late arterial or venous phases of the angiogram. Two of these were verified meningeomas of the tentorium and one was presumably a metastatic lesion in a man with proven carcinoma of the lung (Figure 1).

We have found one aneurysm of the posterior circulation (Figure 2).

There have been many minor and major anomalies of the circulation seen. The vertebral arteries are frequently asymmetrical in size and position. The basilar artery is commonly extremely tortuous from its formation to the origin of the posterior cerebrals. The superior cerebellar arteries sometimes do not fill in patients who do not show brain stem symptomatology. There were three cases in which the posterior cerebral artery on one side received most or all of its blood supply from a carotid artery and not from the basilar artery. An anomalous connection on the clivus between the basilar and carotid systems was seen in one case; and a connection between the basilar artery and a pharyngeal branch of the external carotid was seen in another.

We have four cases of narrowing or occlusion of vessels which were apparently related to the patient's symptoms. In two cases the basilar artery was narrowed and showed poor filling, in one case the posterior cerebral artery was occluded (Figure 3), and in the fourth case the vertebral artery was narrowed in the region of the branching of the posterior inferior cerebellar artery (Figure 4).

The vertebral angiogram was abnormal in three of five cases whose histories

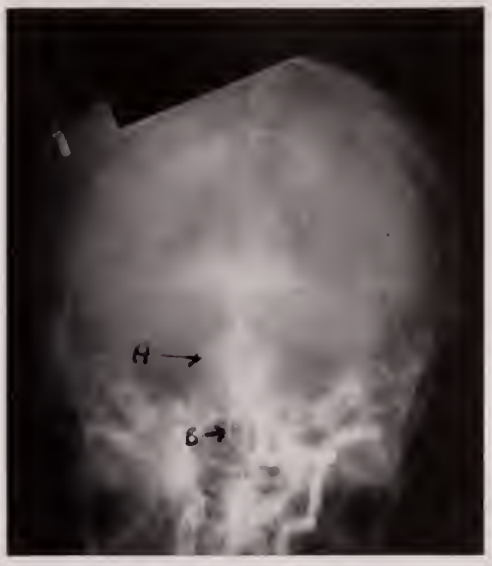

FIG. 1. 49 year old male with proven carcinoma of the lung. He had ataxia, nystagmus, and headache.

Angiogram shows an obvious circular stain in the midline (A). An abnormal vessel (B) is seen entering the region. This is an abnormal pattern which probably represents metastatic carcinoma to the cerebellum. No autopsy was done.

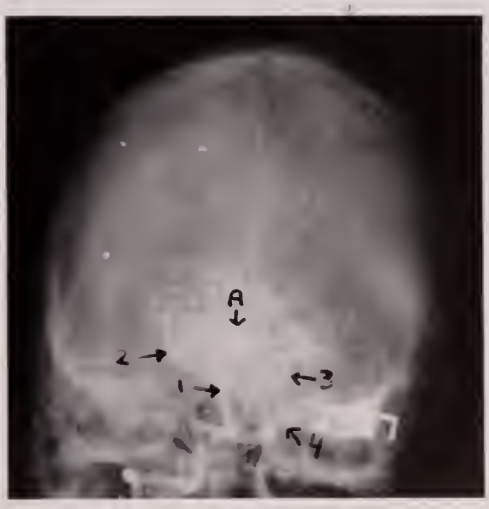

FIG. 2. A 38 year old female with evidence of brain stem disease. There were no episodes of subarachnoid hemorrhage.

The angiogram shows a large aneurysm (A) at the distal end of the basilar artery (1) connecting with the posterior cerebral arteries and the superior cerebellar arteries.

Right posterior cerebral artery (2)

Left superior cerebellar artery (3)

Left posterior inferior cerebellar artery (4)

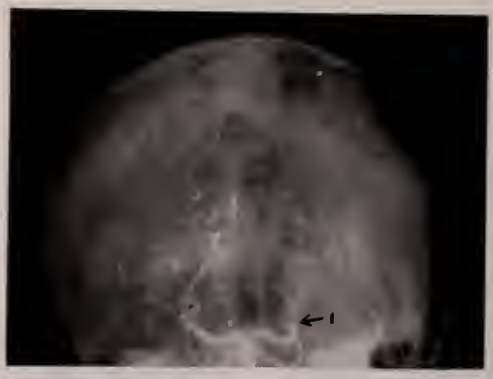

FIG. 3. 35 year old female with right homonymous hemianopsia. The angiogram shows an occlusion of the posterior cerebral artery on the left (1). A left carotid angiogram showed no filling of the left posterior cerebral artery.

FIG. 4. A 66 year old male with evidence of episodic brain stem dysfunction thought to be on a vascular basis.
Angiogram shows narrowing of the right vertebral artery (1) at the region of the branching of the posterior inferior cerebellar artery (2). The significance of this suggestive finding is not certain.

were compatible with the basilar artery insufficiency syndrome. Two showed narrowing and poor filling of the basilar artery and one showed narrowing of the vertebral. The width of the basilar artery could not be correlated with the above syndrome. Variation ranged from one and a half to three millimeter in width as measured on lateral x-ray. On the negative side there have been seven proven neoplasms of the posterior fossa who have had normal vertebral studies. The series include two cerebellar pontine angle neoplasms, three cerebellar tumors one pontine glioma, and one ependymoma of the fourth ventricle. We have seen suggestive deviations of the basilar artery and the superior cerebellar artery in

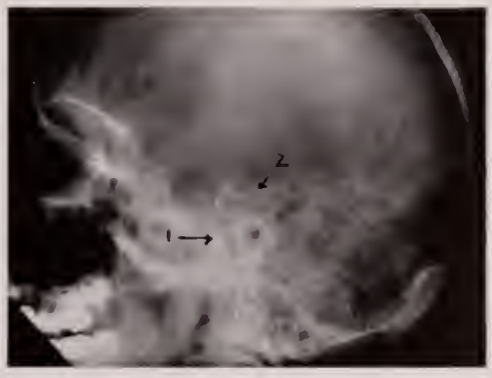

FIG. 5. 23 year old male with proven neoplasm of posterior fossa. The basilar artery (1) is narrow and appears to be flattened against the clivus. The posterior cerebral artery is displaced upwards (2).

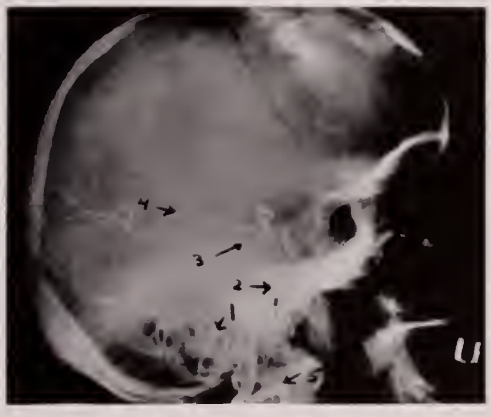

FIG. 6. 67 year old female with evidence of brain stem vaseular disease. The posterior inferior cerebellar artery (1) is seen running below the foramen magnum. The basilar artery (2) the superior cerebellar (3) and posterior cerebral (4) and vertebral (5) are all in normal position. There was no evidence of a mass lesion in this patient.

tumor cases; however, we do not have enough experience to be sure that these films are in the abnormal range.

Downward deviation of the posterior inferior cerebellar artery is hard to interpret. We have two cases in which the posterior inferior cerebellar artery is definitely running below the foramen magnum. The clinical history in these cases did not suggest a mass lesion or herniation of the tonsils, however there were no post-mortem examination or operative procedure in these cases.

CONCLUSION

Our experience agrees with most of the world literature in that neoplasms of the posterior fossa are infrequently defined by angiography. It is possible that with improvement in technique and more experience, we will lower the incidence of false reports.

Vertebral angiography is the only method for making definitive diagnoses for vascular diseases such as occlusive disease, aneurysms, and arteriovenous anomalies. Vertebral studies can be done in the face of posterior fossa neoplasms or basilar artery disease with no great risk. It is a simple benign procedure very similar in discomfort, morbidity and difficulty to routine carotid angiography.

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GASTROINTESTINAL MANIFESTATIONS OF PRIMARY HYPERPARATHYROIDISM: EXPERIENCE AT THE MOUNT SINAI HOSPITAL AND REVIEW OF THE LITERATURE

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The purpose of this report is to discuss the gastrointestinal complications of primary hyperparathyroidism. The experience at The Mount Sinai Hospital and the literature in general have been reviewed in this regard.

The records of The Mount Sinai Hospital reveal 37 proven cases of primary hyperparathyroidism. This group is composed of 26 females and 11 males. Of the total of 37 patients, peptic ulcers were proven in 4 cases. Gastrointestinal symptoms were prominent without proven peptic ulcer in 5 patients and 28 cases had no significant gastrointestinal symptoms.

CASE REPORTS OF HOSPITAL PATIENTS WITH HYPERPARATHYROIDISM AND PEPTIC ULCERATION.

Case 1

M. W. MSH # 50083. This 67 year old male was first admitted to The Mount Sinai Hospital in December 1948, complaining of abdominal pain, weakness and melena. For 15 years he had noted intermittent abdominal pain which generally responded to belladonna therapy. Gastrointestinal series in 1948 revealed a projection from the lesser curvature of the stomach, interpreted as a benign gastric ulcer. The patient was treated conservatively and discharged improved.

The patient was readmitted in July 1955 because of swelling and pain in the right leg. Occasional melena had been noted in the interval since his first hospital discharge. X-rays revealed large cystic areas throughout the long bones, consistent with hyperparathyroidism. Serum calcium ranged from 9.2 to 11.8 mgm. per cent, serum phosphorus from 1.1 to 1.6 mgm. per cent, and alkaline phosphatase was 15.3 King-Armstrong units. The patient was explored and a single parathyroid adenoma removed. The post-operative course was uneventful.

In September 1955 sudden acute abdominal pain developed and the patient expired. Post-mortem examination revealed a dissecting aneurysm of the thoracic aorta and a healed gastric ulcer.

Comments: Symptoms of gastric ulcer were present for 22 years before definitive evidence of hyperparathyroidism appeared. It is interesting to speculate on: (a) the possibility that hyperparathyroidism existed for 22 years, and (b) the possible relationship between the hyperparathyroidism and dissecting aneurysm.

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Case 2

W. L. MSH #64481. This 39 year old male was first admitted to The Mount Sinai Hospital in April 1956 because of epigastric distress. The patient had recurrent renal calculi since 1942. In 1945 he noted the onset of an episodic epigastric burning sensation relieved by alkali and food. In 1951 hyperparathyroidism was diagnosed at another institution and two parathyroid adenomata were removed. The patient subsequently was asymptomatic until April 1954 when he developed a renal calculus. In October 1955 the epigastric pain recurred. In January 1956 a duodenal ulcer was demonstrated on gastrointestinal series.

At the time of his Mount Sinai Hospital admission, the serum calcium ranged from 12.5 to 15.4 mgm. per cent, serum phosphorus from 0.8 to 1.4 mgm. per cent, and alkaline phosphatase from 5.2 to 8.9 King-Armstrong units. Urine calcium excretion was 400 mgm. per 24 hours on a Bauer-Aub diet. Gastrointestinal series revealed radiating folds in the duodenal bulb with a persistent patch of barium. A large parathyroid adenoma was removed from the anterior mediastinum in May 1956. Post operative course was uneventful with normal calcium and phosphorus values. No information is available concerning ulcer symptoms since parathyroidectomy.

Comments: The multiple parathyroid adenomata were an interesting facet of this case. Woolner et al (1) reported multiple adenomata in 8 per cent of cases of primary hyperparathyroidism. It is also of interest to note what appears to be a direct relationship between the ulcer symptoms and parathyroid overactivity.

Case 3

G. S. MSH #80258. This 47 year old female entered The Mount Sinai Hospital in March 1957 because of epigastric pain. The patient first noted transient episodes of abdominal pain in 1931. Several years later a duodenal ulcer was demonstrated by x-ray. In January 1957, severe epigastric pain developed, radiating to the back. This was accompanied by episodes of nocturnal vomiting.

In 1947 and again in 1952, the patient experienced severe left flank pain radiating to the groin. Renal calculi were suspected but no roentgenographic studies were performed.

In 1951 a swelling of the right wrist appeared, and the following year a cyst was removed from the os hamatum which on microscopic examination was a giant cell tumor.

Examination in March 1957 revealed a 2 cm. non-tender nodule in the left lobe of the thyroid. Serum calcium ranged from 11.9 to 13.7 mgm. per cent, serum phosphorus from 1.2 to 4.2 mgm. per cent, and alkaline phosphatase from 5.9 to 9.1 King-Armstrong units. The 24 hour urine calcium excretion on a Bauer-Aub diet was 111.5 mgm. Intravenous pyelogram was normal. Bone x-rays revealed some demineralization but no lesions characteristic of hyperparathyroidism. A markedly deformed duodenal bulb with a persistent patch of barium representing an ulcer crater was visualized on roentgenograms. In May, a left hemithyroidectomy was performed. The excised specimen contained a cystic

parathyroid adenoma. Post operative serum calcium levels were normal. The patient had no post operative gastrointestinal symptoms as of December 1957.

Comments: Symptoms of duodenal ulcer preceded the probable renal calculus by 16 years and preceded the definitive diagnosis of hyperparathyroidism by 26 years. Since there was no evidence of intestinal obstruction on x-ray examination, the persistent vomiting at the time of admission was probably due to hypercalcemia per se. As in case 2, the patient's severe ulcer symptoms cleared dramatically after parathyroidectomy.

This patient had a palpable hyperfunctioning intrathyroid parathyroid adenoma. Aberrant intrathyroid parathyroid tumors have been reported in 3 to 5 per cent of cases of hyperparathyroidism (2, 3). Balch et al (4) reported 2 cases of clinically palpable intrathyroid parathyroid adenomata.

Case 4

J. S. MSH # 608853. This 46 year old female was first seen at The Mount Sinai Hospital in 1948 with a history of renal calculi for 20 years eventuating in a left nephrectomy. For ten years she had intermittent epigastric discomfort relieved by sodium bicarbonate. There was no history of excessive milk ingestion. In 1949 x-rays revealed a definite ulcer crater. Bone x-rays were normal. In 1949 blood urea nitrogen was 33 mgm. per cent, serum calcium 12.6 to 13.8 mgm. per cent, serum phosphorus 2.0 to 2.6 mgm. per cent. On a Bauer-Aub diet, the 72 hour urinary calcium excretion was 586 mgm. Parathyroidectomy was advised but refused. Progressive uremia developed and the patient died in 1950. No post-mortem examination was performed.

GASTROINTESTINAL MANIFESTATIONS OF PRIMARY HYPERPARATHYROIDISM.

One of the earliest reported cases of primary hyperparathyroidism (5) had severe attacks of abdominal pain and vomiting occurring every three weeks in addition to constipation of five years duration. The symptoms disappeared promptly after parathyroidectomy. Gastrointestinal symptoms in primary hyperparathyroidism were first emphasized in 1934 by Gutman, Swenson, and Parsons (6). In their review of 119 cases of hyperparathyroidism they noted skeletal and renal symptoms to be the most common initial and late findings in the disease. However, anorexia, nausea, vomiting and epigastric pain were major initial symptoms in 13 per cent of the cases and major late symptoms in 26 per cent of cases. These authors noted that gastrointestinal symptoms may dominate the clinical picture to the extent of suggesting duodenal ulcer or acute appendicitis. Rogers reported the first three cases of coexistent hyperparathyroidism and duodenal ulcer in 1946 and 1947 (7, 8). Black noted in a review of patients with hyperparathyroidism at the Mayo Clinic that "24 per cent of patients with proved hyperparathyroidism have at the time of examination, or had had in the past, objective evidence of peptic ulcer or had had operations on the stomach presumably because of ulcer. An additional 15 or 20 per cent of patients had some ulcer-like symptoms but an ulcer had never been proved" (9). Howard et al., stated that 15 per cent of cases of primary hyperparathyroidism reviewed at Johns Hopkins Hospital were complicated by peptic ulcer (10). St.

Goar reviewed 137 case records of hyperparathyroidism from Massachusetts General Hospital and found roentgenographically demonstrable peptic ulcers in 12 patients (11). Five additional patients had clinically evident peptic ulcers without x-ray confirmation. Hellström's review revealed that hyperparathyroidism was complicated by peptic ulcer in seven of fifty patients (12). Twelve of the 27 patients reviewed by Bogdonoff et al had gastrointestinal symptoms of severe enough degree to warrant detailed comment in the clinical histories (13). In St. Goar's most recent review (14) of 45 cases of hyperparathyroidism at Presbyterian Hospital, New York, peptic ulcers were demonstrated in four cases and gastrointestinal symptoms were prominent in 16 cases. The gastrointestinal symptoms noted percentagewise in this series were constipation 29 per cent, nausea or vomiting 20 per cent, anorexia 16 per cent, epigastric pain 13 per cent, diarrhea 4 per cent, and right upper quadrant post prandial distress 2 per cent.

In the majority of cases of peptic ulcer complicating hyperparathyroidism the ulcer is duodenal, but gastric and esophageal ulcers have been reported. Elkeles described a case of primary hyperparathyroidism associated with duodenal and gastric ulceration (15), and Berlin reported a case complicated by ulceration of the duodenum and eosophagus (16).

Most cases of coexistent ulceration and hyperparathyroidism occur in the middle and older age groups. However Tsumori et al., described a case where the association existed in a child ten years of age (17).

Primary Hyperparathyroidism Associated with Proven Peptic Ulcer

Male		Female		
Associated peptic ulcer	Total cases	Associated peptic ulcer	Total cases	Source
8	39	4	98	(11)
5	17	2	33	(12)
3	16	1	29	(14)
2	11	2	26	MSH
Total 18 (22%)	83	9 (5%)	186	

As noted in the accompanying chart, females with primary hyperparathyroidism outnumber males in the ratio of 2.2 to 1. Nevertheless, hyperparathyroidism in the male is complicated by peptic ulcer twice as frequently as in the female. These figures emphasize the high relative incidence of peptic ulcer in males with hyperparathyroidism. The actual per cent incidence in males and females with hyperparathyroidism is undoubtedly even greater since x-ray confirmation cannot always be obtained in patients with clinically evident peptic ulcers.

Statistics concerning the incidence of peptic ulcer in the general population are variable, depending on when and where the figures originate and whether they are based on x-ray or post-mortem examinations. Roentgenologic data cannot be used to determine with accuracy the percentage of people in the general population with peptic ulcer since an unknown number with peptic ulcer are never examined roentgenologically. The most valid comparison which could

be drawn regarding the incidence of peptic ulcer in hyperparathyroidism and in the general population would be based on the post-mortem incidence of peptic ulcers in each group. The small number of autopsied hyperparathyroid patients with peptic ulcer precludes this comparison. The only comparison that may be drawn, therefore, is between the incidence of peptic ulcer in hyperparathyroidism based largely on x-ray findings, and the incidence in the general population based on post-mortem findings. The pitfall in this comparison, aside from the fact that x-ray confirmation of peptic ulcer cannot always be obtained, is that the autopsy figures reveal a higher incidence of ulcers than would x-ray data since autopsy study undoubtedly includes cases without significant clinical symptoms and who would therefore not have had x-ray examinations. It has been estimated on the basis of post-mortem findings that approximately ten per cent of all persons, with a sex incidence of four males to one female, suffer at some time in their lives from chronic gastric or duodenal ulcers (18). It follows from these figures that 16 per cent of males and four per cent of females in the general population are so afflicted at some time in their lives. With the above reservations in mind, these figures are to be contrasted with the hyperparathyroid group in which 22 per cent of males and five per cent of females had coexistent peptic ulcers. It has previously been concluded that peptic ulcer complicates primary hyperparathyroidism too frequently for coincidence (19, 20).

Gastrointestinal symptoms in hyperparathyroidism, whether or not associated with demonstrable peptic ulcer, have markedly improved almost without exception after parathyroidectomy (6, 11, 21). In the few patients whose gastrointestinal symptoms have not cleared after parathyroidectomy, other adenomata have been postulated (14). The medical treatment of peptic ulcer complicating hyperparathyroidism has the inherent danger of precipitating acute parathyrotoxicosis and of calcium salt deposition in the urinary tract. Both of Rogers' original cases (7) died of hypercalcemia apparently secondary to high calcium diets prescribed in treatment of the duodenal ulcers.

THEORIES RELATING HYPERPARATHYROIDISM AND GASTROINTESTINAL COMPLICATIONS.

Several theories have been advanced to account for the relationship between hyperparathyroidism and gastrointestinal symptoms, particularly peptic ulceration.

A. *The parathormone theory.* Schiffrin (22) performed dog experiments in which he injected parathormone in amounts sufficient to increase serum calcium approximately two mgm. per cent. In the animals with innervated pouches there was an increased gastric pepsin concentration with a decreased total volume and acidity in response to test meals and histamine. In dogs with denervated pouches, there was an increased gastric volume and acidity with no change in pepsin concentration under otherwise similar conditions. Rutishauser and Majno injected large doses of parathormone into dogs and noted subsequent edema, necrosis and calcification of the glands of the gastric fundas (23). Simultaneously there was a sharp rise in serum pepsinogen levels. Engel injected rats with parathormone and noted a subsequent rise in serum mucoprotein levels

(24). This may have resulted from a breakdown of the gastrointestinal mucosa as well as the ground substance of bone and cartilage. However, no microscopic studies were done on the gastrointestinal mucosa. Sodeman and Williams favor the theory that the parathyroid hormone has a proteolytic action which may account for the peptic ulcers as well as the marked muscle weakness, fatigue, apathy and weight loss of hyperparathyroidism (25, 26).

B. *The genetic or constitutional theory.* St. Goar states that since there is no clear-cut cause and effect relationship between hyperparathyroidism and peptic ulceration, it is possible that both diseases are manifestations of some more basic abnormality (11). Underdahl et al., reported eight cases of multiple endocrine adenomata involving the parathyroids, pituitary and pancreatic islet cells (27). Three of the eight cases were complicated by peptic ulcers. Wermer reported a family in which the father and four of nine siblings were affected by multiple adenomata of the same glands (28). Of the five affected, peptic ulcers were present in four. The author suggests that the entire syndrome is a manifestation of an abnormal gene.

C. *The hypercalcemia theory.* It is generally accepted that the hypercalcemia per se of primary hyperparathyroidism may cause anorexia, nausea, vomiting and constipation (29). These symptoms are a result of the decreased neuromuscular excitability and tone of the upper and lower gastrointestinal tract. These gastrointestinal symptoms may be present when hypercalcemia occurs in diseases other than hyperparathyroidism. Hypercalcemia has been implicated as a possible cause of peptic ulcer in hyperparathyroidism since the sluggishness of the gastrointestinal tract in hypercalcemia may prevent healing of what would otherwise be subclinical, spontaneously healing ulcers (11).

None of the above theories is completely satisfactory, and it remains for future study to clarify the exact nature of the relationship between hyperparathyroidism and peptic ulceration.

SUMMARY

The literature and the experience at The Mount Sinai Hospital have been reviewed in regard to the gastrointestinal complications of primary hyperparathyroidism. The fact that males with hyperparathyroidism have a much higher incidence of peptic ulcer than females has been noted. The difficulty of comparing the incidences of peptic ulcer in the hyperparathyroid group and in the general population has been discussed. Finally, the theories relating the two diseases have been presented.

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RECURRENT HEMATEMESIS AND JAUNDICE FOLLOWING SPLENORENAL SHUNT

A Clinical Pathological Conference

Edited By

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A 51 year old white housewife, was admitted to The Mount Sinai Hospital in May, 1950 because of hematemesis on three occasions in the preceding eighteen months, and again on the day of admission. One month before a bleeding incident had occurred at which time esophageal varices had been demonstrated by x-ray at another hospital but were not seen on endoscopy.

In 1940, following several attacks of biliary colic and one day of jaundice without chills or fever, a cholecystectomy was performed for chronic cholecystitis and stones. In 1946, she had a hysterectomy for fibroids; she had three normal pregnancies during early married life. She was of Italian extraction but born in the United States. Her father and two brothers had diabetes but she was not diabetic. There was no history of hepatitis or other serious illnesses and she did not smoke or drink.

The patient was obese, not icteric, and in no acute distress. No spider angiomata were seen. The temperature was 100° F.; B.P. 116/80. No lymph nodes were felt. The lungs were clear. The heart was not enlarged, rate was 108 per minute and rhythm was regular. A soft diastolic murmur with presystolic accentuation was present at the apex. Inspection of the abdomen showed two operative scars. There were no dilated veins. The liver was palpable four finger-breadths below the right costal margin, and was smooth. The spleen was palpable one inch below the left costal margin. There was no edema or cyanosis of the extremities.

Laboratory studies were as follows: hemoglobin, 8 gm. per cent; RBC, 2.7 million per cu. mm.; WBC, 7,000 per cu. mm.; total serum bilirubin, 1.2 mg. per cent; cephalin flocculation, 2 plus; thymol turbidity, 3 plus; albumin, 2.6 gm. per cent; globulin, 4.8 gm. per cent; alkaline phosphatase, 42 King-Armstrong units; prothrombin time, 12.5 seconds with a control of 12; BUN, 26 mg. per cent; BSP retention, 48 per cent in one hour. The urine showed no sugar or albumin. Chest x-ray and electrocardiogram showed no abnormalities.

Transfusions were given and the bleeding stopped. Esophagram showed varices at the lower end of the esophagus. Bleeding recurred one month later and was controlled by a Sengstaken-Blakemore balloon and transfusions. Two months after admission, a splenorenal shunt was carried out, with splenectomy. The portal pressure was 265 millimeters of water. The liver was moderately enlarged, and the spleen was three times normal size. Dilated collateral veins were present. After the operation, she became mildly icteric, the serum bilirubin

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rising to 2.8 mg. per cent, and alkaline phosphatase to 91 King-Armstrong units. A low grade fever responded to antibiotics. A left pleural effusion was tapped, yielding 180 c.c. of sterile amber fluid. Additional blood studies were reported as: cephalin flocculation, 2 plus; thymol turbidity, 1 plus; albumin, 2.4 gm. per cent; globulin, 4.2 gm. per cent; and cholesterol, 260 mg. per cent with esters of 160 mg. per cent.

Nine months later, in April 1951, she was readmitted for study. She had felt well except for easy fatigue and severe skin itching, which had begun shortly after the operation. She was icteric, her skin had become darker, and numerous scratch marks were present. The liver had not changed in size or consistency. The serum bilirubin was 2 mg. per cent; alkaline phosphatase, 76 King-Armstrong units; cephalin flocculation, 3 plus; thymol turbidity, 24.7 units; prothrombin time, 17 seconds with a control of 12 seconds; albumin, 3.6 gm. per cent; globulin, 5 gm. per cent; BSP, 43 per cent retention in one hour. Barium meal revealed no change in the number and size of the esophageal varices.

On her third admission, June 21, 1951 to August 4, 1951, she complained of chills, fever, cough and substernal discomfort for two weeks. There had been no gastrointestinal bleeding since the operation. The temperature was 102° F. The sclerae were icteric. Pigmentation of the skin and scratch marks were present. Spider angiomata were seen for the first time on the face and arms. Palmar erythema was seen. Fine rales were heard over the right posterior chest. Diminished bronchial breathing was present in the left lung base. The heart was enlarged to about an inch beyond the midclavicular line. A mitral diastolic murmur with presystolic accentuation was heard. The liver was six fingerbreadths below the costal margin but there was no edema. A positive hepatojugular reflux was obtained. X-ray of the chest revealed marked congestion of both lungs and pleural effusions on both sides. There was considerable enlargement of the heart in all dimensions. Electrocardiogram showed low T waves in the standard leads, and slight elevation of ST_2, suggesting myocardial or pericardial involvement. Hemoglobin was 12.8 gm. per cent; WBC, 11,850 per cu. mm. with a slight shift to the left; sedimentation rate, 101 mm. in one hour; urinary urobilinogen, 1:80; BUN, 11 mg. per cent; fasting blood sugar, 135 mg. per cent; albumin, 2.4 gm. per cent; globulin, 4.9 gm. per cent; bilirubin, 2.7 mg. per cent; alkaline phosphatase, 74 King-Armstrong units; cephalin flocculation, 3 plus; thymol turbidity, 9.6; cholesterol, 538 mg. per cent.

Twenty-five cubic centimeters of cloudy amber fluid withdrawn from the left chest showed 17 per cents polys, 83 per cent round cells, and numerous red cells. No organisms were found on smear and guinea pig inoculation, nor were any tumor cells seen on cell block. Pericardial tap produced 325 cc. of blood tinged fluid which revealed 16 per cent lymphocytes, 82 per cent polys, and 2 per cent bands on smear. Again, no organisms were obtained on smear and guinea pig inoculation. The response to penicillin, aureomycin and terramycin was slow, and a low grade fever persisted for several weeks until just before discharge. Blood cultures were sterile, cold agglutinins were less than 1:5, and heterophile agglutination was 1:56. Antifibrinolysin titer was negative.

She returned home and continued to complain of fatigue and skin itching. Her appetite was poor and she had considerable distress after eating. She had lost about 15 pounds. Her urine was dark and the stools were pale. In 1954 she vomited a small quantity of blood and passed a tarry stool. She was treated at home. Three days before admission on October 5, 1955 she again vomited blood and noted tarry stools. On examination she appeared chronically ill. Her skin had become much darker. Xanthelasma was seen on both upper eyelids. Spider angiomata were not present. Dullness and diminished breath sounds were present at the left lung base. The heart was enlarged and apical murmurs were heard as on the previous admissions. The liver edge was three finger-breadths below the costal margin.

The urine showed no sugar or albumin. Urobilinogen was 1:20 but no bilirubin was demonstrated. Hemoglobin 12.9 gm. per cent; WBC, 11,250 per cu. mm.; FBS, 154 mg. per cent; albumin, 3.3 gm. per cent; globulin, 3.3 gm. per cent; bilirubin, 4.2 mg. per cent; cholesterol, 300 mg. per cent (esters, 201 mg. per cent); alkaline phosphatase, 54 King-Armstrong units; cephalin flocculation, 3 plus; prothrombin time, 14 seconds with control of 12. Studies of the blood proteins revealed a lowered serum mucoprotein of 30 mg., low alpha 1- globulin of 3.6 units and elevated gamma globulin of 25.5 units.

Chest x-ray revealed a left pleural effusion and an enlarged diameter of the heart. Barium meal disclosed persistence of the eosphageal varices. Intravenous cholografin test showed no dye in the biliary ducts.

The bleeding was controlled by Sengstaken-Blakemore tube and transfusions. She was discharged thirty-seven days after admission and advised to return for a portocaval shunt.

She returned four weeks later for her fifth admission again because of hematemesis and melena. Significant changes on physical examination included a blood pressure of 190/100, the presence of auricular fibrillation and congestive heart failure.

The total serum bilirubin was now 5.2 mg. per cent and 2.9 mg. per cent prompt direct in 1 minute; cholesterol, 340 mg. per cent (esters, 296 mg. per cent); cephalin flocculation, 2 plus; alkaline phosphatase, 43 King-Armstrong units; albumin, 3.5 gm. per cent; globulin 4.4 gm. per cent. Again the esophageal balloons were used and transfusions given. Digitalis was added. On the third day, she became stuporous and lapsed into coma. Increased deep reflexes in the right upper and lower extremities were associated with a right Babinski and right ankle clonus. She expired shortly after the onset of respiratory difficulty.

DR. ALEXANDER B. GUTMAN: Today's case affords an excellent opportunity to consider the differential diagnosis of cirrhosis, and I hope that, as the clinical story unfolds, you will be thinking about the more important forms of cirrhosis. These include Laennec's cirrhosis, postnecrotic cirrhosis, the cholangiolitic form or primary biliary cirrhosis, and the secondary biliary cirrhosis which follows obstruction of the extrahepatic biliary tract.

The patient was a fifty-one year old housewife, first seen at The Mount Sinai Hospital in 1950, when she entered because of vomiting of blood. Her past

history is informative. In 1940, at the age of 41, a cholecystectomy was performed for repeated attacks of right upper quadrant pain and jaundice of one day duration. No chills or fever were recorded. At the time of operation an inflamed gall bladder containing stones was removed. We have no information as to whether or not the common duct was explored, but it is not unlikely that the duct may have been opened, in view of the presence of jaundice.

The patient was of Italian stock. This is of interest in view of the high incidence of portal or Laennec's cirrhosis in Italians. This does not mean, however that Italians do not suffer from other forms of cirrhosis.

In December 1948, the first sign of cirrhosis, namely hematemesis, appeared and in the next two years before her admission here she had three episodes of massive bleeding. We are told that esophageal varices were demonstrated on one occasion, but even if this is so, the early onset of hematemesis would raise the question of whether she might not have had a peptic ulcer, which is so frequently seen in association with cirrhosis.

The following negative points are relevant to the differential diagnosis: 1. There was no history of alcoholism, but the drinking of wine with meals is prevalent among Italians, and presumably contributes to the high incidence of Laennec's cirrhosis among them. 2. There was no history of dietary deficiency, and, in fact, the patient was an obese person. 3. There was no history of antecedent liver disease, such as hepatitis. 4. There was no story of arsphenamine injection. These were the days before chlorpromazine was introduced.

On examination the patient was not in acute distress. She was not jaundiced. Examination of the heart revealed signs of what must be presumed to be mitral stenosis of rheumatic origin. These signs persist all through the history, which continues for about five years. Examination of the abdomen was rewarding. The liver edge was felt four finger-breadths below the right costal margin and the spleen was easily palpable two finger-breadths below the left costal margin. She had no spider angiomata or other superficial evidences of portal hypertension, although the hematemesis and the x-ray evidence of esophageal varices may be taken as indications of portal hypertension.

The urine showed no bile. There was a slight anemia. The white blood count was 7,000 per cu. mm. with a normal differential. Electrocardiogram showed no abnormalities. The serum bilirubin was 1.2 mg. per cent. There was evidence of some liver cell "irritation"; a cephalin flocculation test was 2 plus, and a thymol turbidity test 3 plus. An important finding was a high serum alkaline phosphatase of 42 King-Armstrong units indicating marked obstruction of the biliary tract. The rest of the blood chemical studies were normal, except for a bromsulfalein retention of 48 per cent at the end of one hour. The chest x-ray was negative.

The clinical story suggests cirrhosis of the liver in an Italian woman, aged fifty-one. Her symptoms included bleeding as evidence of portal hypertension and the blood studies showed obstruction of the biliary tract, as reflected by the high alkaline phosphatase, and some liver cell damage as indicated by the flocculation and turbidity tests.

She was treated for bleeding in the conventional manner with transfusions. Subsequently, esophagram confirmed the presence of large esophageal varices. Approximately two months after admission, a splenorenal shunt was performed. At operation the liver was described as moderately enlarged. There is no mention of nodularity of the liver or of jaundice. The portal pressure was increased. The spleen was three times normal size and had to be removed in the course of the splenorenal shunt. The pathological examination of the spleen, as expected, showed the changes of congestive splenomegaly.

She did well except for a small collection of fluid in the left pleural space. There was little change in her blood chemical findings except for a rise in the serum alkaline phosphatase to 91 King-Armstrong units. The serum cholesterol at this time was 260 milligrams per cent, of which 160 mgms. were cholesterol esters.

She was discharged from the hospital and apparently did very well. She was readmitted ten months later for re-evaluation. Her sclerae were now slightly icteric. Brownish pigmentation was present on the back, together with multiple skin excoriations, indicating marked pruritus. The liver was now three finger-breadths below the right costal margin and there was some suggestion of a pleural effusion on the left. On chemical examination of the blood the previous findings were substantially unchanged. Again there was a three plus cephalin flocculation test and the serum globulin was conspicuously high; 5 grams per cent. The presence of biliary tract obstruction was verified by the high alkaline phosphatase. We do not know whether the obstruction was within the liver or outside it, in the extrahepatic biliary tract. Associated with the obstruction some were indications of parenchymal liver damage.

Now comes an ominous note in the history. Bilateral renal function was tested with ureteral catheters and there was some diminution in urine flow on the left as compared with the right. Also we are beginning to get indications that the splenorenal shunt has closed; an esophagram again revealed varices which she should not have had if the shunt were patent.

Despite all this, she did fairly well. In June 1951, a few months later, she again entered the hospital, but this time because of some infection. I have mentioned that she had mitral stenosis, presumably of rheumatic origin and this episode may have represented a flare-up of rheumatic fever, with acute rheumatic carditis and a related pleural effusion. As far as the liver is concerned, more extensive, diffuse brownish pigmentation of the skin was noted and one begins to think of the possibility of hemochromatosis although this is very rare in women. Again there were scratch marks. Spider angiomata were noted and there were signs of parenchymal liver damage. The liver was now six finger-breadths below the costal margin. There was no edema. X-ray of the chest revealed marked pulmonary congestion and bilateral pleural effusions. The electrocardiogram suggested pericardial effusion. The blood cholesterol had risen to 538 milligrams per cent, fitting the picture of biliary cirrhosis, and there were continued indications of liver cell damage with a 3 plus cephalin flocculation test.

A left thoracentesis yielded 25 c.c. of cloudy amber fluid and a pericardial tap produced 325 c.c. Every effort to find a specific bacterial agent was without result. No evidence of tuberculosis was turned up. I would guess that this acute illness was a rheumatic or viral pericarditis, with pleuritis.

Her fourth admission was in 1955, four years later. She was now 55 years old. When we consider that the onset of her illness was in 1948, with bleeding due to esophageal varices, we realize that this is a rather prolonged course for a patient with cirrhosis under these circumstances. Again, the story is that of recurring hematemesis and melena. Xanthelasma of the upper lids was noted for the first time, a frequent finding in primary biliary cirrhosis. In addition, there was generalized darkening of the skin, but not the kind seen in prolonged deep icterus; this is more like a melanin pigment. There are signs of fluid at the left base, and again there are the signs of rheumatic heart disease.

The liver was now a little smaller. It was beginning to shrink and I think that this indicates more and more cellular damage. The blood chemical findings check with the previous results. Her serum albumin remained very low and the globulin was still very high. The serum cholesterol which was over 500 mg. per cent, was now down to 276 or 300, presumably as a result of progressive hepatocellular damage. The cephalin flocculation test was still 3 plus.

While the obstructive element previously dominated the picture and was still present, liver cell damage was becoming prominent. Esophagram still showed varices in the lower third of the esophagus, again indicating that the splenorenal shunt was inadequate.

Transfusions again controlled her bleeding. By this time, in view of the evidence of closure of the splenorenal shunt, her physicians made the very serious decision to perform a portocaval shunt. She was sent home to convalesce, but had to return in a short while because of renewed bleeding.

On this occasion, in December 1955, she again had signs of rheumatic heart disease. She was now frankly icteric. The serum total bilirubin was 5.2 milligrams per cent. The serum cholesterol was 340 mg. per cent; esters, 296 milligrams per cent. The cephalin flocculation test was again 2 plus. The serum albumin was a little higher at 3.2 grams per cent. The serum globulin was still high.

She was in congestive heart failure and she was digitalized. Again, attempts were made to control bleeding, but apparently this time without success. Because of the continued bleeding, hepatic insufficiency ensued and she became semistuporous and comatose. She developed evidence of tracheobronchitis, required constant suctioning, and died in what might be called hepatic failure.

This is a very instructive case. I suspect that you have decided that this is not the usual type of Laennec's portal cirrhosis. It is probably a form of biliary cirrhosis, and we shall have to decide whether the biliary obstruction is intrahepatic or in the extrahepatic biliary tract.

The biliary tract obstruction could be extrahepatic. She had had a gall bladder operation and stones were found. It is entirely possible that she had a stone impacted in her common duct, perhaps a stone which was in a hepatic duct at

the time of operation. It is possible also that she may have had a common duct stricture, following exploration of the common duct. I think, however, that there are some points in her history that argue against biliary cirrhosis secondary to prolonged obstruction of the extrahepatic biliary tract.

In the first place, there is a long interval between her surgery in 1940 and the onset of symptoms in 1948. It is difficult to conceive of a stone or stricture persisting all that time without causing symptoms such as fever, chills or pain. Because there were no attacks of chills and fever throughout the course, and there was very little pain, I am going to assume that the source of the obstruction is not a stone or a stricture of the common ducts.

This suggests, then, that we are dealing with primary cholangiolitic cirrhosis or what is known as primary biliary cirrhosis. This is a disease which occurs particularly in females, in the forty to fifty age period, and is characterized by an insidious and prolonged course without much jaundice. There is usually severe pruritus, even with little jaundice. There is increased serum alkaline phosphatase and a high serum cholesterol. Skin pigmentation occurs frequently. The liver is large and firm. It is not grossly nodular, as in Laennec's cirrhosis. Portal hypertension may develop, usually not as early as in this case unless we assume that the disease was present for some years before 1948. The biliary obstruction is characterized by cholestasis, bile duct proliferation, "cholangiolitis" and periportal infiltration. As the disease progresses, one sees more and more liver cell necrosis and connective tissue replacement.

I would guess that the splenorenal shunt is no longer patent and that there is a thrombosis of the splenic vein at the site of the shunt. Extensive varices should be present at post mortem as an indication of portal hypertension. I would expect that there would be evidence of rheumatic heart disease, specifically of the mitral valve, and of an old pericarditis. I have no good explanation for the recurrent left sided pleural effusion; this may be related to the rheumatic state or it may be an expression of congestive failure.

DR. HANS POPPER: The surgical specimen of the spleen was available. The record states that it was about three times normal size. The architecture of the spleen (Fig. 1) appears well preserved. The follicles are normal. There is considerable hyperemia, but I would not suspect the presence of portal hypertension. A connective tissue stain (Fig. 2) shows an increase in fibrous tissue. This is the picture of an early stage of fibro-congestive splenomegaly, which has been so well described by Dr. Moschcowitz of this institution.

The skin shows an increase in melanin in the basal layer, a characteristic change. We really do not know the nature of this pigment which leads to the brownish discoloration. There is no iron. We cannot state whether we are dealing with an increased amount of melanin, or with a melanin-like substance of other biochemical origin, possibly derived from the porphyrin series of pigments. The skin also shows a dermatitis or dermatosis. Thus, there are two skin manifestations, an excessive pigmentation and a dermatitis.

The heart is enlarged, weighing 350 grams. There is marked hypertrophy of the right chamber. There is thickening and irregularity of the tricuspid valve,

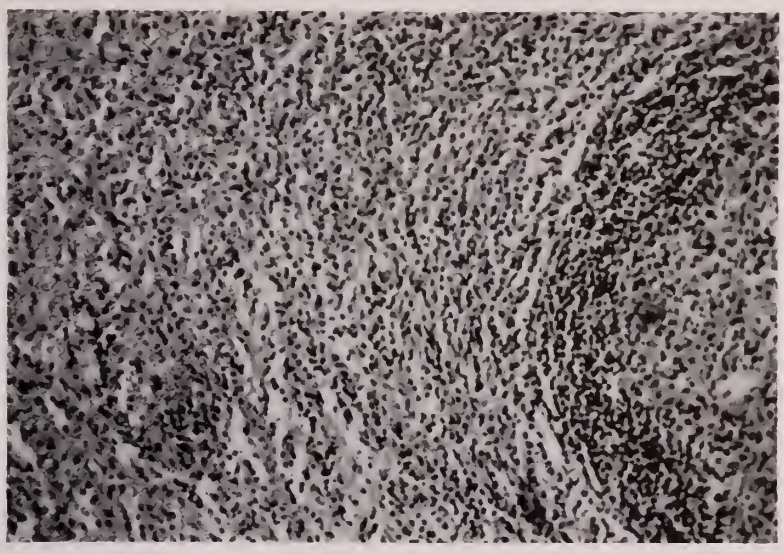


FIG. 1. Spleen (H & E) Normal architecture is noted with lymphoid follicles preserved and hyperemia of pulp.

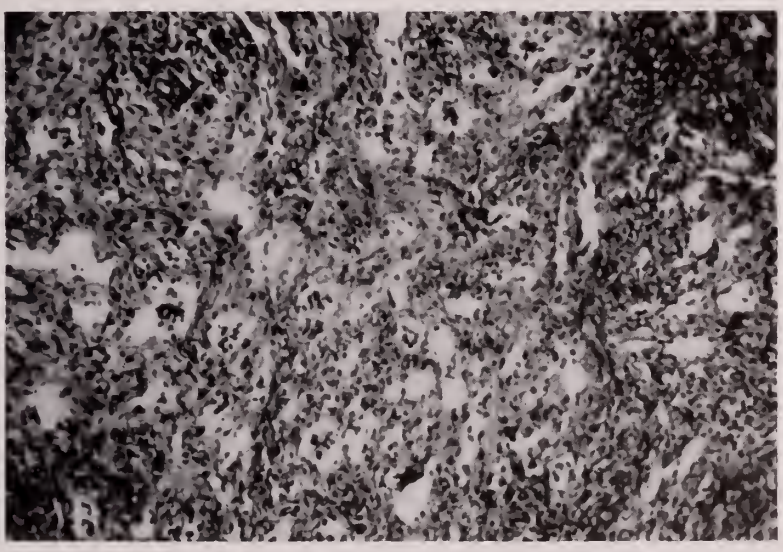


FIG. 2. Spleen (Connective tissue stain) Moderate interstitial fibrosis with dilated empty sinusoids.

which suggests a rheumatic origin. The protocol states that there is some vascularization indicating an old process. The left ventricle is relatively small. The mitral valve is markedly stenotic and the record states that it admits only the tip of the little finger, and that there is some fusion of the leaflets. The microscopic section shows a deformity of the mitral valve with scarring, and fibrotic

narrowing, but there are no acute rheumatic changes. The endocardium is thickened with no acute change. The heart muscle shows extensive fibrosis, arranged in spindle-shaped manner. There is an interstitial myocarditis involving different areas of the myocardium and which has probably contributed to her death. Is this just an interstitial myocarditis, or are the heart muscle fibres involved? Another view shows that the muscle fibres are broken down. This is probably a myocarditis which could be caused by obstruction of a vessel, possibly by bacteria.

The lung shows a pleurisy and a significant thickening of the alveolar septum. There is a pneumonia, a terminal event. There is an extensive diffuse fibrosis involving the entire alveolar septum. Very few of the smaller septa are involved. This picture can occur without cyanosis, and the patient was not cyanotic. The blood vessels are not diseased, but there is some perivascular fibrosis. I would say that this is the picture of pulmonary fibrosis.

The pancreas, which is always interesting in cirrhosis, shows some irritative phenomena, but no definitive changes.

The esophagus shows varices in the lower third. There are also varices in the cardiac portion of the stomach. There is also a mild esophagitis.

The liver is small, weighing 1100 grams. The capsule is not thickened. The cut surface shows some distortion of the architecture. We have to rely on the autopsy record for a report of the state of the extrahepatic biliary tract. This states that the common bile duct is slightly dilated, but that there is no evidence of biliary obstruction. There is no scarring or stricture, and no evidence of an extrahepatic biliary obstruction. On gross inspection, we would not call this a cirrhotic liver, but we would have to say that there is distortion of the lobular architecture.

The original section (Fig. 3) shows some septa extending throughout the liver and contributing to some irregularity. The lobular architecture is intact, except for septa which extend through the liver like the fingers of a hand. There is increased activity in the portal tract, but in most areas there is an intact central lobular vein. There are nodules and increased cellularity in some areas. In one region, the connection between the portal and the central canals can be seen.

There is some disturbance in blood flow, with congestion due to circumscribed compression of the portal veins. However, considering the long story of hypertension, one would expect to see more evidence of cirrhosis. In the portal tract, there is a moderate fibrosis with some cellular compression. The parenchyma too, shows some areas of interstitial fibrosis. Since these are seen in only a few areas, one must conclude that we are dealing with an early cirrhosis in which there is a marked portal inflammatory reaction.

In this inflammatory area, (Fig. 4) there are a large number of cells, but strangely, there is a marked absence of bile duct. Instead, of the expected presence of considerable bile duct proliferation, there are almost no bile ducts to be seen. There is a large number of plasma cells which may be a factor in the patient's hyperglobulinemia. In this area, there is disintegration of liver cells with

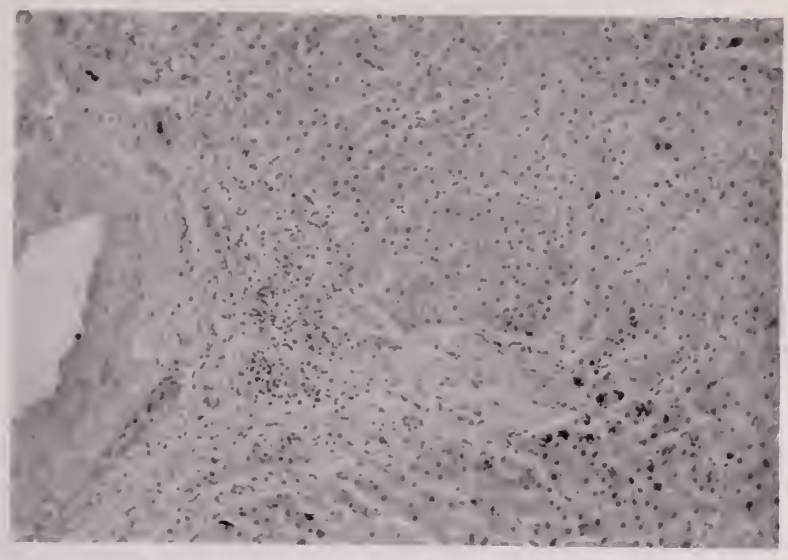


FIG. 3. Liver (H & E) Finger like septa of fibrous tissue seen extending from the portal fields to subdivide the hepatic lobule.

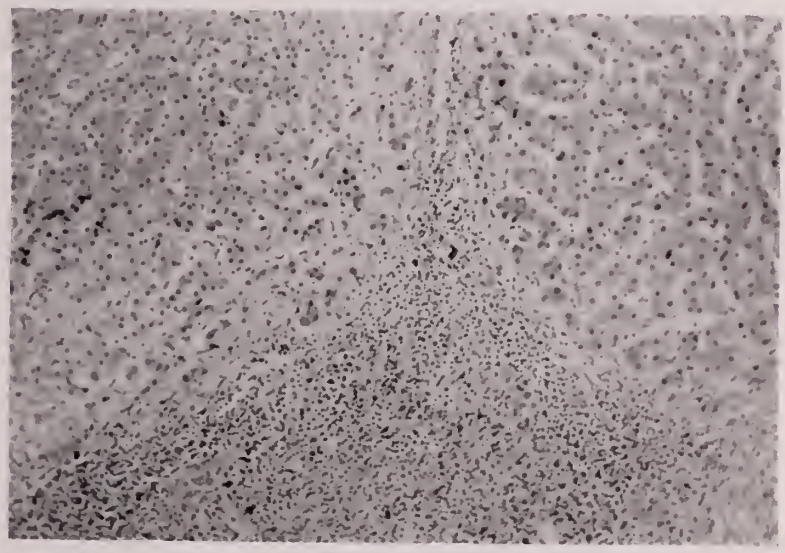


FIG. 4. Liver (H & E) Marked chronic inflammatory reaction seen in the portal field extending into the fibrous septa.

connective tissue replacement. The association of fibrous tissue is not commonly seen with this coagulation necrosis of the liver cells. Bile ducts are also seen in this area.

How is the portal hypertension to be explained? There is insufficient nodular regeneration to explain the compression of the portal vein. The hepatic veins

are patent. It may be that there is a mechanism, not clearly understood, which brings increased arterial pressure upon the portal veins. This portal hypertension was relieved by the splenorenal shunt, but recurred after obliteration of the shunt.

Now, as to the bile duct pathology; we do not believe that there is a stricture, but rather that a change in permeability occurs. This may lead to a regurgitation as well as dehydration of bile, a process operative in the early stages of disease. Eventually, severe inflammation results, as you see in this case. This is probably a response to the regurgitation of bile, but one cannot be certain. Our case does not confirm this hypothesis, because we see only the end stages of inflammation. Fibrosis has caused kinking and destruction of the duct, and later liver cell necrosis. One cannot be certain whether the liver cell necrosis is secondary to the inflammation and necrosis, or whether it is its cause.

In summary, we are dealing with a case of primary biliary cirrhosis in which jaundice and a cholecystectomy preceded the onset by several years. As Dr. Gutman has suggested, we don't think that the operation had anything to do with the lesion, which is intrahepatic. I think that this is primary biliary cirrhosis. Most of these cases occur in young women or menopausal women. Perhaps, an endocrine factor may be implicated, but this is speculative. However, whatever the cause of the periportal scarring and necrosis, a real intrahepatic obstruction develops, and this leads to a primary biliary cirrhosis of unknown etiology. Eventually, death occurs as a result of primary biliary cirrhosis.

A PHYSICIAN: I am puzzled by one thing. The patient presumably died in hepatic coma, and yet the amount of liver damage is minimal. How do you explain the minimal cirrhosis in terms of quantity of involved liver tissue and the gross hepatic disturbance?

DR. POPPER: This is a very pertinent question. One must ask, was she in coma? I am not sure. The hepatic failure might have resulted not from anatomic damage to the liver cells, but rather from failure of the blood to reach the liver cells with resultant hepatic anoxia.

Radiological Notes

Edited By

BERNARD S. WOLF

CASE NO. 41

S. H., a 65 year old white female, was admitted with the chief complaint of colicky pain in the mid and right abdomen for 5 weeks. These pains were described as resembling labor pains, occurring up to 3 times a day and lasting about an hour. They were associated with nausea but no vomiting. There was a history of a black stool on one occasion. For several years, the patient had complained of rather vague upper abdominal pain and heartburn and, as a result, had been treated with a low fat diet. As far as could be determined, there was no unequivocal evidence of cholecystitis or cholelithiasis. There was no history of jaundice or of any previous abdominal operation.

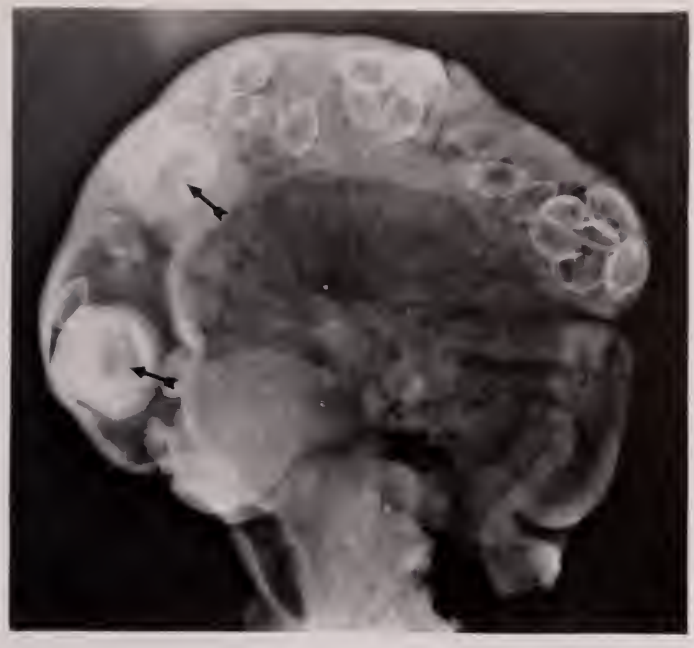
Physical examination showed an obese female in moderate distress. There was tenderness to deep palpation in the region of the epigastrium and to the

Case 41, Fig. 1a. Film from the small bowel series demonstrates a segment of distal ileum about 3 inches in length with marked, rather discrete dilatation. This region contains a large number of filling defects that have the appearance of foreign bodies. In the center, there is a large ovoid defect about 3 cm. in its greatest diameter. Immediately distal to the sac-like dilated segment (arrow), there is a short marked stricture with tapering margins both proximally and distally.

Case 41, Fig. 1b. Another film from the small bowel series with less barium in the dilated segment permits recognition of the majority of the foreign bodies as fruit pits. They are elongated, sharply demarcated with pointed ends and show within their substance arcuate lines of greater lucency paralleling the surface. These lines represent retained gas within the pit. Moderate dilatation of the ileum for a short distance proximal to the segment containing the pits is present.

right of the umbilicus. No masses were palpable. Blood pressure was 210/100. The remainder of the physical findings were not contributory.

Roentgen examination of the small bowel showed a localized, markedly dilated segment in the distal ileum with a stricture at its proximal end, located about 1½ inch from the ileocecal valve. This stricture was about 2 or 3 mm. in diameter and about ½ cm. in length. Barium passed this stricture with little difficulty. Within the sac-like dilated portion of ileum (Fig. 1a), there were a large number of filling defects at least one of which appeared to be about 3 cm. in diameter and somewhat ovoid in shape. However, on closer examination of the small filling defects (Fig. 1b), they appeared to have a surprisingly geometrical or symmetrical boat-shaped configuration with sharpened points at each end. Moreover, within the individual filling defects, lucent lines could be seen paralleling the surface. The appearance was that of fruit pits (usually plum or prune pits), impacted as a result of obstruction due to a stricture. The possi-



Case 41, Fig. 2. Roentgenogram of the specimen showing two dozen fruit pits covered by adherent barium. The two larger defects (arrows) also show pits in their centers. The inspissated fecal material deposited about these pits has a laminated appearance.

bility, however, that the larger filling defect represented a bilary calculus could not be excluded. The ileum for about a foot and a half proximal to the sac-like area of dilatation was moderately dilated but appeared mobile and not intrinsically diseased. The cause of the stricture in the terminal ileum was not apparent from the roentgen examination.

On exploratory laporotomy, the stricture was discovered a short distance proximal to the ileocecal valve. At the site of the stricture, there was no evidence of any extrinsic band or adhesions or of any kink in the bowel. The serosa over the dilated segment was somewhat dulled and its wall was thinned. Within it, a large number of foreign bodies could be palpated. Multiple enlarged mesenteric nodes, some of which were calcified, were palpated. An ileocecal resection was performed.

On opening the specimen, a superficial ulceration was demonstrated in the short stricture which appeared to be fibrotic in nature. About two dozen foreign bodies covered with inspissated brown stool were present in the ileum. A film of the specimen (Fig. 2) confirmed the pit nature of these foreign bodies and demonstrated also that two large concretions had, within their centers, pits as well. None of the foreign bodies appeared to be biliary calculi. Microscopic examination confirmed the gross findings but did not elucidate the nature of the stricture. Incidentally, the patient did not recall swallowing pits.

Final Diagnosis: Benign stricture of the ileum with incomplete obstruction and retention of fruit pits.

CASE NO. 42

(Submitted by Dr. Max L. Som, M.D.)

H. H., A 47 year old male, was admitted with the chief complaint of hoarseness of one month duration. There was a history of occasional dysphagia on swallowing solid food of relatively recent origin. Indirect laryngoscopy revealed a broad-based mass attached to the left arytenoid but covered by intact mucosa. The pyriform fossa on the side of the lesion was obliterated. There was no impairment of motility of the vocal cords and no cervical adenopathy. The remainder of the physical examination was not contributory.

Tomography of the larynx demonstrated (Fig. 1) a soft tissue mass occluding the left pyriform fossa and involving the left arytenoid region. The true and false cords were displaced medially and the ventricle was obliterated. The subglottic region was normal.

Case 42, Fig. 1. Tomography of the larynx in the AP plane prior to operation demonstrates obliteration of the left pyriform fossa, bulging and medial displacement of the left true and false cords with almost complete occlusion of the ventricle. The subglottic region is normal. (Incidentally, two accessory ossicles are seen along the superior aspect of the manubrium between the inner ends of the clavicles.)

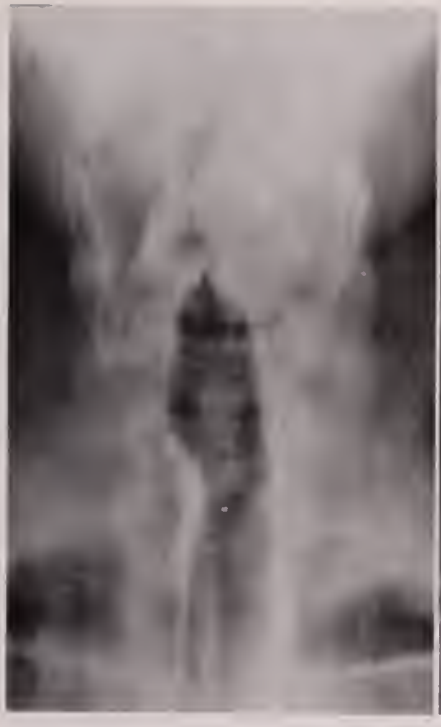


Fig. 2a.

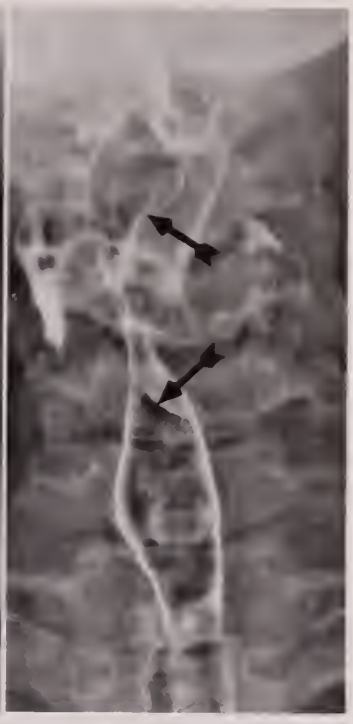


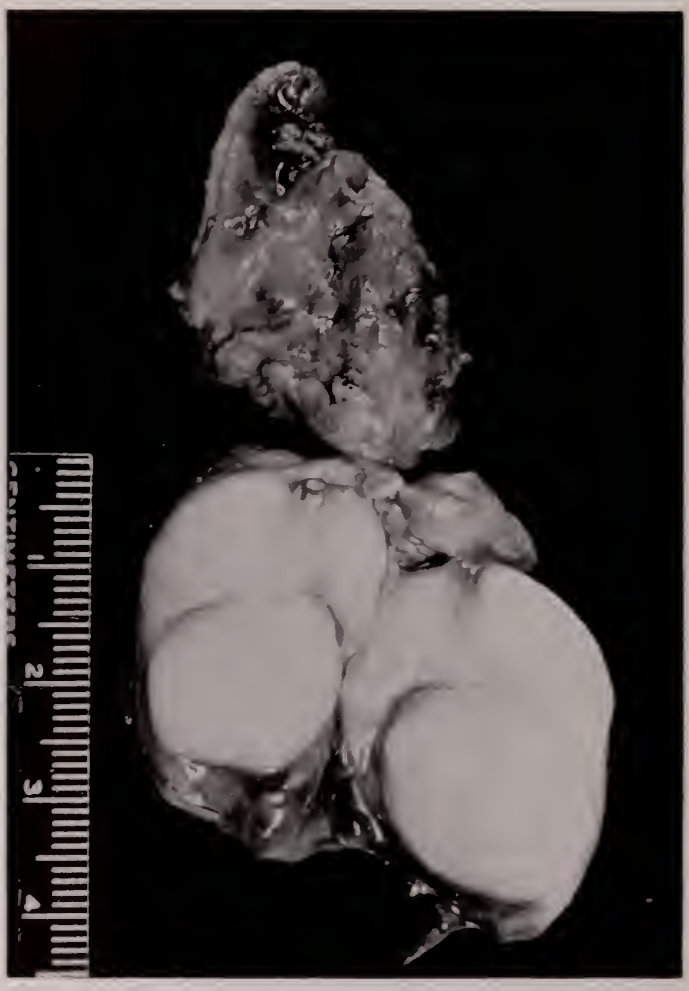
Fig. 2b.

Case 42, Fig. 2a. Tomographic re-examination 8 months after operation shows findings similar to those seen prior to operation. The mass is larger, deforms the left eryepiglottic fold and completely obliterates the ventricle with slight thickening in the left subglottic region. The narrowing of the trachea about 1½ inch distal to the larynx is the result of previous tracheotomy.

Case 42, Fig. 2b. Barium swallow shows aspiration of barium into the larynx and the trachea. No barium entered the left pyriform fossa. The arrows indicate the surface of a hemispherical, sharply demarcated, smooth mass projecting into the larynx, extending from the eryepiglottic fold to the subglottic region.

After tracheotomy, a lateral pharyngotomy was performed and the tumor exposed. It was found to be about 5 cm. in length, attached by a broad base to the posterior surface of the arytenoid and projecting into the esophageal lumen. The tumor was ablated at its attachment and the surrounding mucosa approximated. The pathological report was neurofibroma.

Eight months after the first operation, the patient again began to complain of hoarseness and laryngoscopy revealed thickening and medial displacement of the left true and false cords with limitation of motion. Tomography of the larynx (Fig. 2a) demonstrated a large ovoid mass involving the left side of the larynx and extending into the pyriform fossa with obliteration of the ventricle. Barium swallow (Fig. 2b) demonstrated that the distal extent of the lesion extended to the lower margin of the thyroid cartilage and that its surface appeared to be quite smooth and sharply demarcated. The patient was operated on again



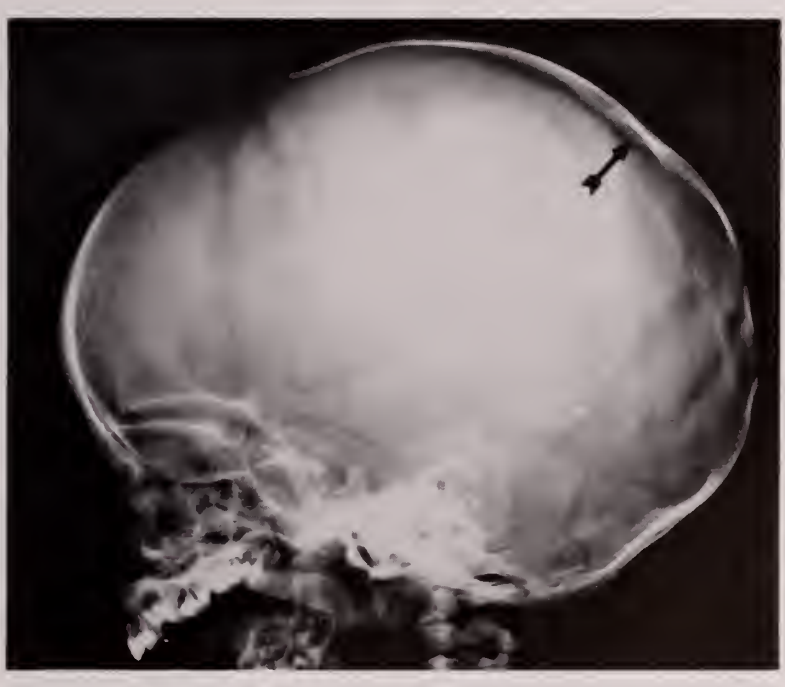
Case 42, Fig. 3. Cut section of the resected specimen demonstrates the tumor to be somewhat lobulated and encapsulated. Above the tumor is seen the resected epiglottis. The tumor measured about 3 cm. in diameter.

and a large submucosal tumor dissected free. The tumor extended from the base of the epiglottis distally to the lower border of the thyroid cartilage and was encapsulated. The mass had to be separated from the wing of the thyroid laterally and the cord mesially by blunt dissection. The major portion of the epiglottis was extirpated in continuity with the neoplasm. Post-operatively, the patient did well, swallowing was normal and both cords moved well. Fig. 3 is a photograph of the resected specimen. Microscopic report confirmed the previous diagnosis.

Final Diagnosis: Neurofibroma of the larynx.

CASE NO. 43

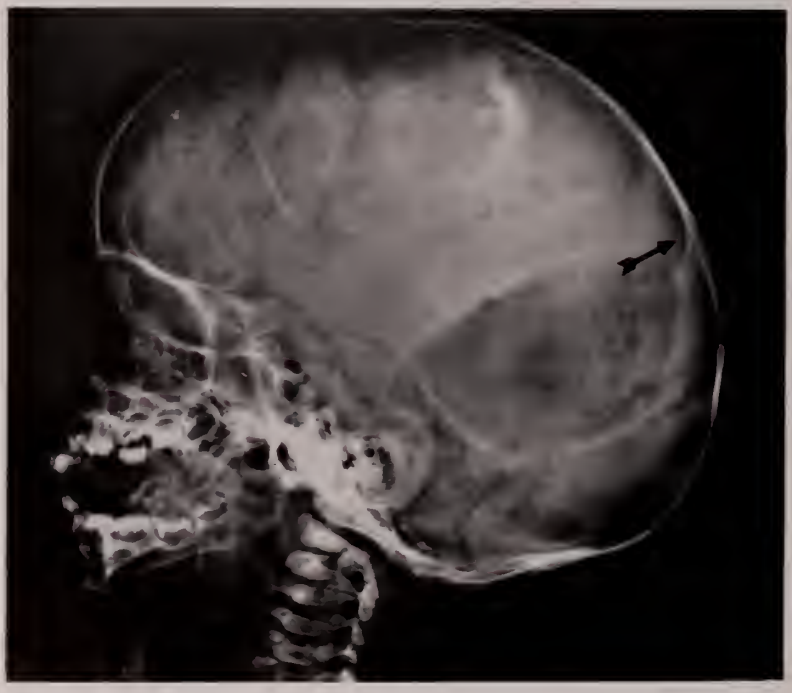
C. M., a female child of 6 months, was admitted with the chief complaint of drowsiness for 8 days. One month prior to admission, the child sustained a burn of her left forearm which healed slowly. Eight days before admission, the child became markedly drowsy, irritable when aroused and took feedings poorly. She preferred to assume the opisthotonus position. The child was a normal full-term spontaneous delivery with a birth weight of 7 lbs. and 8 oz. Family history was not contributory. According to the father, the child always had a rather large head which, however, had become much more marked recently. The mother agreed that the head had increased in size to an unusual degree recently but was uncertain that the head had always been large. No remarkable abnormality in the development of the child had been noted. On admission to a local hospital, the child was treated with a tentative diagnosis of meningitis. Bulging fontanelles were found, a white count of 23,000 and 15 cells in the spinal fluid. The patient was, however, afebrile and the sugar and protein values in the cerebrospinal fluid were within normal limits. The child did not improve and was transferred to this hospital.



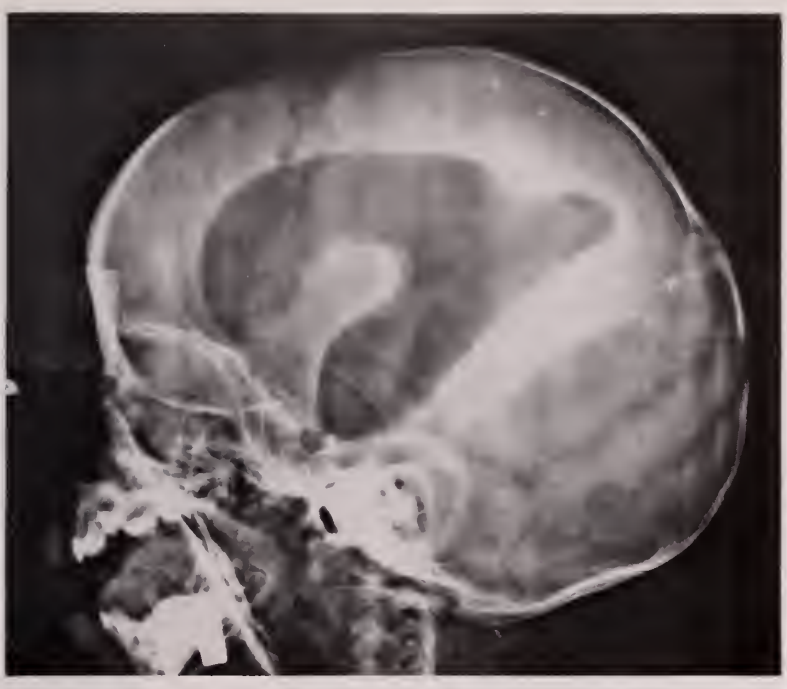
Case 43, Fig. 1a. Lateral view of the skull shows considerable increase in the AP diameter with marked thinning of the bones of the calvarium. The sutures are widened; the sella turcica is not remarkable. The superior portion of the occipital bone, extending on to the parietal bone shows multiple, flat scalloped indentations. The most superior of these (arrow) shows an intact inner table which can be followed downward and laterally when the projection is slightly off the true lateral as in Fig. 1b.

On admission, the child was obviously chronically ill with a hydrocephalic head which measured almost 19 inches in circumference. Temperature was 100.8, respirations 26 and pulse 118. The child weighed 16 lbs. and 8 oz. Both fontanelles were bulging. The pupils were dilated and fixed to light but this was attributed to mydriatic drops. The fundi showed moderate venous distention with questionable blurring of the disc margins but no elevation of the discs and no hemorrhages or exudates. The neck was supple and there were no meningeal signs. No localizing neurological findings were present. Lumbar puncture showed clear colorless fluid with a pressure of 70 mm. of mercury. Protein was 58 mgm. % and 80 mgm. % on another occasion. The sugar was 53 mgs. %. A few red blood cells and white blood cells were seen on smear.

Roentgen examination of the skull showed considerable increase in the AP diameter with widening of the sutures and bulging of the fontanelles (Fig. 1a). There was no evidence of abnormal intracranial calcification. The sella turcica was within normal limits. The calvarium was diffusely thinned but in the occipital squama extending onto the parietal bone, the inner table of the skull showed multiple indentations producing a scalloped appearance. These stopped rather abruptly in the posterior parietal region at a point above the lambdoid sutures. At this point, a more discrete groove with an intact inner table was present



Case 43, Fig. 1b. Lateral view of the skull after pneumoencephalography shows a huge collection of air in the posterior fossa. Only a few bubbles were seen in the ventricular system. Arrow indicates the downward and lateral continuation of the groove for the transverse sinus.



Case 43. Fig. 1c. Ventriculography demonstrated considerable symmetrical dilatation of the lateral ventricles and of the third ventricle. The marked obliquity of the floor of the posterior horns, atria and temporal horns is striking. The lower margin of the ventricular system parallels the upper margin of the air collection in the posterior fossa. Between the ventricular system and this air cyst lies the tentorium of the cerebellum which extends posteriorly to the groove for the transverse sinus. This groove on the parietal bone is abnormally high and indicates the congenital origin of the distention of the posterior fossa.

(Fig. 1a, arrow). The significance of this groove which, in a slightly off-lateral projection, extended downward and laterally (Fig. 1b, arrow), was not appreciated at the time. Pneumoencephalography (Fig. 1b) showed a few bubbles of air in a dilated ventricular system but a huge collection of air was seen occupying the posterior fossa. Ventriculography (Fig. 1c) confirmed the presence of symmetrical dilatation of the lateral ventricles and of the third ventricle and demonstrated a remarkably increased tilt toward the vertical of the floor of the occipital horns, atria and temporal horns. Air was also present in the large cavity in the posterior fossa; the upper margin of this collection appeared to parallel the lower margin of the ventricular system. The homogeneous, band-like density forming the boundary between these two air collections could be traced posteriorly to the groove in the parietal bone—i.e. this groove represents the confluence of the superior sagittal, straight and transverse sinuses, the torcular Herophili. The torcular indicates the level of the posterior margin of the tentorium cerebelli. It was then obvious that the child had a huge cyst of the

posterior fossa of congenital origin which has been designated as the Dandy-Walker syndrome. This also goes by the name of atresia of the foramina of Magendie and Luschka. It is important to recognize, however, that this syndrome is not necessarily associated with complete atresia of the foramina related to the fourth ventricle, so that, as in the case under description, obstruction may not be complete. This syndrome represents a developmental anomaly of the medullary velum of the fourth ventricle as well as of the cerebellar hemispheres, the vermis and the cerebellar commissure. It has been suggested that this type of hydrocephalus may be more susceptible to successful operative intervention than other malformations, for example, the Arnold-Chiari anomaly and, therefore, that it is of importance to recognize this syndrome as early as possible. This can be done on the basis of the relatively greater enlargement of the skull behind the ears and roentgenologically by the elevation of the groove for the torcular Herophili. There have apparently been no reported operative successes as yet. The child under description did poorly and was found dead in bed, presumably as the result of respiratory paralysis.

Final Diagnosis: DANDY-WALKER SYNDROME OR SO-CALLED ATRESIA OF THE FORAMINA OF MAGENDIE AND LUSCHKA.

CASE NO. 44

A.A., a 22 month old child, was admitted with the chief complaint of a tender mass on the medial aspect of the right forearm a short distance above the wrist. Two months prior to admission, the child had fallen and sustained a laceration in this area. Roentgen examination at the time of the injury was negative. A week after the injury, the parents noted swelling and tenderness at the site of injury. One week after this, roentgen examination was repeated and showed thickening of the bone. Another examination, three weeks after the original injury, disclosed in addition to the thickening an area of rarefaction. Swelling increased slowly until the time of admission.

Examination on admission showed a somewhat rubbery mass, 3 cm. in diameter, over the distal portion of the ulna. This mass was moderately tender to palpation. Ths skin over the mass appeared to be movable but the mass appeared to be adherent to the deeper tissues. The overlying skin was not discolored. A healed 3 mm. laceration was evident which had a somewhat darkish color. There was no fever or leucocytosis.

Roentgen examination (Figs. 1a and 1b) of the right forearm showed an area of lamellated periosteal new bone formation along the distal portion of the shaft of the right ulna, most marked on its medial and anterior aspect. Within the periosteal new bone, an ovoid lucent area was seen. This lucent zone was sharply demarcated except superfficially where the bone was defective. Medial to this lucent zone extending distally, there was a soft tissue mass. A definitive roentgen diagnosis was not made.

At operation, a fluctant mass was exposed protruding between the extensor tendons of the wrist. This was incised and several centimeters of purulent material evacuated. The wall of the sac consisted of loose, partially necrotic gelat-

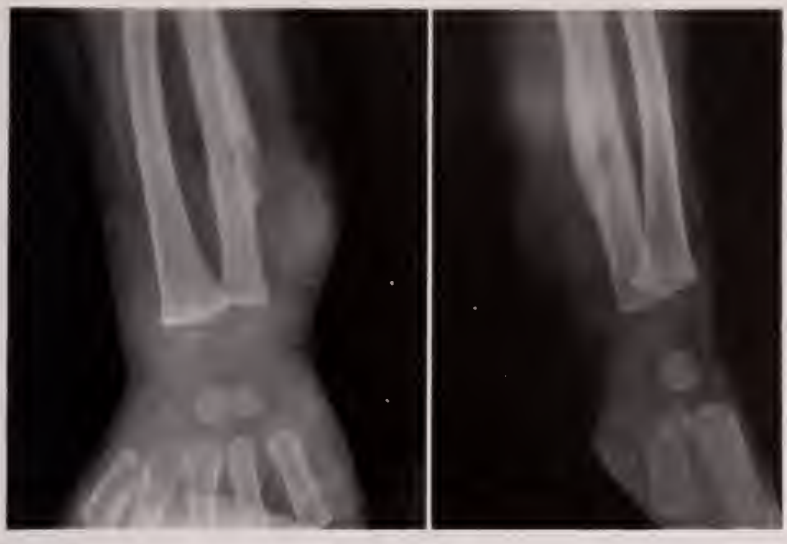


Fig. 1a. Fig. 1b.

Case 44, Fig. 1a. Radiograph of the distal portion of the right forearm shows lamellated periosteal new bone formation on the medial aspect of the distal portion of the shaft of the right ulna. Eccentrically located within the new periosteal bone, there is a sharply demarcated ovoid lucent zone which is broadly continuous with the adjacent soft tissue. The cortex underlying the lucent area is intact. Extending distally on the medial aspect of the forearm, there is a soft tissue mass which elevates the thinned subcutaneous tissue.

Case 44, Fig. 1b. Lateral view of the forearm demonstrates that the periosteal new bone formation is also prominent on the anterior aspect and minimal on the posterior aspect of the shaft of the ulna. The characteristics of the lucent zone are the same as on the antero-posterior projection. The cortex is intact, confirming the location of the lucent zone within the newly formed periosteal bone.

inous tissue and was adherent to the ulna. Within the center of the abscess cavity, there was a one inch splinter of wood which had the appearance of a matchstick sharpened at one end. The pointed end of the splinter was close to the bone. Culture of the purulent material revealed staphlococcus albus A. The pathological report of the excised tissue showed acutely inflamed granulation tissue with foreign body giant cell reaction.

Final Diagnosis: Splinter of the ulna with abscess formation.

CASE NO. 45

A.N., a 37 year old female, had been treated two years previously for a carcinoma of the cervix, stage 1, by means of intravaginal and intrauterine radium and external radiation. She, however, did not complete the course of external radiation and did not return for follow-up examinations. One month prior to admission, the patient fell and subsequently complained of pain in the right knee and in the neck. One week prior to admission, pain in the right wrist appeared.

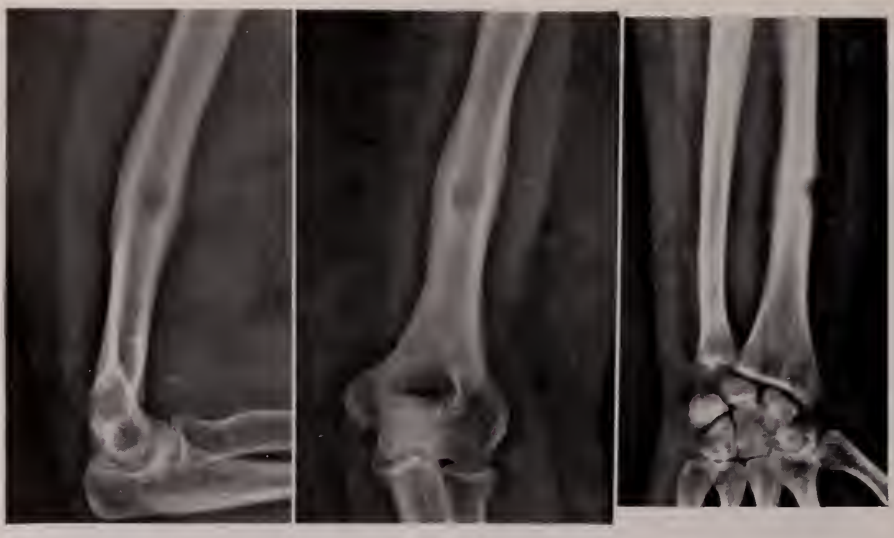


Fig. 1a. Fig. 1b. Fig. 1c.

Case 45, Fig. 1a. A roentgenogram of the right forearm shows a sharply demarcated, somewhat ovoid lucent zone within an area of periosteal new bone formation on the lateral aspect of the shaft of the radius about 2 inches proximal to the wrist. The subjacent cortex is also demineralized. The new periosteal bone on the lateral aspect has a lamellated symmetrical appearance but on the medial aspect of the shaft at the same level it has a somewhat lacy contour.

Case 45, Fig. 1b. The postero-anterior projection of the lower end of the right humerus shows a sharply demarcated, ovoid, lucent area within the medullary cavity which erodes the cortex in symmetrical fashion and is associated with a spindle-shaped configuration of the shaft due to new periosteal bone formation of a lamellated character.

Case 45, Fig 1c. A lateral view of the lower end of the right humerus shows findings similar to the PA projection. Note that within the larger lucent zone there is a smaller, more marked lucent area which presumably indicates localized, more extensive erosion of the overlying cortex.

Examination on admission showed a swelling about 1½ inches in diameter located ¾ inch above the wrist on the radial aspect of the forearm. This swelling was tender to palpation but was not warm; the skin over it was not discolored.

Roentgen examination of the right forearm (Fig. 1a) showed an ovoid, sharply demarcated lucent zone almost 1 cm. in diameter within an area of periosteal new bone formation over the lateral aspect of the shaft of the radius. In addition, in the distal portion of the shaft of the right humerus (Fig. 1b) a sharply demarcated ovoid lucent zone was seen in the medullary cavity associated with marked periosteal new bone formation. Several punched-out areas of rarefaction were also found in the scapula, in the calvarium and in the distal end of the femur. The diagnosis of metastatic carcinoma was confirmed by biopsy of the lesion in the ulna which showed squamous cell carcinoma.

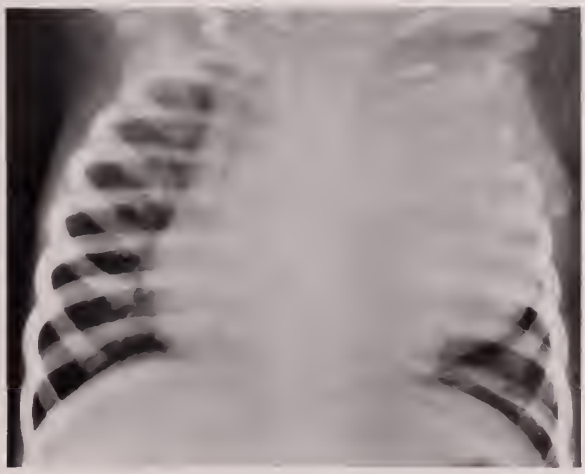
Final Diagnosis: Metastatic carcinoma to the long bones—unusual roentgen appearance.

CASE NO. 46

(Submitted by John E. Moseley, M.D.)

L.G., a 1 year old colored male, had been delivered by Caesarean section, three weeks prematurely, with birth weight 3 lbs. 4 oz. Shortly after birth, he was said to have had pneumonia and was hospitalized for 2 months. At the age of 8 months, he was treated at another hospital for an upper respiratory infection and dyspnea for 2–3 days. Approximately one week prior to admission, he developed a running nose, fever of 103° F. and was treated with penicillin. The symptoms cleared rapidly but 3 days prior to admission, his mother noted that he seemed more irritable than usual when she touched his left chest. There was no associated cough, fever or rhinorrhea but the patient became anorectic and cried continually.

On physical examination, there were several small anterior cervical and axillary nodes palpable. A 2 cm. node was palpable in the left supraclavicular area. The thorax was normal in configuration but there was a slight respiratory lag on the left side. Dullness with absent breath sounds was detected over the upper half of the left lung. The liver was down 2 cm. The laboratory findings were not remarkable. X-ray examination of the chest (Fig. 1a) showed a large homogeneous mass filling the upper $^3/_4$ of the left thorax, displacing the heart and mediastinum to the right and elevating the upper two left ribs. The shafts of these ribs, especially the first, were narrowed, apparently by pressure erosion of the mass. In the lateral projection (Fig. 1b), the mass extended from the posterior to the anterior chest wall. The margins were sharp and relatively smooth. No calcifications were demonstrated. The displacement of the heart and mediastinum associated with erosion of the first rib suggested that this



Case 46, Fig. 1a. Postero-anterior view of the chest shows a huge homogeneous density occupying the upper $^3/_4$ of the left hemithorax. A sharp convex border is present inferiorly. The trachea, heart and mediastinum are markedly displaced towards the right. The first two left ribs are elevated and their posterior portions thinned.

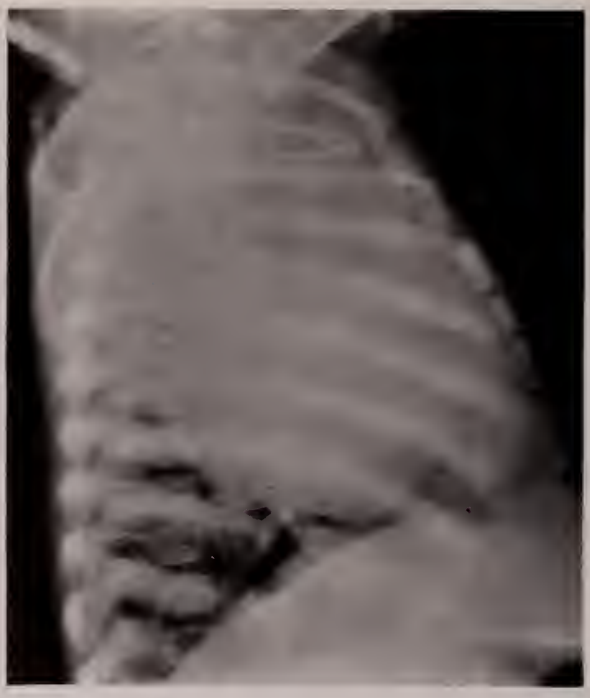


Fig. 1b. Lateral projection shows that the mass occupies the entire sagittal diameter of the thorax. The markedly thinned first rib is well seen.

density represented a tumor mass rather than a collection of fluid. Despite the smoothly rounded margins of the mass, the lymphadenopathy and rib erosion suggested a malignant character of the tumor.

Needle aspiration of the chest was done which revealed a small amount of bloody fluid. Following this, biopsy of the left supraclavicular node showed metastatic neuroblastoma. Bone marrow aspiration showed abnormally large, immature, cells representing metastatic neuroblastoma cells. Search for other lesions, including examination of the abdomen and intravenous pyelography, was unrevealing.

The patient was treated with radiotherapy and at last examination the thoracic mass had diminished considerably in size.

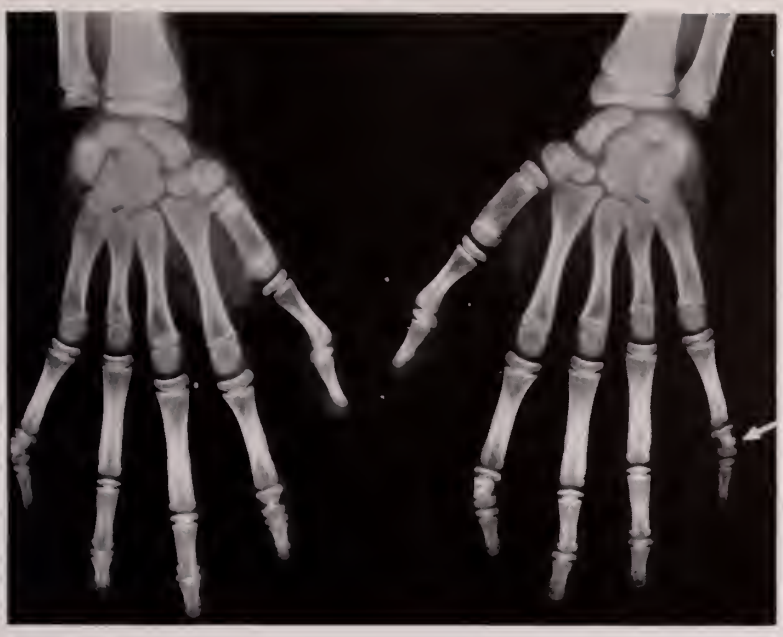
Final Diagnosis: Primary thoracic neuroblastoma.

CASE NO. 47

(Submitted by John E. Moseley, M.D.)

R.M., a 12 year old white male, was referred for roentgen examination of his hands because of slight angulation deformities of both little fingers. There was no history of any remarkable trauma to the hands and the child had no other complaints.

The roentgen examination of the hands (Fig. 1) showed shortening of the



Case 47, Fig. 1. Roentgenogram of the hands shows shortening of the middle phalanges of the 2nd and 5th digits on both sides. The mid-portions of these phalanges show irregular, somewhat fragmented bone, with dense areas of calcification. No proximal epiphyseal plates are noted on these phalanges although distal pseudoepiphyseal plates are well marked. Remnants of distal pseudoepiphyses are seen in the other middle and proximal phalanges. The right 5th middle phalanx (arrow) shows a small bony protuberance medially with dense calcification which, however, does not reach the periphery. Both 1st metacarpal bones are unusually short with wide medullary cavities and thin cortices and somewhat loose trabecular structure. Epiphyses are present on both the proximal and distal ends of the 1st metacarpal bones.

middle phalanges of the 2nd and 5th fingers of both hands. This appeared to be the result of fragmentation in their mid-portions with irregular calcific deposits within the affected areas. Each of the affected phalanges was angulated in their mid-portions. No epiphyseal plates could be identified on the proximal margins of the involved phalanges. Their distal margins had the appearance of pseudoepiphyses which were also present on the other middle and proximal phalangeal bones. The first metacarpal bones on each side were abnormally short with somewhat widened medullary cavities at the expense of the cortices. Epiphyses were present on both the proximal and distal ends of both of these first metacarpal bones. The trabecular structure of these metacarpal bones appeared somewhat looser as compared with the other bones included within the examination.

Closer examination of the changes in the middle phalanx of the little finger of the right hand (Fig. 1 arrow) demonstrated that there was a rather localized bony projection extending beyond the margin of the shaft and that dense calcific deposits were located within this projection but did not reach the surface. The

appearance of this lesion suggested a small osteochondroma. Examination of the feet showed scattered small, lucent zones in several of the metatarsal and phalangeal bones suggesting islands of cartilage, i.e. enchondromata. The remainder of the bones showed no abnormality.

The changes in the phalanges described above are considered to be quiescent stages of enchondromata which have gone on to bone formation and calcium deposition. The shortening and angulation are the result of growth disturbance associated with the origin of these lesions in epiphyseal cartilage. The changes in the first metacarpal bones have a different appearance but are presumably on a similar basis. Involvement of the hands and feet without chondromata elsewhere has been referred to as "acroform dyschondroplasia". The quiescent or healing stage is rarely seen in short bones.

Final Diagnosis: MULTIPLE ENCHONDROMATA OF THE PHALANGES IN A QUIESCENT OR HEALING STAGE; ACROFORM DYSCHONDROPLASIA.

"FAST" FILM FOR BARIUM ENEMA EXAMINATIONS

For many years, the largest size x-ray film available in standard practice has been 14 inches by 17 inches. This size of film is often insufficient to cover the entire abdomen, particularly in the longitudinal direction. This defect is often a source of difficulty, particularly in barium enema examinations. During the second part of a barium enema examination, that is, during the so-called double

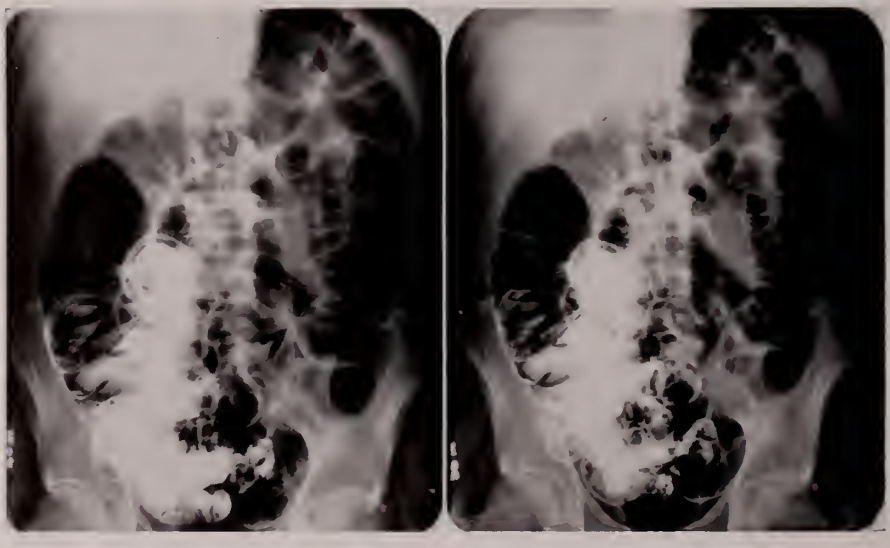


FIG. 1. A pair of films taken during the double contrast portion of the barium enema examination. The film on the left was taken with a target film distance of 40 inches and on the right, with 56 inches. In the film on the left, the lower margin is above the symphysis pubis and the top of the splenic flexure is cut off. These areas are included in the film on the right. The diminished magnification obtained at the longer target film distance is also evident. The quality and the detail in each of the films are comparable.

contrast portion, air is insufflated into the colon. As a result of marked distention, the lack of coverage of the standard size film is even more evident. The reasons for standardizing on this size of film are obscure but it has not been possible to change because of the fact that all accessory equipment such as screens, cassettes and hangers are designed for this size. Whenever a very large patient has to be radiographed for barium enema examination, it is common practice to cover the lower part with one 14 x 17 film and the upper part with a second such film. Since the barium enema examination as currently done usually requires 6 different films, increasing this number to 12 makes the examination very awkward and expensive and more uncomfortable for the patient. Moreover, in patients that are not excessively large, it is quite common to have the top of the splenic flexure or the rectosigmoid cut off on routine films.

It is possible to include more of the abdomen within a given area by increasing the target-film distance. Increases beyond 40 inches have not been feasible because of the fact that the time of the radiographic exposure becomes undesirably long. Within the past year, however, there has become available a type of x-ray film which, when combined with more potent developer, has approximately twice the speed of previous film. Other characteristics of this film, particularly as regards fine grain and bony detail, are not as satisfactory as the more standard type. However, since twice the speed is available, it is possible to increase the target film distance from 40 to 56 inches without changing the exposure factors. Moreover, the radiation exposure to the patient is diminished by at least a factor of two. The utilization of a target-film distance of 56 inches is approximately equivalent to a diminished magnification of 10 to 20 per cent or an effective increase in the length of the 14 x 17 film by 2 or 3 inches and in the width of the film of 1 to 2 inches. Some of the detail lost because of utilization of fast film is regained because of the longer target film distance. In actual practice over a period of a year, this procedure has turned out to be entirely satisfactory and any loss of detail has not been of consequence.

Figure 1 indicates the lesser degree of magnification obtained at 56 inches target film distance as compared with 40 inches and the increased coverage of the abdomen thereby obtainable in double contrast examination of the colon.

ERRATUM

The editors regret that in the May/June 1958 issue of the Journal of The Mount Sinai Hospital Dr. Samuel H. Klein's name was omitted from the table of contents and running heads as a co-author of the article *Primary Anastomosis of the Trachea After Resection of a Wide Segment: An Experimental Study* by Max L. Som, M.D. and Samuel H. Klein, M.D.

ISIDOR CLINTON RUBIN
1883–1958

In Memoriam

ISIDOR CLINTON RUBIN
1883–1958

Dr. Isidor Clinton Rubin died on July 10, 1958, in London, England, while attending the International Cancer Congress. With Dr. Rubin's passing, The Mount Sinai Hospital has lost a most illustrious and distinguished alumnus, who gained international fame in gynecology.

Dr. Rubin was born in Vienna, Austria, on January 8, 1883 and was brought to this country when very young. He received his early education in New York City, and graduated from the College of the City of New York in 1901. After receiving the M.D. degree from the College of Physicians and Surgeons of Columbia University in 1905, he was chosen to be an intern at The Mount Sinai Hospital, upon the completion of which appointment in 1909, he spent a year in postgraduate work and research in Vienna, Berlin, and Paris. In 1910, he was appointed to the gynecological staff of Beth Israel Hospital, and subsequently to similar positions at The Mount Sinai Hospital and Montefiore Hospital, in each of which he eventually assumed leadership. He was Chief Gynecologist to The Mount Sinai Hospital from 1937 until 1945, and then became Consulting Gynecologist. He was also Consulting Gynecologist to Montefiore, Beth Israel, and Harlem Hospitals.

From 1937 to 1947, Dr. Rubin was Clinical Professor of Obstetrics and Gynecology at the College of Physicians and Surgeons, Columbia University; and from 1948, Clinical Professor at the College of Medicine of New York University, and at New York Medical College.

Dr. Rubin was not only author of numerous papers and several books in his specialty, but he undertook many editorial tasks, including membership on the Editorial Board of the American Journal of Obstetrics and Gynecology.

He was a Founding Fellow of the American College of Surgeons, of the American Board of Obstetrics and Gynecology, and of the American College of Obstetricians and Gynecologists; a member of many other medical associations as well as past-President of the New York Obstetrical Society. In 1956, he was unanimously chosen President of the American Gynecological Society, considered the most respected honor that a member of our specialty could attain.

Dr. Rubin was honored for his work in gynecology by England, France, Greece, Italy, Spain, Argentina, Brazil, Chile, Uruguay, Puerto Rico, and Canada. He was Chevalier of the French Legion of Honor and later Gold Officer, recipient of the Key to the City of Paris in 1951, Honorary Member of France's Academie Nationale de Medecine, and Honorary President of the French Gynecological Society. In 1955, he was awarded the Academic Degree by the Sorbonne, the first American to be thus honored.

During the past year, Dr. Rubin was awarded Honorary Fellowship in the

Royal College of Obstetricians and Gynecologists. In 1952, he received an Honorary Degree from the University of Athens. In 1945, Dr. Rubin received the Townsend Harris Medal of the City College Associate Alumni for "notable postgraduate attainments", and in 1947, the Ortho Research Award of the American Gynecological Society. Only six weeks before his sudden demise, on the occasion of the awarding of honorary doctorates at the University of Mexico, it was for one man alone that the whole audience gave a warm, spontaneous standing ovation; that man was Dr. Isidor Clinton Rubin.

Dr. Rubin's contributions in the fields of obstetrics and gynecology have been many, and monumental. As far back as 1910, he was concerned with the early diagnosis of carcinoma of the uterine cervix, the condition we now call carcinoma in situ. The last sentence of his first paper merits quoting: "The important criteria of malignancy in these early cases be not so much in the relation of the cell nests to the stroma, the depth or extent of epithelial invasion, or evidences of surrounding inflammatory changes, as in the intrinsic morphology of the epithelial cells."

Following this, there were numerous publications, encompassing the field of gynecology. He developed and popularized hysterography, which contributed toward the improvement in the diagnosis and technique of myomectomy. He also studied the effect of prolapse of the uterus on the renal tract. His work on the physiology of the tubes and on uterine endoscopy led to the development of the epoch-making insufflation test.

Dr. Rubin had the unusual gift of combining clinical acumen with accurate scientific methods. His crowning achievement came with the perfection of tubal insufflation as a diagnostic test for tubal patency. This test, universally known as the Rubin Test, achieved much success in many barren women, and stimulated research in the field of fertility; and soon created the specialty of fertility and sterility as a branch of gynecology, of which he became its father and leader.

On the occasion of his 75th birthday, he was honored with a special issue of the Journal of Fertility and Sterility, which contained the following tribute: "Few, except gynecologists, are aware of the broad dimensions of Dr. Rubin's talent. Had he not given us kymographic tubal insufflation, Dr. Rubin would have been appreciated for other generous contributions to his chosen field of endeavor. Like a sower 'who had followed many ploughs', his writings show an unusual versatility and mark him as a sound student, avid teacher, astute observer, encyclopedic thinker, and keen but kindly critic. His three books, the several chapters he contributed to well-known systems of surgery and gynecology, and the 140 articles published by him since 1910 are not only enviable examples of expository writing but are sufficiently prolix to indicate the multiplicity of his interests."

In 1947, to express the high regard in which he was held, 111 of his friends, associates, and pupils presented Dr. Rubin with a special issue of the Journal of The Mount Sinai Hospital, a Festschrift to which each contributed a special article.

Though Dr. Rubin belonged to the world, he still considered Mount Sinai his home and in 1956, a lectureship was founded in his honor at The Mount Sinai Hospital. The first lecture was given by Professor Pasteur Vallery-Radot, on "Allergic Manifestations of Interest to the Gynecologist"; this lecture was recorded in the Journal of The Mount Sinai Hospital. The second lecture is scheduled for November of this year, and should serve as a memorial to Dr. Rubin.

We have lost a friend and teacher; but humanity has been enriched by his life, which will be a source of stimulation for future generations.

Heartfelt sympathy is extended by all to his dear wife, Sylvia Unterberg Rubin, whose strength, loyalty, and devotion supported him throughout their married life, and to his children and grandchildren who were a source of joy and happiness to him.

Seymour Wimpfheimer, M.D.
For
Editorial Board

HEPATIC FIBROSIS: PATHWAYS AND MECHANISM

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In the process of fiber formation in the liver, several aspects are of importance: (A) the types of fibrosis, (B) their pathways or histogenesis which can be discussed (a) on a macroscopic or low power microscopic level, (b) on a fine structural and histochemical level, and (c), more or less a supplement to the former, on a chemical level, and (C) their functional significance.

This study is based on human autopsy and biopsy material, particularly of the stages of the fatty liver-cirrhosis syndrome, viral hepatitis, hemochromatosis, and non-specific reactive hepatitis, and on animal investigations with experimental ethionine, carbon tetrachloride, and thioacetamide intoxication, after injection of carrageenin, or while on high fat/low protein diets.

Fibrosis, in the sense of an excess of hepatic fibers, may be found either in the portal tract or only in certain portions of the lobule. Examples are centrolobular fibrosis, particularly in cardiac failure, perilobular fibrosis resulting in diffuse enlargement of the portal tracts, for instance in chronic cholecystitis, granulomas and hemochromatosis, or irregular so-called "stellate" portal fibrosis, in malnutrition and viral hepatitis. It may also be intralobular after focal necrosis or granulomas (1). These types of fibrosis do not disturb the lobular architecture. This has to be contrasted with cirrhosis which has far greater functional and prognostic significance. Cirrhosis is characterized by the formation of regenerative nodules and connective tissue septa (2. 3). Such septa may develop either actively by accumulation of connective tissue or passively after collapse and compression by surrounding nodules (4).

Preliminary to the discussion of the basic mechanism of fiber formation, it appears necessary to review briefly the pathways through which cirrhosis, as the most significant form of fibrosis, develops (5). One pathway is collapse in which, after disappearance of the epithelial liver cells, the preserved framework becomes

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Presented in part before the New York Pathological Society, March 27, 1958.

approximated and local fibrosis results without any actual increase in the number of fibers. This collapse may be massive and include all liver cells in a lobule, submassive, with loss of irregular but contiguous areas of one or several lobules, or focal. All forms may be seen, for instance, in viral hepatitis. Liver cell plates may regenerate and thus re-expand the collapsed area. However, collapse becomes permanent (a) if all liver cells have been lost, (b) where exudate interferes with sinusoidal blood flow, (c) where distortion of the framework hinders ingrowth of the liver cell plates, or (d) where the framework is altered by new formation of fibers.

The interference by perisinusoidal exudate, as seen in benign viral hepatitis characterized by single cell necrosis, can be demonstrated experimentally in subacute ethionine intoxication in the rat where single cell necrosis is also seen. Upon injection of India ink into normal rats, the ink is found uniformly distributed around the portal vein branch whereas in rats with single cell necrosis only a few sinusoids are filled (6). Regeneration is lacking in ischemic areas in such rats but is accentuated in areas where patent and probably dilated sinusoids are found. Distortion is particularly conspicuous in submassive collapse when regeneration of persisting tissue alters the arrangement of the collapsed areas. In collapse the reticulum fibers are initially approximated only, but their basic arrangement is preserved. Under such circumstances the border between the connective tissue of the portal tract and the collapsed framework is clearly apparent. After some time the number of irregular cross fibers greatly increases and distorts the original arrangement without conspicuous accumulation of fibroblasts. In addition, collagen membranes are seen and the border between portal tract and collapsed parenchyma becomes hazy. Such a postnecrotic collapse, large as it may be, is not cirrhosis if the surrounding parenchyma has not been altered, as in atrophy of the left lobe of the liver or in syphilitic hepar lobatum. However, in collapse associated with hepatitis or other diffuse diseases of the liver, the surrounding parenchyma is not entirely normal and exhibits nodules and septa as expressions of cirrhosis which as a rule are irregular in distribution. The end result is postnecrotic cirrhosis, characterized by such features as preservation of the lobular architecture in large nodules, broad bands of fibrosis, and excessive regeneration.

An entirely different mechanism of fiber formation in cirrhosis is diffuse septa formation, most frequently seen in this part of the world associated with fatty metamorphosis. The development of septa under these circumstances has been explained by a wide variety of mechanisms. These include the formation of membranes from the center of the lobule where usually the fat accumulation is the most marked (7). It may also take place on the lobular periphery in the form of radiating membranes which condense to septa. Here fiber formation is not necessarily associated with fat but is usually found around bile ductular structures. Fibers are also found around areas of hepatic necrosis. Finally, membranes which are straight on three-dimensional reconstructions appear to separate territories of different degrees of regeneration (8). Fusion of the various septa results in the characteristic subdivision of the lobules and parallel formation of

regenerative nodules in fatty cirrhosis. Apparently fatty metamorphosis alone does not lead to cirrhosis and other factors producing necrosis are required, the fatty liver possibly being more susceptible to them (9, 10). An example of another type of diffuse septal cirrhosis is hemochromatosis, better studied in the florid form which characterizes secondary hemochromatosis than in the slowly developing idiopathic type. The liver cell plates on the lobular periphery loaded with iron connect with abundant bile ductular cells rich in iron and surrounded by excess fibers. Similarly, extracellular iron in the portal tracts is associated with marked increase of reticulum fibers and only in later stages with an excess of collagen (11). Chronic passive congestion and possibly prolonged exposure to toxic agents result in the same type of lesion. Granulomas such as sarcoidosis or, rarely, tuberculosis, or brucellosis, with subsequent fibroblastic reaction leading to a diffuse septal type of cirrhosis, are relatively rare.

A third type of cirrhosis is related to changes in the bile ducts and smaller bile ductules. This is the so-called primary or secondary biliary cirrhosis, in both of which fibers accumulate around proliferated ductules in the periportal zone of the lobular parenchyma. In addition, fibroblasts may accumulate particularly in the portal tract in association with the formation of thick collagenous fibers and membranes.

The three different pathways of cirrhosis formation, postnecrotic, diffuse septal, and biliary, none necessarily characterizing a specific etiology, are associated with several basic types of fiber formation (Table I). They deserve consideration not only from an academic viewpoint but particularly because rational treatment may be modified according to the type of cirrhosis. The mechanism of collapse and of fiber formation associated with the presence of fibroblasts is not confined to the liver and basic studies in other organs can be applied. The specific problem which requires additional consideration is fiber formation around fatty liver cells, damaged liver cells and ductular cells. For this it was advantageous to study the distribution of fibers in the normal liver not only in routine sections but particularly in ultrathin sections made with the microtome used for the electron microscope as applied by Churg and Grishman for the study of renal disease (12).

The normal liver cell has no material within its cytoplasm giving, after removal of glycogen by diastase, a periodic acid Schiff (PAS) reaction, but has a fine layer of PAS positive material on its base, part of which is amorphous and part appears fibrillary. It seems to indicate the border between liver cells and sinusoids. A few Kupffer cells exhibit small PAS positive granules. In chromotrope aniline blue stains, this zone appears hazy and purple and barely recognizable fine bluish reinforcements are seen. These bluish reinforcements in chromotrope stains are clearly impregnated with silver and are assumed to be reticulum fibers (Fig. 1A). In thin sections this layer is a row of fine black points or short dashes. They are therefore cross sections or tangentially cut fibers (13) (Fig. 1B). Collagenous fibers, recognized by their brown color in the silver impregnation and their distinct staining with acid fuchsin (van Gieson), are seen only as occasional reinforcements within the parenchyma and

TABLE I

Mechanisms of Fiber Formation

Histogenetic pathways	Synonyms	Etiology	Distribution	Histogenetic
Diffuse septal	Portal Laennec	Malnutrition Alcoholism Viral hepatitis Hemochromatosis Very severe passive congestion Repeated exposure to poisons Granulomatosis (incl. parasitic)	Diffuse	1. Condensation of septa around fibers and membranes formed around a. fatty liver cells b. damaged liver cells c. ductules d. extracellular iron 2. Focal, often slit-like collapse 3. Portal fibroblasts
Postnecrotic	Posteollapse Posthepatitis Coarse nodular	Viral hepatitis Intoxication ?	Focal accentuation	Collapse without and with subsequent fiber new formation. Usually associated with mechanisms of diffuse septal cirrhosis.
Biliary	Cholangitis Cholangiolitis Hanot	Biliary obstruction with or without infection Intrahepatic cholestasis ("cholangiolitis") Viral hepatitis? Cholangitis	Usually periportal	Fibrosis around proliferated ductules. Fibroblasts in portal tract in chronic obstruction and inflammation.

mainly in the portal tracts. Around intralobular and perilobular bile ductules (cholangioles), which are the connections between the bile canaliculi and the bile ducts, a continuous black line is seen even in thin sections in silver impregnations. It is thus a membrane in the sense of a basement membrane although it is interrupted in places (Fig. 2). It also gives a PAS reaction and a distinct blue color with chromotrope stains. Around damaged liver cells with vacuolated and coagulated cytoplasm, as in viral hepatitis and florid cirrhosis, a thicker purple layer is noted in chromotrope stains which gives an amorphous PAS positive reaction and positive reactions with colloidal iron and Alcian blue. Under these conditions, a few irregular granules with similar staining reactions may be found in the liver cell cytoplasm and more distinctly stained granules are found in the Kupffer cells (Fig. 3A). In the latter the granules vary greatly in size. Moreover, on the base of the liver cell, an almost continuous PAS positive line which is blue in chromotrope stains appears either as more points or as longer dashes in thin sections impregnated with silver, suggesting a transition into a basement membrane similar to that of bile ductular cells. This surrounds even cells which are much larger than normal, excluding an accumulation of fibers caused by loss of shrinkage of cells (Fig. 3B). Around cells with fatty metamorphosis even without cytoplasmic clumping, a similar

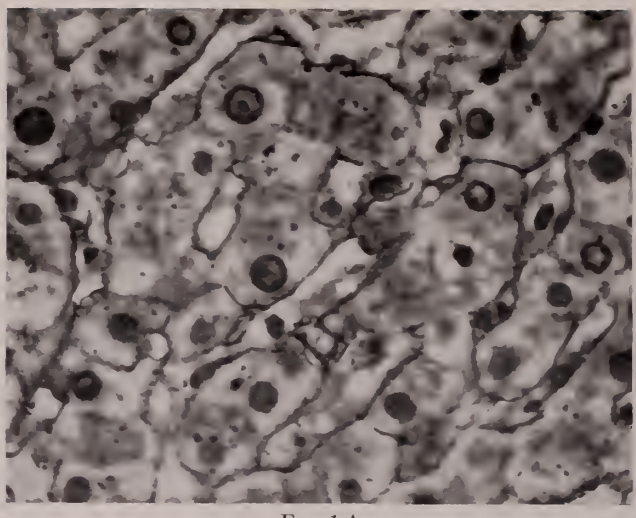

FIG. 1.A.

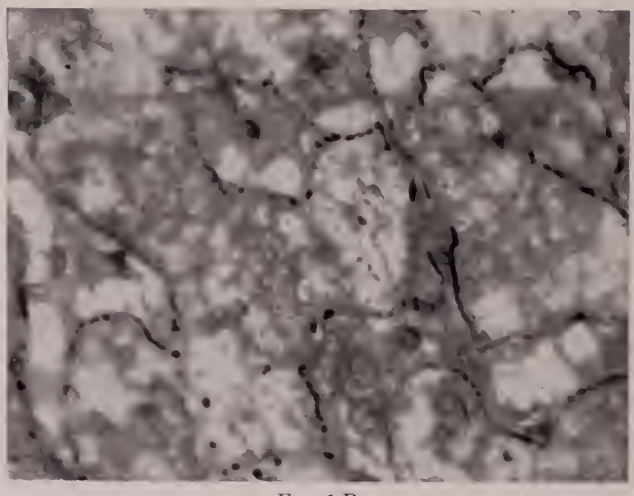

FIG. 1.B.

FIG. 1. Normal human liver (silver impregnation). A. 6-micron thick section (400×). Irregular network of interwoven fibers frequently producing the appearance of continuous basement membrane. B. 1-micron thick section (630×). Reticulum framework represented by individual fibers appearing in section as a row of black dots.

membrane is noted which sometimes is even duplicated and in extreme cases it gives a collagen reaction. In silver impregnations a brown material is contiguous with the fibers. This may or may not be associated with accumulation of the amorphous PAS positive material. Fibroblasts are not seen. Similar PAS positive material in the cytoplasm of liver cells, and particularly in the Kupffer cells, and in amorphous and fibrillar forms on the sinusoidal surface of the liver cells, are seen in ethionine intoxication in which single cell necrosis and hepatocellular degeneration is present (14). This is typically associated

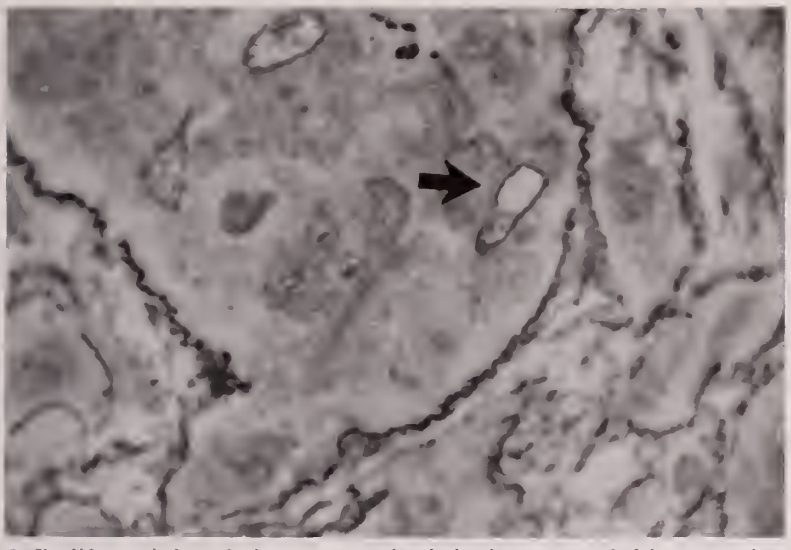

FIG. 2. Proliferated ductule in postnecrotic cirrhosis, surrounded by a continuous appearing basement membrane. The outline of the lumen (arrow) is impregnated (silver impregnation of 1-micron thick section). (900×)

with accumulation of cells between the liver cell plates which are intermixed with segmented leucocytes in acute stages. They have oval- and spindle-shaped nuclei and arrange themselves occasionally as ductules. The nature of these cells, called oval cells by Farber, has been the subject of much argument (14). Upon injection of India ink into the bile duct of a rat, a fine canalicular system is injected between these cells which are mesenchymal in appearance, indicating their epithelial origin. Around such organized and unorganized appearing ductular cells, a large amount of amorphous and fibrillar PAS positive material can be seen, and, in silver impregnations, increased fibers as well as continuous membrane can be recognized even in very thin sections. Many of these fibers and membranes in contact with the ductular cells continue into the interstitial tissue independently from them. Frequently the membranes are in multiple layers, especially where ductular cell reaction is most conspicuous. Fibroblasts are not recognized. The relation of fiber formation to ductular cell proliferation is especially conspicuous in cholangiofibrosis and also in the far advanced and collapsed stage of the ethionine cirrhosis in which collagenous membranes around ductular cells account for the bulk of the fibrosis. Such ductular cells seem to arise from bile ducts and ductules in most instances. In the florid stages of ethionine intoxication, transitions between liver cells and ductular cells are apparent and recent investigations imply that during embryologic development ductular cells are derived from liver cells rather than vice-versa (15).

Similar fibrosis associated with ductular cell reaction is seen in man in and around the portal tract, particularly in cirrhosis or biliary obstruction. In both instances it is again associated with accumulation of reticulum fibers and in florid stages with the PAS positive amorphous material.

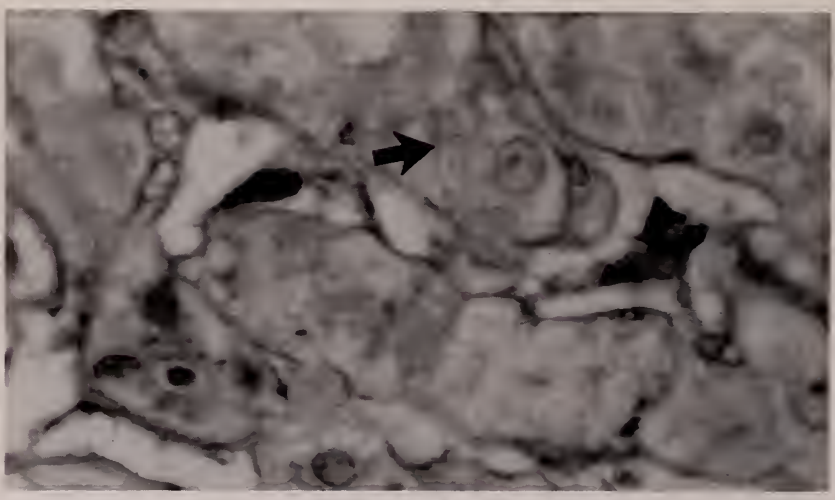

FIG. 3.A.

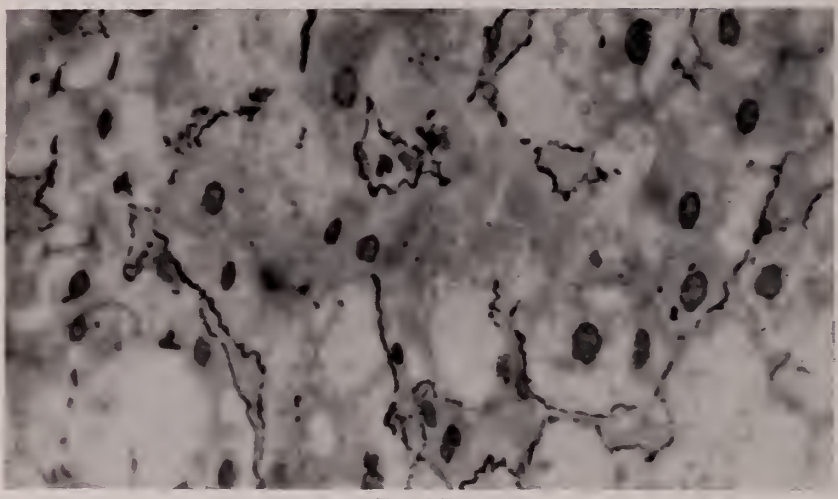

FIG. 3.B.

FIG. 3. A. Periodic acid Schiff reaction in 6-micron thick section of acute hepatitis. Positive reaction of granules in liver cells (arrows). Kupffer cells and material on the sinusoidal base of the liver cell. (630×) B. Silver impregnation of 1-micron thick section of nutritional fatty liver. The cells are surrounded in many places by a continuous appearing membrane obviously derived from aggregation of fibers. (630×)

Two types of material can be demonstrated on the sinusoidal surface of liver cells and in increased amounts near damaged and fatty liver cells as well as around ductules, especially proliferating and disorganized ones. One is fibrillar, black in silver impregnation, gives a positive PAS reaction and aniline blue reaction, metachromasia after sulfation, and is not digested by trypsin or hyaluronidase. This is reticulum and transitions into collagen can be seen in silver impregnations and van Gieson stains. The second substance is amorphous on the sinusoidal border of the liver cell and granular in the liver and

Kupffer cells. In damaged liver cells and in Kupffer cells proliferating in the presence of damaged liver cells, this substance gives a positive PAS reaction, appears purple in chromotrope aniline blue stains, is metachromatic on sulfation, and at least partly gives a reaction with colloidal iron and Alcian blue like that of acid mucopolysaccharides. It is digested by trypsin and loses its PAS reaction on acetylation. This, however, returns on chromation. It is not destroyed by hyaluronidase, pectinase, or ribonuclease and, therefore, most probably it is a polysaccharide protein complex. From its morphological behaviour, it can be assumed to serve as the matrix for the formation of the scleroproteins, collagen and reticulum just as this is assumed to occur in fibrogenesis anywhere in the body (16, 17). In general, fibroblasts apparently secrete into the tissue spaces sulfated polysaccharides which serve as the basis of fibers. S^{35} appears shortly after administration in the fibroblasts of the skin and after two hours in the fibers (18).

The mechanism of formation of both the amorphous and the fibrillar substances in the liver has been incompletely elucidated. Fibers form in the liver in the vicinity of fibroblasts and, in tissue cultures of liver, fiber formation from fibroblasts with production of hyaluronic acid has been shown (19). However, in the characteristic instances of human cirrhosis, no or few fibroblasts are seen. The question arises whether the Kupffer cells act as fibroblasts or whether fiber formation occurs without assistance from mesenchymal cells. In tissue cultures of non-hepatic connective tissue, fibers are formed without fibroblasts (20), and in lower animals fibrils of the basement membrane of the skin are formed by epithelial cells (21, 22).

The perisinusoidal amorphous material, presumably the matrix, could be produced by liver cells or by Kupffer cells, or could be derived from the bloodstream. Origin from the bloodstream as the result of altered permeability of the sinusoidal wall in the presence of liver damage revives the old argument of serous inflammation (23, 24). However, electron microscopic studies have failed to demonstrate the existence of a continuous sinusoidal membrane (25). Whether the perisinusoidal material is identical with the granules in the cytoplasm of damaged liver cells and of Kupffer cells remains to be investigated, despite the similar reactions with the histochemical techniques applied. The relation to the Kupffer cells is of particular interest since the Kupffer cells, in the absence of fibroblasts, could possibly act as such by providing the matrix for fiber formation.

The increase of the pericellular material in acute fibrosis speaks in favor of the argument that the PAS positive granules in the Kupffer cells are a fiber precursor. However, the Kupffer cells could act as scavengers and the granules would then be extracellular or intracellular material that has undergone phagocytosis. This is supported by (a) the great variation in the size of the granules, (b) their distinct increase near by damaged liver cells, (c) their presence in portal macrophages, and (d) their lack of continuity with extracellular amorphous material. On the other hand the Kupffer cell granules are not liver cell breakdown products (wear-and-tear pigment) since they are not fluorescent,

acid fast, and give no Sudan black reaction as does lipofuscin in hepatic macrophages primarily in the portal tract.

The increased formation of the fibers themselves takes place around altered liver cells exhibiting cytoplasmic coagulation or fatty metamorphosis or around ductular cells particularly when they proliferate. In all these instances the reticulum fibers are replaced by membranes, or preformed membranes are duplicated, associated with the appearance of protein which contains polysaccharides. The damage of the liver cells may be the common factor causing membranes to form around them and ductular cells can in this respect be considered dedifferentiated hepatic cells. One can thus assume that dedifferentiation of hepatic cells stimulates fiber formation. This does not imply that epithelial cells, either damaged liver cells or ductular cells, act as fibroblasts by forming fibers. The histologic evidence so far suggests that they act as a mold inducing or determining the new formation of fibrillar material, sometimes encasing markedly enlarged cells (Fig. 4).

The concept presented found some support in recent experiments with injection of carrageenin, a polysaccharide derived from Irish moss (26, 27), into the liver (28). This has been used in histochemical studies of fibroplasia in skin. Injection of carrageenin into the hepatic parenchyma results within two days in development of an area of massive necrosis surrounded by a zone in which fibroblasts are found imbedded in a ground substance with characteristic PAS and acid mucopolysaccharide reactions. The fibroblasts with vesicular nuclei are PAS negative and seem to develop from both Kupffer cells and adventitial cells of arteries and capillaries. Simultaneously the ductular cells proliferate profusely, are bizarre in shape, are piled up, exhibit mitoses, and are surrounded by PAS positive membranes often several in number Frequently ductular cells seen outside the ductules cannot be sharply separated from fibroblastic cells. PAS positive fluorescent macrophages are found on the edge of the lesion. After about three days, abundant reticulum is formed in approximation to the ductular cells but some of the fibers around the ductular cells continue away from them. This violent fibroblastic reaction, which illustrates rapid formation of ground substance and reticulum in the vicinity of fibroblasts and ductular cells, subsides within two weeks. It is protracted by the administration of cortisone and shows more bizarre and abundant ductular cell reaction in livers

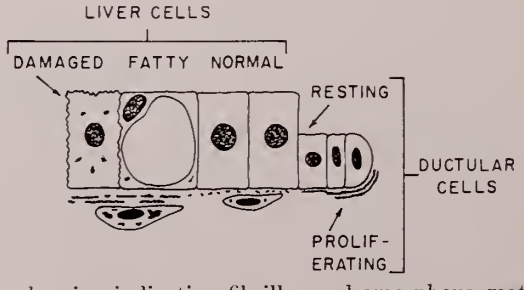

FIG. 4. Schematic drawing indicating fibrillar and amorphous material on the base of the liver cells.

with ethionine induced changes. The reaction is significantly altered in rats which were exposed to the lathyrus factor (29) or guinea pigs which have been made scorbutic (30).

The actual contribution of the various cells in the liver to the formation of both the polysaccharide proteins (mucoprotein) and scleroproteins (reticulum and collagen) requires further study. Chemical analysis may provide some insight. The amino acid, hydroxyproline, is found almost solely in collagen, of which it is approximately 14 per cent. Other amino acids such as proline and glycine are found also in other tissue proteins including the hepatic parenchymal cells. The hydroxyproline content of tissue has therefore been used as a measure of its collagen content (31, 32) and this checks well with older measures, which were based on simple physical criteria utilizing the extraction of gelatin from hepatic tissue (33). Less is known about the amino acid concentration of reticulum, the other scleroprotein. From the available evidence based on the examination of reticulum in kidney and other places, glycoproteins and lipoproteins are present (34). In confirmation of previous studies, particularly those of Morrione (31, 32), the hydroxyproline content of cirrhotic liver was found to be significantly elevated. Hydroxyproline was determined not only in dehydrated, fat-free, whole liver tissue primarily consisting of the hepatic proteins, but also in several fractions of this material. Of particular interest has been the fraction extractable by 0.1 N NaOH, considered to contain procollagen (35). It appears to be relatively increased in human cirrhosis and in livers of infants. The ratio between NaOH-soluble and total hydroxyproline averages 0.20 in the adult human liver, 0.40 in the cirrhotic liver, and 0.47 in infant livers. To obtain reproducable conditions with acute new formation of scleroproteins, experimental ethionine intoxication in the rat was used. While on control diets, the hydroxyproline concentration remains constant,

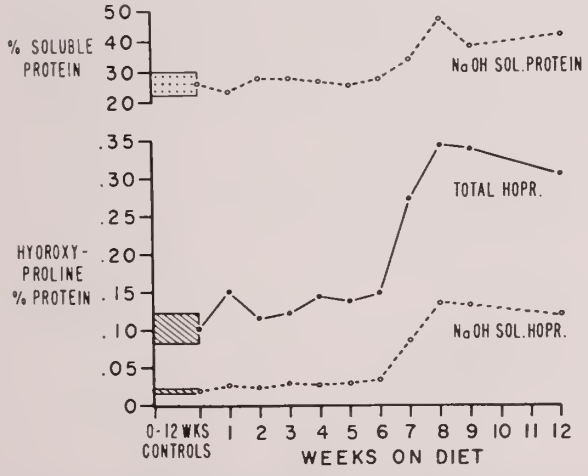

FIG. 5. Hydroxyproline content of defatted dried liver and of the fraction soluble in 0.1 N NaOH as well as the fraction of protein soluble in 0.1 N NaOH in normal control rats and in rats kept on a synthetic diet containing 0.5% ethionine.

around 0.1 per cent of defatted liver; it rises precipitously on the ethionine diet in the seventh week to more than three times the normal. The greatest part of this rise is in the procollagen fraction soluble in NaOH. Parallel with this rise, NaOH soluble protein is elevated (Fig. 5). Simultaneously, the hexosamine content rises, again particularly in the soluble fraction. Histologically, at this time, the reticulum is very conspicuously increased and this is reflected in this chemical data. The nature of the soluble protein is uncertain. It can be extracellular protein used in fiber formation, hepatocellular breakdown products, or cytoplasm of proliferated ductular cells. No significant rise in proline occurs in the total liver tissue, but a recognizable peak is seen in the NaOH soluble proline fraction preceding the rise of hydroxyproline (Fig. 6). The curves suggest a precursor relationship in that proline is made available from the total proline of the parenchymal cells, and converted to hydroxyproline to form procollagen, necessary in the formation of collagen. Taking the chemical and histologic evidence together, both admittedly fragmentary and in need of further study, it appears that during the time of the most active fibrosis, at least in the ethionine liver, an excess of extracellular polysaccharide is visible around the liver cells, while a NaOH soluble and subsequently insoluble scleroprotein is formed utilizing hepatic proline, which is partly transformed into hydroxyproline. The relative roles of reticulum and collagen in this process are not clarified and it would probably be unrewarding to speculate to what degree procollagen may be related to reticulum.

Assessing the significance of hepatic fibrosis is a major challenge. The interposition of a mucoprotein or scleroprotein material between sinusoids and liver cells must interfere with some hepatic functions. Normal liver cells have microvilli on their base dipping into the sinusoids, and, at least under the electron microscope, no definite membrane seems to separate them from the bloodstream (36). The ductular cells are devoid of these microvilli but a basement membrane is seen. Further electron microscopic studies will have to demonstrate whether fatty or damaged liver cells have a similar straight sinusoidal base as an indication of a disturbance of the normal exchange of metabolites be-

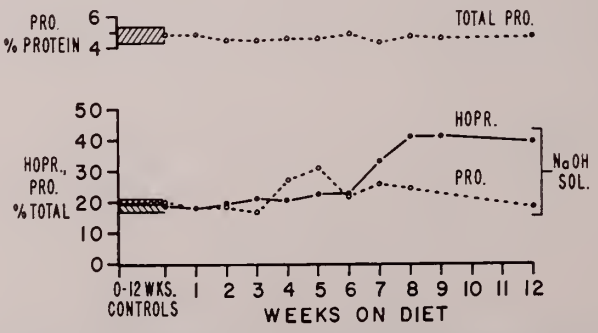

FIG. 6. Proline content of defatted dried liver and proline and hydroxyproline content in the fraction soluble in 0.1 N NaOH of control rats kept for several weeks and of rats on a synthetic diet containing 0.5% ethionine.

tween liver and blood and if disappearance of the villi precedes the membrane formation.

The interruption of the bile flow through such a connective tissue accumulation can easily be visualized in primary and secondary biliary cirrhosis, in both of which an intrahepatic obstructive phenomenon parallels the development of a thick fibrotic layer and bile retention in the peripheral hepatic cells.

The functional significance of the connective tissue septa in cirrhosis is well established. They carry multiple vessels which form anastomoses between hepatic artery, portal vein and hepatic vein. By shunting blood from the hepatic parenchyma and by transmitting hepatic arterial pressure into the portal vein, they create many of the cardinal symptoms of cirrhosis (37).

In conclusion, hepatic fibrosis poses basically the same problems as accumulation and new formation of fibrous tissue anywhere else, modified (a) by the conspicuous participation of altered epithelial elements in determining fiber formation, and (b) by consequences which are related to the endocrine, metabolic, and excretory functions of the liver and to its double blood supply.

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POLIOMYELITIC PROPERTIES OF CERTAIN NON-POLIO VIRUSES: ENTEROVIRUSES AND HEINE-MEDIN DISEASE*

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Louisville, Ky.

Doctor Schick, Doctor Hodes, Ladies and Gentlemen:

I am most appreciative of the honor of appearing tonight as the Schick Lecturer. To the Schick lecturer of 1944, Doctor Albert B. Sabin, I owe much of my understanding of experimental poliomyelitis in animals, and to the Schick Lecturer of 1952, Doctor John Enders, my first experiences with tissue-culture techniques. But I must at once absolve these gentlemen from any responsibility for my remarks which may still be considered by some as speculative or even deviant. Speaking of enteroviruses and paralytic disease only last month Doctor Gilbert Dalldorf (1) said, "At the time many workers hesitated to accept these viruses as significant human pathogens and Steigman's views were received with some skepticism."

The chief point which I should like to develop tonight is that the clinical and pathological state which we call acute anterior poliomyelitis may be a syndrome of multiple etiology and is not necessarily synonomous with poliovirus infection. I shall cite some personal observations in some of which Doctors Kokko, Lipton and Ranzenhofer have variously participated; I shall refer to recent observations of others; and I shall discuss the possible meaning of some of these findings. My concern will be largely with human neurologic disease with particular emphasis on clinical paralytic poliomyelitis.‡

The speed with which the virological work in this field has moved is astonishing. Only ten years ago it became generally agreed that there are three serotypes of poliovirus and that to them should be ascribed the entire tragic toll of anterior poliomyelitis. But very recently it became appropriate to group under the major heading of *enteroviruses* three large families and their currently recognized individual members, namely: poliovirus with its three types; the coxsackie viruses of which Group A has to date nineteen numbered types and the Group B with five numbered types; and thirdly the ECHO family with nineteen individual members today (4). Generally speaking, these three major families are separable

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‡ The clinical and pathological criteria enumerated in a booklet of The National Foundation for Infantile Paralysis—"Definitive and Differential Diagnosis of Poliomyelitis"—will be adhered to largely as will the nomenclature criteria for paralytic and nonparalytic disease recommended by the W.H.O. Expert Committee on Poliomyelitis, July, 1957 (2, 3).

on the basis of certain pathological changes which they produce in a variety of experimental hosts and the individual serotype members are distinguishable on immunological grounds. Most members of all three families have a great many physical, chemical, biological and epidemiological characteristics in common with one another; these will not be detailed here. From the standpoint of tonight's discussion, the fact that they all inhabit the human alimentary tract and may on occasion invade the central nervous system, will be the focus of interest. I shall choose to take more interest in the similarities among these families of viruses than in their immunological differences.

From the standpoint of human disease, what a given strain of virus *does* is vastly more important than what it is called in serological baptism. In addition to more mundane likenesses, there are even some serological relationships amongst the three large families of enteroviruses. The evolutionist must be sorely tempted to believe that they originated from a common stem.

I would like to pass on now to the following personal observations.

Coxsackie Virus, Group B, Type 2, Producing Paralytic Poliomyelitis in a Monkey

In the summer of 1947 in Cincinnati, Sabin and Steigman conducted a study of "epidemic summer grippe or sore throat" in children (5). Tests in monkeys revealed neuronal lesions of a nature and distribution ascribable to poliovirus. Inability to serially transmit paralysis in monkeys led to the conclusion that the patients concerned were eliminating a strain of poliovirus of limited capacity for multiplication in the nervous system of the monkey. The donor of one of these specimens, W. H. age three years, had such an undifferentiated febrile illness with no clinical evidence of aseptic meningitis and no pleocytosis of his cerebrospinal fluid. His alimentary specimens produced neuronal lesions in Rhesus monkeys, one of whom was prostrate seven days after nasal, cerebral and peritoneal inoculation. The following is quoted from our findings, "Histological examination revealed acute poliomyelitic lesions in the medulla, midbrain, thalamus and olfactory lobes but not in spinal cord. In the medulla there was almost complete bilateral destruction of the dorsal motor nuclei of the vagus, with acute necrosis of the nerve cells." Cerebral subinoculation into two other Rhesus monkeys with a twenty per cent suspension of this animal's medulla resulted in histologically confirmed nonparalytic poliomyelitis in both monkeys. That medulla and spinal cord were kept frozen. After Dalldorf introduced the suckling mouse method for Coxsackie viruses I was able to recover from the medulla and also from the spinal cord (which was free of lesions) a virus identified as Coxsackie Group B, Type 2. Substantial confirmation of the fact that this monkey's central nervous system harvested only seven days after inoculation of the human specimens did not also contain poliovirus comes from the fact that when mixed with Freund's adjuvants and inoculated into other monkeys, the resulting serum contains no poliovirus antibodies, only Coxsackie B2 antibody. The patient developed antibody to the Coxsackie B2 virus in convalescence. The conclusion seemed inescapable that in this monkey, and those subinoculated with his medulla, there had appeared histologically typical acute poliomyelitis

and nonparalytic poliomyelitis respectively, ascribable to Coxsackie B2 virus and not to poliovirus.

Acute Paralytic Poliomyelitis in the Human Resulting From Coxsackie B5 Virus Infection

In 1952 two brothers, ages three and six years, were hospitalized, one with a trivial febrile illness associated with mild nuchal rigidity without pleocytosis, the other with clinical paralytic poliomyelitis, pleocytosis and resulting residual atrophy of the right deltoid and the abdominal muscles detectable at the final check-up examination fifteen months later. From the alimentary tract of one was isolated a Coxsackie B5 virus with a homologous rise in antibody titer of from 1:16 to 1:256 between the admission serum and the serum taken fifteen days after onset, and in the other, in whom serum was available one day after onset, a rise of titer from 1:4 to 1:8192 against homologous virus. No alteration of neutralizing antibody titer to the three serotypes of poliovirus was discernible. The serum of monkeys inoculated with the patients' alimentary material and their initial isolates in tissue culture revealed no polioantibody but antibody to the Coxsackie B5 virus. At the time it was still widely held that the Coxsackie viruses had not been shown to produce *any* kind of illness of the human central nervous system. In view of my observation of monkey paralytic poliomyelitis ascribable to Coxsackie B2 virus, it did not seem incredible that this particular Coxsackie B5 virus strain was responsible for the residual paralysis in the youngster just described (6).

Fatal Paralytic Poliomyelitis in a Child Ascribed to ECHO Type 2 Virus

In 1952 T. T., a two year, four month old girl, was admitted to another hospital because of abrupt onset of high fever, irritability, stiff neck. She was found to have clinical signs of meningitis with pleocytosis of 1170 cells per cu. mm., ninety per cent polymorphous; a white blood count of 20,000 per cu. mm., ninety per cent polymorphous, and appeared acutely ill. Within forty-eight hours she developed weakness of both lower extremities and of the diaphragm and intercostal muscles, leading to transfer to the Children's Hospital. Here she was found to have the signs of spinal paralytic poliomyelitis with respiratory insufficiency; a discrete macular rash, consisting of several dozen scattered lesions of the chest and upper abdomen, were duly noted. (It is of interest that this was recorded as at the time the term ECHO virus had not been coined nor any association with eruptions suspected.) In short, her subsequent course in the ensuing sixteen days was that of bulbospinal paralytic poliomyelitis with the pulmonary complications not infrequently seen in a tracheotomized small child treated in a respirator. Death thus occurred eighteen days following onset of illness. Post mortem examination revealed the typical findings associated with fatal bulbo-respiratory poliomyelitis. The lungs revealed acute purulent bronchitis and scattered areas of pneumonitis. The sections of the central nervous system revealed the typical distribution and character of lesions ordinarily associated with poliovirus. The cerebral cortex showed no microscopic changes apart from some scattered round

cell infiltration in the meninges. In the midbrain intensive ganglion cell loss was noted, particularly in the substantia nigra on one side and to a lesser extent in the contalateral red nucleus, together with mild ganglion cell loss in the reticular formation. The pons revealed extensive ganglion cell destruction involving most of the nerve nuclei, their sites consisting of spongy glial tissue with either no ganglion cells or just a few necrotic, swollen non-nucleated remnants. A number of gitter cells were scattered throughout and there was considerable perivascular lymphocytic cuffing. The medulla revealed less damage than the pons, the dorsal half being the more markedly involved. The spinal cord revealed particularly marked destruction of the anterior horn cells which were largely replaced by a mass of gitter cells, lymphocytes and occasional polymorphonuclear leukocytes. Inclusion bodies were not observed (Figs. 1–4).

A section of the cervical and of the lumbar cord were collected aseptically and found to be sterile in thioglycholate culture. Although it had been eighteen days since onset of illness and the relatively insensitive monkey testicular implant method of tissue culture was in vogue, a cytopathic agent was isolated which subsequently proved to be ECHO Type 2 virus. Monkeys inoculated with the patient's spinal cord and tissue culture fluids derived from the same developed neither histological nor clinical evidence of central nervous system infection; their serum acquired only ECHO Type 2 antibodies and no poliovirus antibodies. Here then was a strong suggestion that this virus had been responsible for fatal bulbospinal paralytic poliomyelitis. This patient was presented and discussed five years ago at the Society of Pediatric Research meeting (7).

Fig. 1. Cerebral Cortex eighteen days after onset of bulbospinal poliomyelitis due to ECHO type 2 virus. Illustrates freedom of cerebral lesions apart from mild meningeal reaction.

Recently there appeared a report of aseptic meningitis with recovery of ECHO Type 2 virus from the cerebrospinal fluid, in one child five days after onset of illness (8). That poliomyelitis lesions may occur in monkeys following intramuscular inoculation of ECHO viruses has been brought out by Wenner and Chin (9) who found it most commonly with the ECHO Type 2. This is not

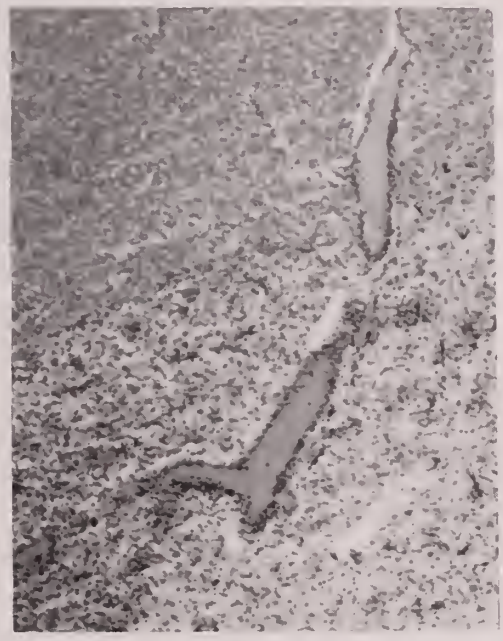

FIG. 2. Pons eighteen days after onset of bulbospinal poliomyelitis due to ECHO type 2 virus. Extensive ganglion cell destruction of nuclei pontis.

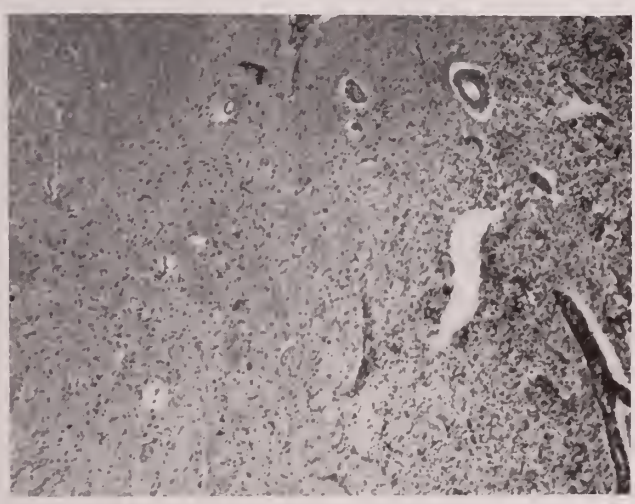

FIG. 3. Cervical spinal cord eighteen days after onset of bulbospinal poliomyelitis due to ECHO type 2 virus. Marked destruction of anterior horns with replacement by gitter cells, lymphocytes and occasional polymorph leucocyte.

FIG. 4. Lumbar spinal cord eighteen days after onset of bulbospinal poliomyelitis due to ECHO type 2 virus. Almost complete destruction of anterior horns with replacement by gitter cells, lymphocytes and occasional polymorph leucocyte.

necessarily offered as support for the idea that our child's fatality from poliomyelitis was brought about by the ECHO 2 virus. It is clear that what a naturally occurring or laboratory manipulated strain of any virus may do in a given child is not necessarily the same as it will do in a monkey.

Acute Paralytic Poliomyelitis in the Human due to Coxsackie A7 Virus

A three year old boy was hospitalized July 9, 1956 with clinical evidence of the aseptic meningitis syndrome accompanied by pleocytosis of 245 cells per cu. mm. of which 68 per cent were polymorphs, 32 per cent lymphocytes, total protein 32 mgm. per cent, sugar 56 mgm. per cent and chlorides 121 meq per liter; white blood count was 13,000 per cu. mm. with 58 per cent polymorphonuclear cells. The day following admission to the hospital generalized weakness and right lower facial paralysis were noted; the latter disappeared at the end of the week during which asymetrical paralysis of the right and left lower extremities progressed. When last seen one year following acute onset of paralysis, deformity of the right foot and mild atrophy of the right gluteus group were the most prominent residual defects.

This child's stools yielded no virus in tissue culture but inoculation of suckling mice revealed an agent identified as Coxsackie group A type 7. To date monkeys inoculated with the child's stools and suckling mouse preparations have revealed neither disease nor central nervous system lesions.

Serial bleedings from this child revealed the development of neutralizing antibody to the Coxsackie A7 virus in tests performed in suckling mice; the child continues to have no demonstrable neutralizing antibody to any of the three standard polioviruses. Again the conclusion seems inescapable that this young child was rendered paralytic from his infection with this particular strain of Coxsackie A7 virus.

Russian investigators have recently described strains of Coxsackie A7 virus recovered from an *epidemic* of apparently typical clinical poliomyelitis and capable of producing the histological picture of poliomyelitis in some monkeys.

Certain selected supportive evidence of others will now be cited. A complete review will not be attempted.

First, a number of children who have been adequately vaccinated against poliovirus with Salk vaccine have had clinical paralytic poliomyelitis caused, however, by *nonpolio enteroviruses* (10). The importance of this is self-evident. Hammon and his colleagues (11) have placed at my disposal a report which contains further evidence that members of the Coxsackie and ECHO group at times may or actually do cause paralysis; these include Coxsackie A9, Coxsackie B3, B4, and ECHO 4 and ECHO 16. Furthermore, their studies tend to confirm the observation by others which lends strong support to the concept of antigenic links between polio and non-polio enteroviruses in certain complement fixation tests. These observations, by the way, are revealed only in human serums.

Kibrick, Melendez and Enders observed spotty, asymetrical paralysis in an outbreak of ECHO Virus type 6 infection. They say, "It is unlikely that concomitant infection with poliovirus was responsible for the muscle weakness observed in these cases. Thus in the acute and convalescent phase sera of three of these patients no antibodies capable of neutralizing any of the three types of poliovirus were demonstrated and in the sera of the remaining six patients no increase was revealed in the poliovirus neutralizing antibodies initially present" (12).

Verlinde (13) in a personal communication describes the recovery of ECHO virus Type 9 from the brain of an encephalitic infant; this particular strain gives rise to lesions in monkeys difficult to distinguish from acute poliomyelitis. Interestingly, the same serotype isolated from that infant's alimentary tract does not exhibit this poliomyelitic property in the monkey.

Sabin (14) has reported that among the patients infected with the ECHO 9 virus in Milwaukee last summer one had mild bulbar poliomyelitis and another had spinal paralysis requiring ambulatory assistance for several months.

Doctor Dalldorf who has made enormous contributions to this field has experimentally adapted a strain of Coxsackie virus Group A Type 14 so that it now produces poliomyelitic lesions without paralysis in Cynomolgus monkeys and has more recently informed me that this virus in synergism with an equally non-paralyzing Type 1 poliovirus (Sabin's 80-A strain) given at suitable intervals under suitable circumstances produces severe paralysis in monkeys (1).

Von Zeipel and Svedmyr (15) have pointed out that human poliovirus convalescents react in complement-fixation tests with ECHO 6 antigen in the same manner as they do with the group specific poliovirus antigen and ECHO 6 patients react with polio antigens just about as they do with the homologous antigen, rises being common. Apparently the ECHO 9 patients of last year also often responded against polio antigens. Svedmyr closes a personal communication on this question by saying, "My point would thus be that those enteric viruses suspected to have some paralytogenic capacity (Coxsackie A7, ECHO 6) might have more in common with polioviruses than previously thought" (16).

The Swiss have reported an interesting family outbreak of ECHO Type 4 infection involving seven of nine members of the household (17). Five of the seven experienced a grippe-like illness consisting of fever, headache and vomiting, two individuals had a meningeal reaction, and one adult developed paralysis of the right leg and weakness of the right arm. ECHO virus Type 4 was recovered from the feces of three individuals including the paralyzed adult in whom poliovirus antibodies failed to emerge. In previous years this outbreak would simply have been regarded as an instance of poliovirus infection producing paralysis in only one individual of the family.

Chumakov and coworkers at the Poliomyelitis Research Institute in Moscow (18) isolated strains of virus from the stools of Russian children during the acute phase of paralytic poliomyelitis. Their virus was isolated directly in monkeys inoculated with the pooled stools of two patients with fatal bulbar paralysis. The virus produced paralysis and typical poliomyelitic lesions following either intramuscular or intracerebral inoculation of monkeys. It was also capable of producing paralysis in suckling mice and has since been identified as Coxsackie A7 virus. Their strain has been studied by others (19, 20, 21) with confirmatory findings; Habel and Loomis have studied two American strains of Coxsackie A7 and conclude, "These are likewise pathogenic in monkeys and in certain inoculated animals produce histological changes in the central nervous system which are indistinguishable from those caused by polioviruses" (19). In some monkeys poliomyelitic lesions were occasionally observed outside of the "classical areas" of the central nervous system in experimental poliovirus infection. However, I have occasionally observed typical lesions in atypical areas of the human central nervous system in proven poliovirus Type 1 infections, and poliovirus-proven cases of acute encephalitis in children are being uncovered (22). There can be little doubt that some strains of the Coxsackie A7 virus are capable of producing paralysis as in our patient described earlier tonight.

The first demonstration of poliovirus by Landsteiner and Popper in 1908 (23) resulted from the intraperitoneal inoculation of the monkey with a patient's spinal cord. We must all be grateful that *by chance* this particular strain produced a *comparable disease* in a *particular monkey* inoculated by a peripheral route. As Sabin stated two years ago at the conference on "Viruses in Search of Disease" (24), "Imagine for a moment what the situation might be if the currently available tissue-culture methods had been used before an etiological association had been established between the polioviruses and the paralytic syndrome (sic!) we call poliomyelitis. Applying these methods to healthy children one or two years of age in Veracruz, Mexico, at a time when poliomyelitis was not diagnosed in the community, it was possible by means of a single rectal swab to find that approximately 12 per cent of the children were infected with poliovirus. In such an area and under these conditions, the recovery of a similar virus from the stools or even from the spinal cord of a rare case of poliomyelitis, would, by itself, provide little evidence for an etiologic association."

At a joint meeting in 1935, Doctor Thomas Rivers said "Everyone working with viruses and tumors is entitled to a guess" (25). Seizing upon this invitation

I guess that it will soon become clear that acute anterior poliomyelitis will be viewed as a clinical and pathological state of diverse viral etiology.

Table I illustrates a reciprocal reluctance to accept certain ideas. To the left you see the clinical states ascribable to poliovirus. Although epidemiological and other evidence was clear to Wickman and others fifty years ago that poliovirus could bring about clinical states other than flaccid paralysis, complete acceptance among investigators came only when such could be shown *in monkeys* about 1940. Nonparalytic monkey poliomyelitis—call it the aseptic meningitis syndrome if you like since monkeys often show pleocytosis on cisternal puncture—reveals disseminated neuronal lesions scattered throughout the neuraxis. There is little doubt in my mind that the aseptic meningitis syndrome in children—call it nonparalytic poliomyelitis if you like—when caused by the enteroviruses is accompanied by disseminated neuronal lesions. If we view the right hand side of Table I it will be noted that the nonpolio enteroviruses were first viewed as having no consequence, reluctantly viewed as producers of undifferentiated febrile illnesses, then as producers of the aseptic meningitis syndrome and finally there is a growing consensus of opinion that paralytic disease may be caused by certain strains of these agents under given circumstances.

Since speculation need not be stifled in The Schick Lecture, I would raise the question of whether these agents may not even remain latent but viable in the central nervous system of an occasional child, perhaps to serve a role in the production of some subtle or dramatic clinical mischief later on. Our own studies show that non-lesion producing strains of poliovirus can be detected in the central nervous system of mice long after inoculation. Sabin and Ward (26) once described an interesting monkey whose central nervous system yielded poliovirus 35 days after inoculation of human material, the monkey having had neither the clinical nor the histological criteria for poliovirus infection. Is it not possible that the more elegant current techniques for unmasking and demonstrating viruses may show latent viruses in the human central nervous system?

The extent to which these nonpolio enteroviruses may be important in the production of serious neurological disease is unknown. Characterization of a given strain of virus does not end with the assigning of immunological type and number to it, for in terms of disease it is the pathogenic properties which are important. A good many years back Doctor Theobold Smith (27) wrote, "There is scarcely a specific disease known today whose causal organism is not represented by at least several variants or a parasite which does not appear under

TABLE I

Reciprocal historic reluctance to accept some etiological relationships in primates of

Polioviruses	Some Nonpolio Enteroviruses
Paralytic disease	Non-pathogenic visitor
Nonparalytic polio (Aseptic meningitis)	Undiff. febrile illness
Undiff. febrile illness	Aseptic meningitis (Nonparalytic polio)
Non-pathogenic visitor	Paralytic disease

several forms. The subjective factor or the personal equation naturally plays a certain part in recognizing relationships or in associating forms at first regarded as unrelated. If we maintain that the host tends to modify the parasite enough so that the invasion of different hosts by the latter necessarily leads to races, we are also faced by the fact that different races of the same parasite may be found in the same host." I can think of no more striking example than that communicated to me by Kibrick (28) who isolated Coxsackie B4 virus from several organs of a neonate with encephalomyelitis and aseptic myocarditis. Only the strain isolated from this infant's liver and not the one isolated from the badly diseased heart and brain exhibit the remarkable property of producing anterior horn cell degeneration of poliomyelitic type in the spinal cords of suckling mice as seen in Figure 5. When this sort of dissociation of pathogenic properties can occur *within a single baby,* is it surprising that a virus may act very differently from year to year and from place to place? Any current descriptions therefore of, let us say, ECHO 9 disease or Coxsackie B5 disease or for that matter even poliovirus disease should be regarded as tentative and subject to change.

There is no longer any doubt that Coxsackie B viruses may affect the human heart (29), with or without appreciable central nervous system disease and the reciprocal may occur (30). It may be of more than passing interest that poliovirus patients may have myocardial disease, the frequency varying with the particular outbreak (31). In the virologically well documented outbreak of 1953 in Stockholm all 26 autopsied poliovirus patients revealed myocarditis (32).

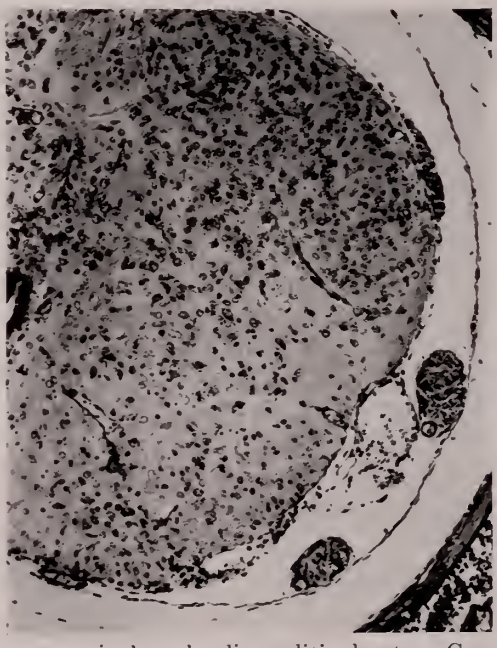

FIG. 5. Suckling mouse spinal cord poliomyelitis due to a Coxsackie B4 virus strain. The patient's hepatic strain only shows this property; strains isolated from the same patient's brain and heart lack this property. (From Kibrick, S., and Benirschke, K. To be published.)

There may thus be strains of poliovirus more myocarditic than others and bearing in mind the vagaries of viral variation there may even exist strains of poliovirus more myocarditic than neurotropic. Just as the complete spectrum of viral etiology of anterior poliomyelitis is uncertain, so may be the complete pathological spectrum of diverse strains of poliovirus.

Virus mutability is a fascinating phenomenon to the microbiologist and a constant threat to the clinician. The recent large epidemics of ECHO 9 infection with variable clinical patterns and viral strains of variable pathological properties in the laboratory bespeaks a ferment which is disquieting. At a time (33) when the Coxsackie viruses were not even entirely accepted as causative of Bornholm disease, and prior to its association with human central nervous system disease or of aseptic myocarditis, Burnet wrote, "Suppose the potential power of the Coxsackie viruses to attack muscles was greatly enhanced in a certain mutant and circumstances allowed it to spread freely. I can imagine as a result a completely new type of epidemic in which intense generalized pain in the muscles would immobilize the victims, many of whom would die with symptoms of acute heart failure when the muscles of the heart were involved. There has never been an epidemic of this sort but equally there has never since 1560 been an epidemic with the symptoms of the English sweats" (33).

I cannot resist the temptation to speculate in another area concerning the relationship of these families of viruses to one another in association with paralytic disease. Until relatively recently it was believed that there was only one poliovirus but ten years ago three were agreed upon and the membership firmly closed, at least temporarily. Although distinct from one another there are numerous similarities among them suggesting a common stem in the evolutionary scale. That this may have clinical meaning may be inferred by the interesting observation of Hammon's group among others that previous experience with *type 2 virus* affords considerable protection against the paralytic consequences of exposure to *Type 1 poliovirus* (34).

Johnsson (35) has also presented evidence showing antigenic links amongst the three enterovirus families following infection in humans. Although this makes interpretation of complement-fixation diagnostic tests difficult, let us hope that exploration of these relationships can be put to good use in terms of understanding and preventing human disease.

A very exciting line of investigation in the field of relationships among the three major families of the enteroviruses has held the attention of the imaginative Gilbert Dalldorf for some time. Without detailing the evidence, suffice it to say that he has assembled impressive epidemiological and experimental data which suggests that under appropriate conditions some of the Coxsackie A viruses may enhance the neurotropism of poliovirus and some of the Coxsackie B viruses may retard, interfere, or, as Dalldorf so well puts it, exhibit a sparing effect on poliovirus infections (1). Table II illustrates a remarkable epidemic of "poliomyelitis" occuring in Hadersley, Denmark almost twenty-five years ago (36) when in a short period of time 734 individuals were hospitalized in the small area, yet only 27 were paralyzed; the total mortality was infinitesimal. We shall

TABLE II

Unusual epidemic of poliomyelitis

Haderslev, Denmark

7/20–11/30, 1934*

Hospitalized	730	
Paralyzed	27	(3.7%)
Fatal	3	(0.4%)

* Nissen, N. I., Acta Paediatrica, 18: 1, 1936.

Was this due to (1) poliovirus of low virulence; (2) a nonpolio but mildly paralytic enterovirus; (3) a mixed epidemic of poliovirus and Coxsackie group B virus? All ages affected but most paralytic cases and all deaths in the young; Bornholm disease was widespread then in Denmark.

never know with certainty whether this was all due to a strain of poliovirus of very low pathogenicity, whether it was due to a nonpolio enterovirus infection in which only a small number of individuals were paralyzed and a smaller number of infants killed, or whether this was an example of a Coxsackie B virus producing a sparing effect on a simultaneous poliovirus infection.

It is obvious that the suppression of poliovirus infection by various methods of vaccination will make paralysis due to these other viruses more conspicuous. No less important than the immediate clinical implications of this is the reward to be gotten through careful study of the relationship of these infections to each other.

To quote Dalldorf (37), "The importance of these agents may become clearer once poliomyelitis has been suppressed. It may be that these viruses will only seem to be more important, but possibly they will become truly so and will fare better—and we worse—when they are not overgrown by the polioviruses. This of course is only speculation and it proves nothing more than that hard work is needed. However, is it unlikely that the changes in our manner of living that seem to have contributed to the growing danger of poliomyelitis have not affected related agents in the same way? Perhaps the change already has occured and is one reason for our present interest in these viruses."

To you, Doctor Schick, my sincere thanks for this opportunity to present opinions in transition.

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PECULIARITIES OF SYMPTOMATOLOGY IN CHRONIC POLIOMYELITIS PATIENTS

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The development and improvement of tank-type respirators, cuirass respirators, rocking beds, and so-called positive pressure devices during the past two decades represent noteworthy advances in the field of mechanical artificial respiration. The availability of these aids together with a broader understanding of pulmonary physiology and patho-physiology have resulted in improved medical care for poliomyelitis victims with respiratory paralysis. As a consequence, many such patients now survive who would not have done so in the past. An appreciable number of these have extensive muscle paralysis and require mechanical respiratory assistance for various periods each day.

The severely paralyzed "chronic poliomyelitis" patients are susceptible to all human ills but they are particularly subject to pyelitis, pyelonephritis, ureteral obstruction due to calculi, pneumonia, lung abscess, and phlebitis. However, the severe and extensive neuronal damage caused by poliomyelitis virus often results in the failure of these patients to respond to the illness in a manner familiar to the physician. Pain, fever, and localization of symptoms often are misleading or absent. An increasing number of chronic poliomyelitis patients now are being discharged from hospitals to their homes and then come under the care of their private physicians. It is estimated that there are now 1100 such patients at home and that about 550 more will soon be returning to their homes. It is important, therefore, to call attention to the altered response to illness which these patients present.

PAIN

In the chronic poliomyelitis patient, pain may be absent in a disease in which it is ordinarily a major manifestation. For example, it is not uncommon for ureteral obstruction to cause no pain to the chronic poliomyelitis patient (1, 2). Large calculi have traversed the entire length of a ureter without discomfort to such patients. Occasionally, partial or complete ureteral obstruction due to a stone has occurred without renal colic. The first case history presented below is that of a patient with ureteral obstruction who had no pain arising from genitourinary structures per se.

Peritonitis without associated pain has been observed twice in our experience. A very dramatic case of this type was that of a 39 year old female. About ten months after her discharge from the hospital, she began to complain of fatigue and general malaise. These vague complaints continued for about ten days with progressive general deterioration. Her physician could find nothing to explain

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the down-hill course and he advised hospitalization. She died before she could be transported to a hospital. Post-mortem examination revealed acute hemorrhagic pancreatitis and peritonitis. Hemorrhagic pancreatitis is generally referred to as one of the most painful diseases to which man is susceptible, yet this symptom was entirely absent in this patient. Peritonitis without pain is further illustrated in the second illustrative case history presented below.

In our experience, it has been only severely and extensively paralyzed patients who have failed to have pain in circumstances such as those mentioned above. Blossom and Affeldt (3) found, at autopsy, esophageal and gastric ulcerations in patients who had no symptoms other than distention. It is possible that pain might be absent in other disease states with which we have had no experience. That the failure to have pain under the circumstances mentioned is not due to a general loss of pain perception, is attested to by the fact that all of the patients under our observation experienced pain to pin prick, muscle pain during physical therapy, or pain during cystoscopic examinations. However, there seems to be a diminution in visceral pain sensation, although pain has occurred with distention of the urinary bladder or of the bowel. In contrast with the above conditions, there are certain diseases which never, in our experience, fail to cause pain. This is true of phlebitis, otitis media, sinusitis, decubiti, paronychiae, and physical trauma. Women who have had dysmenorrhea prior to poliomyelitis invariably again suffered pain when menstruation was reestablished. The pain during the three stages of labor in the chronic poliomyelitis patient is less severe than that seen in normal women. However, it has been postulated that this is due to the flaccidity of the perineal musculature.

FEVER

The absence of fever in the chronic poliomyelitis patient with an inflammatory process is a moderately frequent occurrence. We have encountered several patients with both viral and bacterial infections who have not experienced an appreciable elevation of temperature. The lack of febrile response has been associated with infections due to various bacteria. A remarkable example is that of pneumococcal pneumonia which is nearly invariably associated with fever in the average patient. It has not been uncommon to find patients who are afebrile in the presence of pyelitis and obstructive uropathy accompanied by pyelitis due to E. coli, B. proteus or A. aerogenes. Pharyngitis and bronchitis due to streptococci, staphylococci and other organisms have been seen frequently without associated pyrexia. Peritonitis due to A. aerogenes was observed to occur without fever in one case which is presented below. As with the absence of pain, lack of fever occurs only in the very severely affected poliomyelitis patients.

The reason for the failure of some chronic poliomyelitis patients to exhibit a febrile course in circumstances in which it is expected is obscure. And, to compound the confusion, some patients who have failed to have fever at one time, have had temperature elevations at others even with the same causative bacteria. It would appear that a greater than ordinary pyrogenic stimulus is necessary to produce a rise of body temperature in these patients. The chronic polio-

myelitis patient "normally" has a lower temperature than the healthy person. The poliomyelitis patients usually have a temperature of about 97.4° to 98.0° F. orally and, therefore, relatively greater increases in temperature are necessary to reach levels usually accepted as being abnormal. Consequently, temperatures over 102° F. are encountered infrequently. It is clear, too, that temperatures lower than 100°F. may represent fever in those patients whose daily temperature is subnormal according to usual standards. It is our practice to relate individual temperature readings to the patient's usual temperature pattern in order to be certain that significant elevations in temperature have not occurred below 100°F.

LOCALIZATION OF SYMPTOMS

Although the chronic poliomyelitis patient may not have fever or spontaneously localizing pain with various intercurrent diseases, there is usually some "displaced" complaint presented. On occasion, this may be the only indication that all is not well. Gastrointestinal complaints not infrequently are associated with non-alimentary disease processes. Vague abdominal discomfort and/or distention have been observed in patients with partial or complete ureteral obstruction, hypoxia, tension states and, in one of our patients, with peritonitis. The gastrointestinal symptoms are due to adynamic ileus, gastric dilatation or both. Because of its relationship with emotional states, gastric dilatation is by far the most common gastrointestinal abnormality. The causal relationship between the two is not known. Studies have revealed that some chronic poliomyelitis patients have an abnormality in the central control of gastric tone and secretion (4). It is possible that in certain patients the central response to stimuli goes awry because of neural damage by the poliomyelitis virus to the hypothalamus or the vagus nuclei. Whatever the mechanism, gastric dilatation commonly occurs with emotional upsets whether or not the psychological disturbances themselves are organic in origin. We have encountered dilatation of the stomach in patients at the time of family disputes, when discharge from the hospital has been postponed, or when other news of a disturbing nature has been received. Whether organic illness per se produces gastric dilatation is difficult to determine, for the occurrence of complicating illness represents a great threat to the survival of an already insecure individual and, therefore, produces marked anxiety and apprehension.

We have not observed adynamic ileus without associated organic disease. It is most frequently associated with ureteral irritation due to complete obstruction, partial obstruction, or to the passing of stones or "gravel".

ILLUSTRATIVE CASES

The following case histories illustrate the peculiarities of symptomatology in chronic poliomyelitis patients.

Case # 1

J. S. (# 52938), a 15 year old boy, was admitted to The Jack Martin Poliomyelitis Respirator Center at The Mount Sinai Hospital in September, 1955 with

acute poliomyelitis. His illness was severe and was characterized by evidence of extensive disease of the spinal cord and some evidence of bulbar involvement (gastric dilatation, paralysis of the soft palate and bilateral paralysis of the lateral recti of the ocular globes). Within twenty-four hours after admission to the hospital, the patient required artificial respiration. He survived the acute phase of his illness, following which there was moderate weakness of the neck muscles, total paralysis below the neck except for some poor supinator function at the left wrist and severe respiratory muscle involvement (vital capacity 250 cc.). By early October, the patient was able to breathe without mechanical assistance for twenty minutes and was using a cuirass respirator instead of the tank-type respirator. Function had returned to a moderate degree in the left upper extremity so that, with assistance, self-feeding could be done.

X-ray examination revealed each kidney to have a double pelvis. No evidence of urinary tract calculi was demonstrated roentgenographically; however, occasional red blood cells were noted on examination of the urine.

The patient improved slowly and was doing well until late one day in January when he complained of epigastric fullness. Examination did not reveal fever or abdominal tenderness, and the patient did not appear to be ill. A nasogastric tube was inserted into the stomach, but no gas or liquid could be removed. The abdominal discomfort slowly increased in severity so that ten hours after the onset of symptoms the cuirass respirator caused so much discomfort during inspiration that the patient was placed in a tank-type respirator. He then was comfortable, afebrile, and without pain until fifteen hours after onset of symptoms when pressure changes within the respirator caused diffuse abdominal pain. Twenty hours after onset of symptoms, the patient was afebrile and abdominal palpitation revealed diffuse tenderness. Rebound tenderness was elicited. Rigidity of the abdominal wall was not present nor could it occur since the muscles of the abdominal wall were totally paretic. The white blood cell count was 22,200 per cubic millimeter.

It is believed that the patient was suffering from peritonitis, but the cause was not clear. He was taken to the operating room in a tank-type respirator. After pentothal anesthesia was started, a cuffed endotracheal tube was passed and through this respiration was maintained by manually squeezing an anesthesia bag. Although perforation of an inflamed appendix seemed to be the most likely cause of the peritonitis, a paramedian incision was made. Free pus was found in the peritoneal cavity. Culture of this material revealed Aerobacter aerogenes. A perforated Meckel's diverticulum was found and amputated. In addition, the normal appendix was removed. Following surgery, the patient was returned to the respirator, the endotracheal tube was removed, artificial respiration was continued with the tank-type respirator, and the patient was returned to the Center.

He was treated with chloramphenicol and intravenous fluids and made an uneventful recovery. He was out of the tank-type respirator and again using a cuirass respirator in three weeks. The patient remained in the Center for a lengthy period after the above episode. During his stay, there was considerable

improvement, and he was discharged to his home fourteen months following admission.

Case # 2

L. A. (# 62730), a 26 year old white male, was admitted to a contagious disease hospital on October 24, 1955, because of acute poliomyelitis. He very quickly developed paralysis of the muscles of all extremities, the neck and the trunk. The muscles of respiration became paralyzed too so that artificial respiratory assistance was necessary. Because he was unable to void, an indwelling bladder catheter was employed. The catheter was removed after three weeks. During the third week of illness, a state of delirium occurred which was considered to be due to respiratory alkalosis. The patient was critically ill and was not expected to survive. Nevertheless, he responded to treatment and shortly was able to be removed from the tank respirator with the use of a cuirass respirator and a rocking bed for respiratory assistance. He had several transient episodes of abdominal discomfort which were relieved by insertion of a rectal tube.

Five weeks after the onset of his illness, the patient was admitted to The Jack Martin Poliomyelitis Respirator Center at The Mount Sinai Hospital. At that time his vital capacity was 200 cc., and for respiratory assistance he used a cuirass respirator at night and a rocking bed during the day.

A week after admission to the Center, the patient awoke at night with abdominal discomfort described as fullness. The patient had no fever, abdominal tenderness, tenderness over the kidney regions posteriorly or spontaneous pain. He insisted that this type of problem was a chronically recurring one, and he merely required the insertion of a rectal tube in order to gain relief. This was done, but he was not relieved. An emergency excretory urogram was done and revealed prompt visualization on the right but none on the left. One oval opaque calculus was present in the mid portion of the left ureter, and two stones were seen in the lower third of the left ureter. Cystoscopy revealed the bladder mucosa to be diffusely and markedly inflamed. Within the bladder, there were many small stones and incrustations. Left ureteral catheterization failed to by-pass the obstruction, but the lower stones were pushed up to the level of the mid ureteral stone. During this time the patient's complaints of abdominal fullness increased, and it was increasingly difficult to provide him with adequate breathing with a cuirass respirator. There was still no fever or pain, but gastric dilatation was evident. The patient was placed in a tank-type respirator and taken to the operating room where pentothal anesthesia was begun. After the patient was anesthetized, a cuffed endotracheal tube was inserted. He was moved to the operating table while the anesthesiologist provided artificial respiration manually by means of an anesthesia bag. Thereafter, a left ureterolithotomy was performed, the patient was returned to the tank-type respirator, the endotracheal tube was removed, and he was taken back to the Respirator Center.

The patient recovered from the procedure without difficulty. He ultimately attained a vital capacity of 560 ccs. With the help of glossopharyngeal breathing and ad libidum use of a portable positive-pressure device, he is able to be up in

his wheelchair all day. Although he has only poor wrist and finger function of the right upper extremity, with mechanical assistance he can feed himself, shave, use a telephone, and operate a tape recorder. As a result of the effort and energy of a dedicated staff, this patient lives at home with his wife and is back at work in his office.

CONCLUSION

The occurrence of intercurrent disease in chronic poliomyelitis patients may go unnoticed or evade detection because the patient frequently fails to respond to the illness in the usual manner. Of the many such cases which have been seen by the author, two exemplary ones are presented in the above case histories. The high incidence of calculi of the urinary tract, together with the lack of pain frequently associated with ureteral obstruction, require excretory urograms be obtained whenever gastric dilatation, ileus or vague abdominal complaints are presented. In patients with vague abdominal discomfort, abdominal paracentesis may be diagnostic of peritonitis although fever and leukocytosis are absent. Subjective feelings of inadequate ventilation may be the only indication of pneumonia or atelectasis, but gastric dilatation or anxiety may cause the same symptoms. Because of the difficulties involved in the procedures necessary to reach the proper diagnosis in chronic poliomyelitis patients, it is suggested that such patients should be hospitalized promptly if the cause of intercurrent illnesses is not immediately apparent.

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THE FIRST FIVE YEAR OBSTETRICAL REPORT OF THE MOUNT SINAI HOSPITAL, NEW YORK

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The Maternity of The Mount Sinai Hospital, which opened in 1953, is in its sixth year of operation. Concurrently with the inception of the Department of Obstetrics, a system of code-sheet, punch-card tabulation of all patient data was introduced. Essential details from each patient's chart are transferred to an 80 point IBM card at the time of discharge, before the history is sent to the record room. The cards are stored in special metal filing cabinets and constantly available for mechanical sorting and study. The work has been continually supervised by one of the authors (W.A.E.); the details of performance being carried out by the intelligent code-clerk, Miss Nina Smith.

Taking stock of performance is as essential in hospital medicine as in business. Therefore the Department of Obstetrics has prepared semi-annual and annual reports each year. These have been combined in the first five year report which has been mimeographed and is available to any reader on request.

This analysis will abstract the most salient points from this detailed, five year compilation. It is hoped that this article will establish a precedent and that every five years, next in 1963, The Journal of The Mount Sinai Hospital will publish such a study.

The material in Table I is largely self explanatory; however some items require comment.

In 1953, 2781 babies were delivered. This figure rose rapidly to 4920 in 1957. The proportion of two private patients to one ward patient has been constant throughout the five year period; this excess of private patients is unique when compared to other major services of the Hospital. In the fifth year of its existence the Maternity at The Mount Sinai Hospital delivered more women than any other hospital in Manhattan.

It is common practice in statistical studies to include all deliveries in which the fetus exceeded 400 grams (14 ounces) regardless of length of gestation. Since it is exceedingly rare for a fetus with a birthweight less than 1000 grams (2 pounds, 3 ounces) to survive, these are ordinarily eliminated from the total perinatal death rate, yielding a corrected perinatal rate for fetuses of 1000 grams and over.

The combined term and premature operative rate was 63.9%. This figure is high when compared to other maternities, the difference being mainly in the higher incidence of elective low forceps.

Table III requires no interpretation except for the fetal loss figures in the last column. An infant may be stillborn or die from one of several factors; such as prematurity, diseases of the newborn, malformations, maternal antepartum

From The Department of Obstetrics and Gynecology, The Mount Sinai Hospital, New York, N. Y.

TABLE I

Summary of the Statistics of the First Five Years of Activity of the Department of Obstetrics

Patients Delivered			
Private	14089	66.6%	21169
Ward	7080	33.4%	
Deliveries (Infants)			
Private	14247	66.5%	21439
Ward	7192	33.5%	
Maternal Deaths		7	
Rate per 1000 Live Births			0.3
Live Births		21076	
Stillbirths		363	
Rate per 1000 Births			16.9
Stillbirths (Over 1000 Gms)		257	
Rate			11.9
Neonatal Deaths (First 28 Days)		269	
Rate			12.7
Neonatal Deaths (Over 1000 Gms)		203	
Rate			9.6
Perinatal Deaths (Stillbirths and Neonatals)		632	
Rate			29.4
Perinatal Deaths (Over 1000 Gms)		460	
Rate (Deducting 172 Immature Births) (400–999 Gms)			21.4
Multiple Deliveries (11 Sets by Section)		264	1.2%

TABLE II

Maternal Discharges by Type of Delivery

	Private	%	Ward	%	Total	%
Fullterm Spontaneous Del.	4121	29.0	2707	38.2	6828	32.2
Fullterm Operative Del.	8965	64.0	3683	52.0	12648	59.8
Premature Spontaneous Del.	344	2.4	306	4.3	650	3.1
Premature Operative Del.	556	3.9	315	4.5	871	4.1
Immature Delivery	103	0.7	69	1.0	172	0.8
Total	14089		7080		21169	

Abortion	0–399 Gms.
Immature	400–999 Gms.
Premature	1000–2499 Gms.
Fullterm	2500–Gms. and Over

hemorrhage, cord difficulties, etc etc. Therefore the specific factor under which a fetal loss is listed may have had no causal connection with the death of the infant. This should be born in mind when interpreting fetal loss figures throughout this study, for example in Table III, breech extractions. Very few of these infants died as a result of the mechanics of the breech birth itself. Premature infants and abnormal infants have a greatly increased tendency to present by the breech; the real factors responsible for the infant's death and not its breech presentation.

The eight failed forceps were delivered by cesarean section, all resulting in surviving infants.

The forceps rate for four other comparable teaching institutions was 14% (1), 30% (2), 57% (3), and 61% (4) respectively.

Episiotomy was performed in 82% of all vaginal deliveries, half median and half medio-lateral. Extension of the episiotomy to involve the anal sphincter was six times more frequent following the former; however when anatomically repaired such a third or fourth degree extension ordinarily heals without sequelae.

In Table V the use of pitocin requires clarification. Pitocin induction is the initation of labor through its administration; whereas pitocin stimulation is the enhancement of labor already established. The higher incidence of induction on the private service becomes understandable when one realizes that a fair proportion of the multiparous private patients live some distance from the Hospital and labor by appointment is more convenient and safer. To induce such a patient is common practice in other hospitals. However not all pitocin inductions are done for convenience, since not infrequently complications of pregnancy necessitate the procedure.

TABLE III

Deliveries by Presentation

	Private	Ward	Total	% of Delivery	Fetal Loss	
					No.	%
Vertex	13557	6818	20375	95.0	451	2.2
Breech	600	309	909	4.2	158	17.4
Face	17	15	32	0.2	3	9.4
Brow	12	7	19	0.1	0	0
Compound	18	20	38	0.2	9	23.7
Transverse	43	23	66	0.3	11	16.7
Total	14247	7192	21439	100.0	632	2.9
Twins	150	110	260	1.2	42	8.1
Triplets	4	0	4	0.01	4	33.3

TABLE IV

Forceps Deliveries

	Private		Ward		Total		Fetal Loss	
	No.	%	No.	%	No.	%	No.	%
Failed Forceps	6	0.1	2	0.1	8	0.1	—	—
Low Forceps	5694	40.0	2711	37.7	8405	39.2	74	0.9
Mid Forceps	2325	16.3	686	9.5	3011	14.0	39	1.3
Total	8019	56.3	3397	47.2	11416	53.2	113	1.0

Table V shows that 20.1% of our patients received antepartum or intrapartum pitocin. The reports of five other large institutions list 6% (1), 15% (2), 23% (5), 29% (3) and 32% (4) of their cases under the same heading.

Since both puerperal infection and pregnancy toxemia have become unimportant and infrequent in the last decade, the relative gravity of hemorrhage has increased since it remains the one serious obstetric problem in which little progress or change has occurred.

Table VI summarizes our experience with antepartum and postpartum hemorrhage.

TABLE V

Miscellaneous Operations and Conditions

	Private		Ward		Total		Fetal Loss	
	No.	%	No.	%	No.	%	No.	%
Breech Spont.	44	0.3	25	0.3	69	0.3	38	55.1
Breech Extraction	454	3.2	254	3.5	708	3.3	112	15.8
Breech Pipers	110	0.8	68	0.9	178	0.8	13	7.3
Breech At Section	96	0.8	38	0.5	134	0.6	8	6.0
Cleidotomy	1	0.1	1	0.1	2	0.1	2	100.0
Pit. Induction	2093	14.7	186	2.6	2279	10.6	55	2.4
Pit. Stimulation	1536	10.8	496	6.9	2032	9.5	75	3.7
Prolapse of Cord	81	0.6	58	0.8	139	0.6	18	12.9
Version & Extraction (Single Preg.)	7	0.1	6	0.1	13	0.1	4	30.8
Version & Extraction (Multiple Preg.)	22	0.2	17	0.2	39	0.2	6	15.4
Simple Transfusion	264	1.9	416	5.8	680	3.2	—	—
Multiple Transfusion	134	0.9	158	2.2	292	1.4		
Craniotomy	1	0.1	6	0.1	7	0.1	7	100.0

TABLE VI

Deliveries with Hemorrhage

	Private		Ward		Total		Fetal Loss	
	No.	%	No.	%	No.	%	No.	%
Antepartum								
Low Implantation	29	0.2	11	0.2	40	0.2	4	10.0
Placenta Previa	70	0.5	25	0.3	95	0.4	13	13.7
Abruptio	191	1.3	75	1.0	266	1.2	72	27.5
Marginal Sinus	46	0.3	25	0.3	71	0.3	4	5.6
Ruptured Uterus	20	0.2	13	0.2	33	0.1	7	20.6
Total	356	2.5	149	2.1	505	2.4	100	19.8
Postpartum								
Early P.P. Hem.	383	2.7	264	3.7	647	3.1		
Late P.P. Hem.	42	0.3	17	0.2	59	0.3		
Outlet Hematoma	35	0.3	9	0.1	44	0.2		
Total	460	3.3	290	4.1	750	3.5		

The 33 ruptured uteri include the separation of 20 previous cesarean section scars. In 18 this was a relatively benign complication, unsuspected scar dehiscence being found accidently at repeat low cervical cesarean section. All 18 babies survived. In one, the 600 gram infant died neonatally, the repeat cesarean section having been done for a central placenta previa. In the remaining case, rupture was antepartum through the site of two previous classical cesarean sections. The dead baby and placenta were found extruded into the abdominal cavity. All mothers did well.

Thirteen intact uteri which had not been operated for cesarean section ruptured. One was an inexplicable, spontaneous rupture in a secundipara; the others were traumatic. Two cases followed version and extraction, four fundal pressure, four mid-forceps, and two breech extraction, the latter through incompletely dilated cervices. Eight babies and all mothers survived.

The rare occurrence of eclampsia in modern, urban obstetric practice is indicated by a total of nine cases in five years. None of the nine patients was seriously ill, the maximum number of convulsions being three. The almost three-fold greater incidence of toxemia on the ward compared to the private service has been observed in other institutions. At The State University in Brooklyn, which has an all ward service, the total toxemia rate was 7.7% (1). In two other institutions with combined private and ward services the total rate was 6.7% (2) and 8.7% (4), materially higher than our incidence, 4.3%.

It is difficult to compare the perinatal rate of one institution with another. However since we include all fetuses over 400 grams, which is the minimum weight fetus any other hospital considers in their compilations, our rate of 29.4 per 1000 is exceptional. The good results are obviously the result of superior pediatric as well as obstetric care. The rates for sister institutions were 34.4 (6), 35.6 (5) and 38.6 (7) per 1000 respectively.

The preferential rate at The Mount Sinai Hospital for infants of private patients compared to those of ward patients is probably due more to socio-economic factors than to differences of management.

Table IX shows the excellent maternal results in patients suffering from severe medical complications of pregnancy, without doubt an expression of the magnificent cooperation given this department by the other medical dis-

TABLE VII

Toxemias

	Private		Ward		Total		Fetal Loss	
	No.	%	No.	%	No.	%	No.	%
Pre-eclampsia	229	1.6	356	4.9	585	2.7	42	7.2
Eclampsia	7	0.1	2	0.1	9	0.1	0	0
Chr. Hypertension and Toxemia	21	0.1	51	0.7	72	0.3	13	18.1
Chr. Hypertension, no toxemia	124	0.9	131	1.8	255	1.2	18	7.1
Total	381	2.7	540	7.5	921	4.3	73	7.9

TABLE VIII

Total Number of Live Births and Neonatal Deaths

Birth Wt. Grams	Private			Ward			Total		
	Total Live Births	Died	% Deaths	Total Live Births	Died	% Deaths	Total Live Births	Died	% Deaths
400–999	40	38	95.0	32	28	87.5	72	66	91.7
1000–1499	70	37	52.9	46	22	47.8	116	59	50.9
1500–1999	171	19	11.1	130	14	10.8	301	33	11.0
2000–2499	682	20	2.9	455	8	1.8	1137	28	2.5
2500–& Over	13079	46	0.4	6371	37	0.6	19450	83	0.4
Total	14043	160	1.1	7033	109	1.5	21076	269	1.3

Total Number of Stillbirths

Birth Wt. Grams	Private			Ward			Total		
	Total Births	Still-births	% Still-births	Total Births	Still-births	% Still-births	Total Births	Still-births	% Still-births
400–999	105	65	61.9	73	41	56.2	178	106	59.6
1000–1499	103	33	32.0	65	19	29.2	168	52	31.0
1500–1999	198	27	13.6	146	16	11.0	344	43	12.5
2000–2499	705	23	3.3	479	24	5.0	1184	47	4.0
2500–& Over	13136	56	0.4	6429	59	0.9	19565	115	0.6
Total	14247	204	1.4	7192	159	2.2	21439	363	1.7

Total Number of Stillbirths and Neonatal Deaths (Perinatal)

Weight Grams	Private			Ward			Total		
	Total Births	Still-births and Neo-natal Deaths	%	Total Births	Still-births and Neo-natal Deaths	%	Total Births	Still-births and Neo-natal Deaths	%
400–999	105	103	98.1	73	69	44.5	178	172	96.6
1000–1499	103	70	68.0	65	41	63.1	168	111	66.1
1500–1999	198	46	23.2	146	30	20.5	344	76	22.1
2000–2499	705	43	6.1	479	32	6.7	1184	75	6.3
2500–& Over	13136	102	0.8	6429	96	1.5	19565	198	1.0
Total	14247	364	2.6	7192	268	3.7	21439	632	2.9

ciplines of the hospital. There was one death among 203 pregnant women with cardiac disease, no deaths among 391 cases of pulmonary tuberculosis, one death among 150 diabetics and 2 deaths in 31 patients with severe hematologic complications.

Special clinics have been established for the major medical complications of pregnancy: heart disease, pulmonary disease, diabetes, etc., presided over by members of the medical and obstetric departments jointly.

Cardiac patients who could not have survived pregnancy a decade ago have been carried through pregnancy and vaginal delivery with safety. The only cardiac patient lost was an unregistered ward multipara who was admitted in terminal failure and died 36 hours later.

Today with the aid of the specific drugs, patients with active and inactive tuberculosis can almost always be carried through pregnancy without increasing the gravity of their pulmonary condition. As a matter of fact most patients improve remarkably while pregnant if maintained under the proper drug regimen, even when ambulatory.

In diabetics the drastic maternal and fetal mortality of gestation has been greatly reduced through vigilant medical care and premature delivery, the latter to reduce fetal loss. Our policy is to terminate pregnancy 28 days before the calculated delivery date by induction when feasible, otherwise cesarean section. Fetal salvage of 86 per cent in diabetic patients is good, but not as good, we trust, as the next five year report will show.

Table X summarizes our results with diabetes.

TABLE IX

Deliveries with Medical Complications

	Private		Ward		Total		Fetal Loss	
	No.	%	No.	%	No.	%	No.	%
Heart Disease								
No Failure	85	0.6	107	1.5	192	0.9	7	3.6
Failure	6	0.1	5	0.1	11	0.1	1	9.1
Tuberculosis								
Pulmonary, active	3	0.1	32	0.4	35	0.2	1	2.9
Pulmonary, inactive	40	0.3	216	3.0	256	1.2	5	2.0
Non-Pulmonary	1	0.1	13	0.2	14	0.1	3	21.4
Diabetes	62	0.4	88	1.2	150	0.7	24	16.0
Sickle Cell Anemia	0	0	18	0.2	18	0.1	2	11.1
Afibrinogenemia	8	0.1	5	0.1	13	0.1	5	38.5

TABLE X

Analysis of 150 Diabetics

Type of Delivery

A. *Cesarean Sections* (64) *Fetal Loss*—5

Primary (38) 2

Repeat (26) 3

B. *Vaginal Delivery* (86) *Fetal Loss*—19

Perinatal Mortality (24)—16%

A. *Stillbirths*—16

2—Immatures

14—No F. H. on Adm.

B. *Neonatals*—8

2—Prematurity

1—Apnea and anoxia

1—CNS hem. Pit. induction—spont. del.

2—Hyaline membrane disease

2—Congenital Anomalies

In previous publications we discussed the functioning of an Abortion Committee at The Mount Sinai Hospital (8, 9). It is interesting that it was found necessary to terminate pregnancy in only 9 out of 212 cardiac patients, 2 out of 293 cases of pulmonary tuberculosis.

In their classic study on the incidence of cesarean section in New York City, 1954 and 1955, Erhardt and Gold include a table giving the incidence figures for all the voluntary hospitals of the city (7). The 11,352 cesarean operations gives a total incidence rate of 5.7%; 6.3% among private patients of voluntary hospitals and 4.2% for their ward patients. As can be observed by comparing

TABLE XI

Therapeutic Abortions: 112 (0.52%)

	Private	Ward
	81 (0.57%)	31 (0.43%)
Indication		
Familial Dysautonomia (Daughter)	1	0
Psychiatric	26	17
Rubella	26	3
Cardiac	4	5
Osteogenesis Imperfecta (Mother)	0	1
Lobectomy	1	0
Metastatic Melanoma	2	0
Diseased Single Kidney	2	0
Post Conception Therapeutic X-ray	1	0
Severe Tuberculosis	1	0
Chronic Ulcerated Colitis	1	0
Advanced Hodgkins	1	0
Hemophilia (son)	2	0
Radicular disease (Chr. back)	1	0
Ca Cervix	0	1
Severe Ilio-jejunitis	1	0
Chronic Nephritis	0	1
Ca Thyroid	3	0
Chronic Lung Infection	0	1
Thrombosis-Retinal Artery	1	0
Amputation—Both Legs	0	1
Rh-sensitization—severe	1	0
Ca Breast	6	1

TABLE XII

Primary and Repeat Sections (1250)

	Priv.		Ward		Total	
	No.	%	No.	%	No.	%
Primary	458	3.2	171	2.4	629	2.9
Repeat	469	3.3	152	2.1	621	2.9
Total	927	6.5	323	4.5	1250	5.8

TABLE XIII

Cesarean Sections

	Private		Ward		Fetal Loss	
1. *Type of Operation*						
Low cervical	790		220		38	
Classical	29		9		4	
Classical and Tubal sterilization	11		14		1	
Low cervical and Tubal sterilization	83		66		3	
Cesarean Hysterectomy	14		13		4	
Extraperitoneal	0		1		1	
Total (1250) (5.8%)	927	(6.5%)	323	(4.5%)	50	(4.0%)
2. *Indications*						
A. *Contracted Pelvis and Mechanical Dystocia*	189		101		2	
B. *Previous Operations on Uterus*						
1. Previous section	467		144		16	
2. Previous myomectomy	34		3		1	
3. Previous abdominal hysterotomy	5		0		0	
4. Previous repaired ruptured uterus	1		1		1	
5. Previous fundectomy	1		0		0	
6. Previous plastic for double uterus	1		0		0	
Previous Operations on Cervix and Vagina						
1. Previous Vaginal Plastic	14		5		0	
2. Previous cervical operation	2		0		0	
3. Previous recto-vaginal surgery	1		0		0	
C. *Hemorrhagic Complications*						
1. Prem. Sep. Placenta	41		8		13	
2. Previa	47		17		6	
3. Marginal Sinus Rupt	1		0		0	
4. Low Implantation—Placenta	2		1		0	
D. *Toxemias*						
1. Eclampsia	1		0		0	
2. Pre-eclampsia	9		1		0	
3. Chronic Hypertensive Disease	0		2		0	
E. *Intercurrent Disease*						
1. Diabetes (Primary section only)	25		13		2	
2. Ca Thyroid and Fibroids	1		0		0	
3. Permanent Iliostomy	1		0		0	
4. Gastrectomy, malnutrition, cardiac failure	1		0		1	
5. Residual cerebral palsy	1		0		0	
F. *Miscellaneous*						
1. Fetal Distress	36		13		4	
2. Elderly primip. plus other factors	24		1		1	
3. Prolapsed Cord	12		8		2	
4. Prev. Subarachnoid Hem.	3		0		0	
5. Bad Obs. History	7		1		0	
6. Teaching (Section-Hysterectomy for sterilization	0		2		0	
7. Rupt. uterine vessels during appendectomy	0		1		1	
8. Ca. Cervix in Situ	0		1		0	

TABLE XIV

Summary of Cesarean Section Fetal Loss (50—4.0%)

	Number
A. Immatures (500–999 grams)	5
B. Congenital Abnormalities (over 1000 grams)	8
C. No Fetal Heart on Admission to Hospital (over 1000 grams)	6
1. Diabetics: (Twin B); (3 previous sections for diabetes)	2
2. Premature separation of placenta	2
3. Afibrinogenemia—previous myomectomy	1
4. Twin B	1
D. Diseases of the Newborn	15
1. Hemolytic disease	1
2. Hyaline membrane disease	5
3. Atelactasis or asphyxia	5
4. Prematurity only	1
5. CNS. hemorrhage—long labor	1
6. Septicemia	1
7. ABO—incompatability	1
E. Anoxia	16
1. Fetal Distress—cause unknown	1
2. Placenta Previa (includes prematurity)	5
3. Premature separation of placenta	6
4. Post mature (questionable F.H. before section)	1
5. Ruptured uterus through 2 previous classical scars	1
6. Diabetic (mother)	1
7. Prolapsed cord (Twin A)	1

these figures with Table XII, the incidence at The Mount Sinai Hospital closely approximates the community figure for voluntary hospitals.

Table XIII summarizes the type of cesarean sections done and the indications for each operation.

Table XIV shows the cause of death in 45 infants weighing over 1000 grams who were either stillborn (15) at the time of cesarean section or who died neonatally following the procedure (30). As may be observed cesarean section issues no guarantee that a baby will survive its delivery.

One woman among the 1250 delivered by cesarean section died. This patient succumbed suddenly, 31 hours postoperatively of a massive saddle embolus. Our very low mortality, 8 per 10,000 is considerably less than reported by Erhardt and Gold for all of New York, 22 per 10,000 (7). We trust the difference is not due to sampling, after adding together the figures for four such five year reports this answer will be known.

Vaginal delivery after previous cesarean section was permitted to 8.3% of the patients; 5.1% were private and 17.2% ward patients.

STERILIZATION

Cognizant of the almost insuperable socioeconomic burden excessive fecundity places upon poor families living in a great metropolis, we determined

to offer puerperal sterilization to those clinic patients desiring it who were being delivered of at least a sixth living child, regardless of the mother's age. As it was felt that older women were more mature and less likely to act impulsively in respect to sterilization, we permit mothers 30 to 35 years old to be sterilized with their fifth living child, and those over 35 with the fourth.

Soon after these rules were put in force for the clinic population, the staff requested that the private patient should not be discriminated against and asked that the same rules be applied to all, regardless of socio-economic status. The logic of the request made its acceptance automatic.

Even the short period of five years covered by this statistical report shows a shift in obstetrical thinking. In 1953, the majority of the patients were sterilized at the completion of the second cesarean section; today we rarely sterilize the woman at the first repeat cesarean section unless the operation gives the couple a third living child. It has been proved by recent studies that the precise number of previous cesarean operations has little or no relationship to the safety of either another pregnancy or another cesarean delivery (10). The only

TABLE XV

Sterilizations: 796 (3.76%)

	Private		Ward	
Operation				
Tubal, puerperium	56		506	
Cesarean—Tubal Ligation	93		71	
Cesarean Hysterectomy	4		12	
Hysterectomy, puerperal, elective	0		54	
	153	(1.08%)	643	(9.08%)
Indications				
Bad Obs. History (Abnormal Children)	2		2	
Chronic Nephritis	1		1	
Acute Asthma	1		1	
Obstructing Pelvic tumor	1		0	
Previous Section	86		62	
Multiparity	36		544	
Prev. Vaginal Plastic	6		0	
Brain Tumor	0		1	
Psychiatric	2		8	
Heart Disease	5		6	
RH-sensitization	1		0	
Chronic Hypertension	3		5	
Collagen Disease	0		1	
Mental Retardation	0		1	
Prev. Nephrectomy	1		0	
Severe Varicosities	5		3	
Diabetes	1		5	
Third Degree Uterine Prolapse	1		0	
Obstructive Jaundice	0		1	
Epilepsy	1		1	
Hodgkins	0		1	

patients in our opinion who truly qualify for sterilization on the pure grounds of the repeat operation are those few who live in fear and dread of another delivery by laparotomy.

The 54 elective puerperal hysterectomies shown in Table XV on the ward service following a vaginal delivery were done in large measure to provide the resident staff with ready experience in this major obstetric procedure. However some experienced obstetricians prefer this method of sterilization routinely since it is almost fool proof as far as reimpregnation is concerned, and surgically eliminates a useless organ which may become the site of potential pathology.

As far as known there were no immediate or remote deaths associated with a sterilization procedure and no pregnancies have been reported to date.

MATERNAL MORTALITY

In the course of 21,169 pregnancies and deliveries, 7 women died of maternal causes, giving a rate of 3.3 per 10,000. In the same five year period, no patient died on either the obstetrical or gynecological service of this hospital from an ectopic pregnancy or septic abortion. In addition to the 7 maternal deaths there was one adult death. The death appeared to have no causal relationship with the pregnant or delivered state. This private patient had a normal delivery at the Hospital and suddenly died at home two weeks postpartum. Post mortem by the medical examiner showed death from a congenital cerebral aneurysm.

As in most reports of this type, there was a preferential mortality on the private service compared to the ward. The rate on the private service was 2.1 per 10,000 and on the ward service, 5.6 per 10,000. The national rate for the whole country fluctuates between 4 and 5 per 10,000. In New York City for 1954–1955, the rate was 5.0 per 10,000 (7).

An abstract of the 7 maternal deaths follows:

1. The patient, an 18 year old clinic Puerto Rican, primigravida was due 2/27/54. There were 5 prenatal clinic visits, the first on 11/12/53. Past history was negative. Urine negative for sugar and albumin on several occasions. The significance of one urine positive for glucose was overlooked. Admitted on 1/7/54 because of vomiting, blurring of vision, and no fetal movements for 24 hours.

The total weight gain was 10 pounds. She showed 1 plus edema, no F.H., B.P. 150/90, vertex engaged, 34–35 weeks pregnant. Diagnosis, pre-eclampsia, not in labor, possible premature separation of the placenta and intrauterine death. She was treated for toxemia and delivered a macerated 3130 gm spontaneously after 4½ hours of labor. A catherized urine at time of delivery showed a trace of albumin and a 3 plus sugar (I.V. pitocin in glucose for induction) and no acetone. It was erroneously interpreted by the house staff that the positive urinary sugar resulted from the I.V. glucose solution. Her blood pressure was normal on the second postpartum day and discharged to the Postpartum clinic on 1/24/54 in good condition.

That same evening 1/24/54, she was seen in the emergency ward because of inability to sleep, hallucinations, palpitation, and retching. A diagnosis of anxiety reaction was made by a member of the medical house-staff and the patient sent home. She returned later in the evening with the same complaints. She was examined again by the admitting physician and the psychiatric resident, whose diagnosis was acute psychosis. She was advised hospitali-

TABLE XVI

Analysis of Perinatal Deaths (632)

	Stillbirths	Neonatal	Total
Immatures	107	65	172
Malformations	25	33	58
Deaths before Admission (No F.H.)	163	0	163
Diseases of Newborn	0	64	64
Prematurity & Prematurity with Disease	22	65	87
Other causes—Anoxia, Trauma, etc.	46	42	88
Total	363	269	632

Immatures (172) (400–999 gms)
107 still births: No F.H. (82); Intrapartum (25)
65 Neonatals
Malformations (60) (1000 gms. and over)
27—Still births
33—Neonatals
Deaths Before Admission (161) (1000 gms. and over)
13—Rh. neg. mothers—sensitized
20—Prem. Sep. Plac. (1 with Afibrinogenemia)
8—Severe toxemias
7—Tight cord around neck
14—Diabetics
2—ABO—Incompatibility
1—Rupt. Uterus (Prev. Classical Scar)
2—Prolapsed cord
1—Drug Addiction
93—Cause unknown
Diseases of Newborn (64) (1000 gms. and over)
20—Atalectasis and asphyxia
2—Pneumothorax
1—Anoxia (Diabetic Mother)
1—ABO—Incompatibility
13—Hemolytic Disease
4—Cardiac
1—High temp. before death—cause unknown
8—Hyaline membrane disease
5—Pneumonias
4—Intestinal malformations—operated
1—Septicemia
1—Diarrhea—severe
2—Hemorrhagic Disease
Prematurity and Prematurity with Complications (87) (1000 gms. and over)
22—*Intrapartum*
9—Prematurity
8—Prematurity with Prem. Sep. Placenta (7) or Previa (1)
1—Prematurity with Congested Lungs
3—Prematurity with Pre-eclampsia
1—Prematurity with Prolapsed cord
65—*Neonatal*
32—Prematurity
16—Prematurity with Prem. Sep. (14) or Previa (2)

TABLE XVI—*Continued*

2—Prematurity with Diabetes
11—Prematurity with Atalectasis
1—Prematurity with Endometritis
1—Prematurity with Pre-eclampsia
1—Prematurity with Pneumonia
1—Prematurity with Subarachnoid Hem.

Other Causes—Anoxia, Traumatic, etc. (88) (1000 gms. and over)

47—*Intrapartum*

A. *Anoxia*—Previa and Prem. Sep. Placenta (4)
—Cord around Neck (9)
—Prolapsed Cord (6)
—Rupt. Uterus (1)
—Fetal Distress (7)
—Pit. Induction—Unattended (1)

B. *Traumatic*—Br. Extractions (8) with rupt. uterus—1
—Craniotomy (2) Br.—1, mistaken Hydrocephalus—1
—Mid Forceps (3) CNS—Hem.—2, Asphyxia—1
—Shoulder Dystocia (All vertex) (4)

C. Amnionitis (1)

D. Cause Unknown (1) Spont. Del.

41—*Neonatal*

A. *Anoxia*—Previa and Prem. Sep. Placenta (5)
—Fetal Distress (7)
—Br. Extraction (2)

B. *Traumatic*

Forceps (9), CNS hem.—7, pneumothorax—1, cause unknown—1
Breeches (10) CNS hem.—8, pneumothorax—2
Pit. Induction (2) Diabetic spont. CNS hem.—1, Rising antibodies, spont. CNS hem.—1

C. *Cause Unknown* (6) Spont.—4, Low Forceps—2

zation on the Bellevue Psychiatric Division but the patient's husband objected and signed the patient out.

The next information was that the patient died at home the following day. Autopsy done at Bellevue Hospital attributed death to diabetic acidosis. Death preventable.

2. A private 35 year old white para 0010, who had had a myomectomy in 1953. Physical examination was normal. Pelvimetry done 2 weeks before term showed slight pelvic contraction. Admitted 16 days past expected date, with a normal blood pressure, an unengaged vertex, and a long closed cervix. The following morning 1/25/55, under spinal anesthesia, a low flap cesarean section resulted in a 2890 grams living child. Postoperative course uneventful until 9 A.M., 1/27/55, when the floor nurse heard a moaning and groaning sound in the patient's room. The patient was found on the floor, near her bed, cyanotic and moribund. Autopsy revealed, fresh clots in the lower, left calf veins and a saddle pulmonary embolus. Nonpreventable.

3. A 38 year old private para 2002, with a negative past history and two previous normal deliveries. Admitted on 9/27/55, at term, membranes ruptured. Induced by I.V. pitocin drip; four hours later when 8 cm. dilated developed moderate watery vaginal bleeding which did not clot. A sample of venous arm blood did not clot, although blood which had been drawn on admission clotted well and the clot persisted. Twenty minutes later the patient delivered a 3850 grams stillborn. There was profuse bleeding. The blood did not clot and the patient went into profound shock. Had a terminal premature separation of the placenta with afibrinogenemia. In the space of 4 hours she received 11 units of blood and 8 grams of fibrinogen. For several days she failed to rally from her profound shock despite

constant, heroic therapy. Her urinary output was 30-50 cc. every 3 to 4 hours. On 9/29/55, the third postpartum day, the total 24 hour output was 420 cc. The fibrinogen level before delivery was 144 mgm percent. After the transfusions and fibrinogen it rose to 244 mgm. percent. The Hgb was 12.2 grams and the blood platelets were 113,000.

On 9/30/55 the patient appeared alert, the urinary output was 1150 cc. in 12 hours. She appeared improved. On 10/2/55 she showed marked improvement and her output was 2500 cc. On 10/4/55 her fibrinogen level was 197 mgm. %; the clotting time was 10 minutes; the clot still friable. The prothrombin time was 17 seconds and her urinary output decreased. On 10/5/55, 8 days after delivery the patient had a mild convulsion and died 10 minutes later. Autopsy revealed a thrombophlebitis of the right lower extremity with pulmonary embolism secondary to severe shock from hemorrhage and afibrinogenemia. She had fresh vegetations on the heart valves and an extensive necrosis of the anterior pituitary (Sheehan's syndrome). Death nonpreventable.

4. The patient was a private 29 year old para 0000, with a normal past history and a normal prenatal course. She was admitted at term at 5 A.M., 4/22/56 in early labor. At 10:20 A.M. after 8 hours of labor she was delivered by low forceps of a 3450 grams living infant over a right mediolateral episiotomy. The second stage was 50 minutes, placenta delivered spontaneously. There was a sudden gush of about 1000 cc. of blood. Inspection of the vagina revealed an episiotomy extension up to the right lateral fornix, but no definite bleeding site. The apex of the extension was sutured. The active bleeding subsided and complete visualization of the cervix and manual intrauterine exploration failed to reveal tears. The uterus remained contracted and firm following the delivery of the placenta. The episiotomy and its extension were repaired, the vagina was packed. The patient began to hemorrhage again and went into shock. The shock persisted despite multiple transfusions. The uterus became boggy and there was bleeding through the vaginal packing, which was removed. With blood running, a subtotal hysterectomy performed. The patient died about 4 hours after delivery. Death was attributed to postpartum hemorrhage. Death deemed preventable, as all postpartum hemorrhage deaths should be considered. Transfusion may have been initiated too late.

5. The patient was a 32 year old, clinic, negress, para 3003. Her past obstetrical history and prenatal clinic visits were normal. She was admitted at term in spontaneous early labor. She received demerol and scopolamine sedation and was taken to delivery room after a first stage of 5 hours. Meconium stained fluid obtained on rupturing the membranes. Low forceps done and a 3370 grams living child delivered. Placenta delivered during the episiotomy repair. The blood was dark and the color did not improve with oxygen. At this point there was no noticeable pulse or blood pressure. Intravenous levophed was started with no effect on the blood pressure. ECG revealed a ventricular tachycardia of 300. The clinical impression was massive amniotic fluid embolism. There had been no bleeding. The cardiac rhythm returned to normal following the intravenous administration of one minim of epinephrine and the blood pressure was obtainable at 120/80. But vaginal bleeding supervened at this point and the blood tested showed no tendency to clot. In the next 30 minutes 6 grams of fibrinogen and 4 units of whole blood were administered under pressure. Two hours after delivery, ventricular fibrillation occurred, then cardiac standstill. Autopsy confirmed the clinical impression of amniotic fluid embolism. Non-preventable death.

6. The patient a 36 year old, unregistered negress, para 5-1-3-6, was admitted at 33 weeks gestation. Her past obstetrical history was normal except for hypertension since her third pregnancy in 1945. After several of her previous deliveries sterilization had been advised at Harlem Hospital which the patient refused. During the current pregnancy she first attended the Harlem Hospital prenatal clinic at 30 weeks gestation. They found her to be hypertensive with clinical signs of congestive heart failure. She consulted a private physician who treated her with a low salt diet, mercurials and digitoxin. After one week of treatment without response, she finally consented to hospitalization and was admitted to this service.

The admission physical revealed dyspnea at rest, B.P. 230/110, grade three hypertensive

retinopathy, enlarged heart, systolic and diastolic murmurs, clear lungs and enlarged liver. Laboratory studies were normal. Chest x-ray revealed marked increase in the cardiac diameter. The ECG showed evidence of digitalis toxicity. Treatment consisted of diet, sedation and mercurials. The diagnosis by the medical consultants was pregnancy 35 weeks, hypertensive cardiovascular disease, probable old rheumatic heart disease with mitral stenosis and insufficiency and congestive heart failure.

A rapid spontaneous delivery occurred in bed after 44 hours of hospitalization, before any real response of therapy. Acute pulmonary edema developed during the first stage of labor. Despite vigorous treatment, she became comatose and went into vasomotor collapse and died 3½ hours after delivery. Death was due to congestive heart failure. Autopsy confirmed clinical impression. Preventable death. Patient's responsibility for not seeking earlier hospital care.

7. The patient was a 28 year old clinic negress, para 6-1-0-6 with known sickle cell disease. Her prenatal course was normal. The anemia was followed in the special hematologic-obstetric clinic. Last visit 8/9/57, 29 weeks gestation. She had no complaints. She was to return in 3 days for repeated laboratory work and possible transfusion, but failed to keep the appointment. In follow-up by phone we discovered that the day after her clinic visit she complained of severe headache, but had seen no doctor. The following morning headache worse. When her husband returned home, he found the patient dead in bed. The coroner's impression was sickle-cell disease of pregnancy. We did not learn of these events until 3 days after the patient died. Since the coroner was satisfied homicide was not involved, autopsy was not done. We therefore have little information and can only assume that death resulted either from a ruptured intracranial aneurysm or cerebral thrombosis with a silent sickling crisis. Preventability of death difficult to evaluate.

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EFFECTS OF CHLORPROMAZINE* ON NORMAL MONKEYS AND MONKEYS WITH LESIONS IN THE BRAIN STEM†

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INTRODUCTION

Chlorpromazine in both our laboratory and clinic has been observed to alter signs and symptoms of diseases of the nervous system. This action is reminiscent of the effect of amobarbital on disorders of the nervous system, as demonstrated in previous communications from this department (1–4). We have observed, for example, that amobarbital will stop the pathological spontaneous nystagmus of forward gaze. It may also make a hemiparesis more apparent, or, in disease of the nervous system, induce a motor deficit which was not noticeable before the amobarbital was injected.

These results illustrate the principle that a change in the background physiological activity of the nervous system induced by drugs may change the pattern of a physiological response. With this principle in mind, a study of the effects of chlorpromazine was carried out on two series of monkeys. One group was neurologically normal. The second had brain stem lesions which were made by Drs. Teng, Shanzer and Bender and described in their studies (5, 6) on oculomotor deficits caused by lesions in the brain stem.

MATERIALS AND METHODS

The effect of a single dose of chlorpromazine (5 mgm./kgm., I.M.) was studied in seventeen neurologically normal, young Macaca mulatta monkeys before and after placement of an electrolytic lesion in the brain stem. Seven additional monkeys were studied only after a brain stem lesion was made. In both groups, chlorpromazine was administered in each case at least two days post-operatively. In addition the effects of larger doses of chlorpromazine (10–15 mgm./kgm., intramuscularly repeated twice a day for two to three days) were studied in three monkeys. Two of the latter group were normal and unoperated, while the third had a brain stem lesion. To compare the effects of chlorpromazine and barbiturates, five of the monkeys with lesions were also examined following administration of amobarbital (20–30 mgm./kgm., intravenously).

The electrolytic lesions were made with the aid of a stereotaxic instrument. Most of the lesions were in the paramedian zone between the pretectal area and

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the level of the sixth nerve nucleus. A few lesions were made 6–9 mm. from the midline. The location and size of these lesions have been histologically verified to date in nine animals. These lesions were in the medial parts of the reticular formation of the brain stem. The details of the technique employed for making the lesions, their post-operative effects on eye movements and the anatomical studies of these lesions have been described (5, 6).

The monkeys were evaluated neurologically before and after operation and before and after administration of the drugs. General behavior, hopping and placing reactions, motor power, tonus, coordination, deep tendon reflexes and eye movements were examined. The latter were evaluated by observing spontaneous activity, ability to follow a target, and the nystagmus produced by rotary and caloric vestibular stimulation. The nystagmus was also studied by recording the corneoretinal potential with the aid of an electroencephalograph.

The EEG was repeatedly recorded before and after administration of chlorpromazine in the three monkeys given the larger, multiple doses described above. Eight intradermal leads were placed symmetrically over the occipital, parietal, temporal, and frontal regions. Recordings were made between each electrode and a vertex electrode in a manner standard for this laboratory. During the recording the animal was relaxed in a restraining chair.

RESULTS

The results may be best described under five headings: (a) generalized effects on behavior; (b) effects upon animals with electrolytic brain stem lesions; (c) effect of prolonged administration of larger doses of chlorpromazine; (d) changes in the EEG; and (e) comparison between effects of chlorpromazine and amobarbital.

Effects on behavior

All monkeys pre- and post-operatively were normally aggressive and frequently attacked when the observer approached the cage. They could not be handled without gloves or restraints. After the injection of a single dose of chlorpromazine (5 mgm./kgm., intramuscularly) changes in behavior were observed in all twenty four monkeys studied. The effect appeared within one-half hour and lasted six to eight hours. At the height of intoxication, the previously active and alert animals appeared somnolent, did not attack when approached, and could be caught and handled without resistance. They did not attempt to escape when unrestrained outside their cages. Each exhibited a marked decrease in spontaneous motor activity and in responsiveness to all external stimuli. They often remained in one position for prolonged periods and could be put into strange postures which were maintained. This was reminiscent of the waxy flexibility of catatonia.

Effects of Chlorpromazine on animals with brain stem lesions

These results are discussed in relation to three groups as follows:

A. This group contained three monkeys with permanent post-operative

neurologic defects. In two, the eyes were fixed in right conjugate deviation. All attempts, including caloric and rotary vestibular stimulation, to make the eyes move towards the left or to cross to the left of the midline failed. After injection of chlorpromazine, however, the right eye could be driven to the left of the midline by both rotary and caloric stimulation, while the left eye moved only to the midline (figure 1). (The last observation indicated the existence of a left sixth nerve palsy in addition to the defect in left conjugate gaze with which we were concerned.) The third monkey of this group developed a post-operative paresis of upward gaze and bilateral upper-lid retraction. Chlorpromazine completely abolished the lid retraction for as long as the drug was effective. The paresis of upward gaze was unaffected.

B. This group consisted of four monkeys which had transient post-operative neurologic deficits. The first monkey developed a paresis of left lateral gaze which lasted for six days. After this defect subsided, administration of chlorpromazine was followed by reappearance of the gaze paresis which now persisted only as long as the drug was effective. The second monkey, immediately after the brain stem lesion was made, presented a partial left third nerve palsy, manifested by ptosis and pupillary dilation. After 8 days, the ptosis disappeared almost completely but the pupillary dilation remained. Chlorpromazine given at this time was followed by a complete reappearance of ptosis (figure 2). Postoperatively, the third animal developed a persistent, moderate weakness of the right lower extremity with increased deep tendon reflexes. A motor deficit could not be detected in the right upper extremity. After injection of chlorpromazine and only during the period of its effectiveness, a marked flaccid paralysis of the right upper extremity appeared. Concomitantly, the weakness of the right lower extremity increased. The fourth monkey in this group developed, post-operatively, ataxia and intention tremor of the left extremities; the upper was more affected than the lower. After the operation there was a gradual, steady improve-

FIG. 1. The effects of chlorpromazine on the eye movements of a monkey with permanent paresis of gaze due to a lesion at the level of the sixth nerve nucleus.

A. The postoperative permanent position of the eyes in right conjugate deviation.

B. The maximum effect of cold caloric stimulation of the left ear. Note that the eyes are still in right conjugate deviation although the right eye is closer to the midline.

C. Spontaneous position of the eyes one half hour after the administration of chlorpromazine (5 mgm./kgm., I.M.). Note that the right eye is closer to the midline than in A.

D. The maximum effect of cold caloric stimulation of the left ear one-half hour after chlorpromazine administered as in C. The right eye is adducted to the left considerably beyond the midline. The left eye which has a sixth nerve palsy is at the midline.

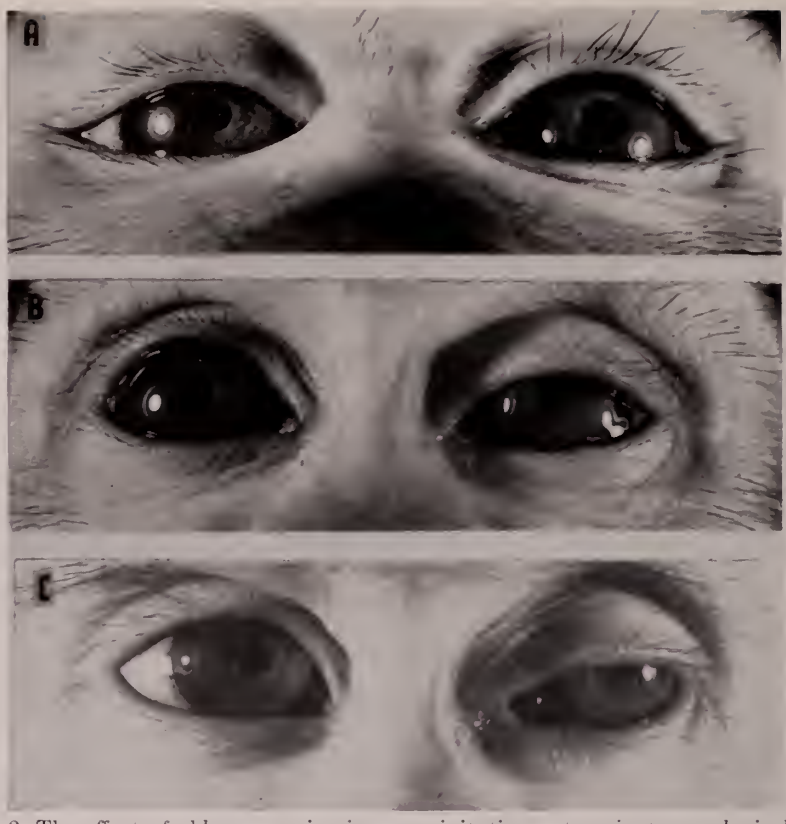

FIG. 2. The effect of chlorpromazine in reprecipitating a transient neurological defect which persisted for 8 days following a lesion in the paramedian zone of the brain stem. The defect was a partial left 3rd. nerve palsy, manifested by ptosis and pupillary dilation.

A. The usual appearance of the eyelids after the neurologic defect has disappeared. Note that although the ptosis is not evident, the left pupil remains enlarged.

B. A partial ptosis has appeared 15 minutes following the administration of chlorpromazine (5 mgm./kgm., I.M.).

C. The ptosis is more marked one half hour following the chlorpromazine administration.

ment. During this stage chlorpromazine transiently aggravated these defects which became more marked than even immediately after the operation; the animal could not use the left upper extremity, and the ataxia and intention tremor became grossly apparent in the left lower extremity.

C. This group contained seventeen animals in which brain stem lesions did not produce neurologic deficits. The only effect of chlorpromazine was that described above as behavioral.

Effects of repeated administration of larger doses of chlorpromazine

When administered in larger doses (10–15 mgm./kgm., twice a day) over a period of several days, chlorpromazine produced a picture characterized by fine tremor and rigidity. Two of the three monkeys studied were normal unoperated animals. The third was the monkey which had the ataxia and tremor already described (see B above). After the second day on such a regimen, all three ani-

mals developed marked rigidity manifested by slowness of spontaneous movements and increased resistance to passive stretch. There was also a fine resting tremor characterized by small amplitude, six to eight per second, and to and fro movements most marked in the digits of all four extremities. The animals remained in this condition for two to three days after the administration of the drug stopped. Recovery was gradual and complete. While these effects were present the animals were far more alert than following the single smaller dose as described above.

Changes in EEG

The EEG was recorded before and after the administration of chlorpormazine to the three monkeys just described (see above). During the stage of intoxication, the following changes in the EEG were noted. There was a reduction in all leads in the percentage of low voltage, 8–12 per second activity characteristic of the normal monkey record. In two monkeys bursts of high voltage slow activity dominated the record especially in the frontal leads. In the third animal (the monkey, described in B, which manifested ataxia and intention tremor following a brain stem lesion) bursts of spike and wave activity were a prominent feature. These EEG changes became increasingly evident as the symptoms of intoxication became more marked and decreased concomitantly with the progressive return to the normal state. Figure 3 illustrates the development of the slow activity and the spike and wave pattern in the third monkey. Although the tremor was as marked in the other two monkeys, no evidence of spike and wave was ever noticed in their EEGs.

Comparison between the effects of chlorpromazine and barbiturates

In five of the monkeys which had either transient or permanent defects following lesions of the brain stem, amobarbital (20–30 mgm./kgm., intravenously) produced marked drowsiness and changed the neurologic signs just as did chlorpromazine. Amobarbital, like chlorpromazine, did not produce signs in those animals which were not affected by operation (Group C). However, here the similarity ended. In the doses used, amobarbital produced drowsiness or sleep without the behavioral changes induced by chlorpromazine. To compare the effects of prolonged administration of barbiturate to similar administration of chlorpromazine, amobarbital (20 mgm./kgm, intramuscularly) was given every 3 hours for 12 hours on each of 3 consecutive days. This regimen was used on two normal, unoperated animals. Slight drowsiness was the only observed effect.

DISCUSSION

The site and mode of action of chlorpromazine has been the subject of many recent investigations. These studies indicate that this drug acts as a central nervous system depressant. Whether the effects of chlorpromazine can be attributed to its depressant action at one or a few discrete sites in the central nervous system or to a more general action on this entire structure is a moot point. There is evidence to support both concepts.

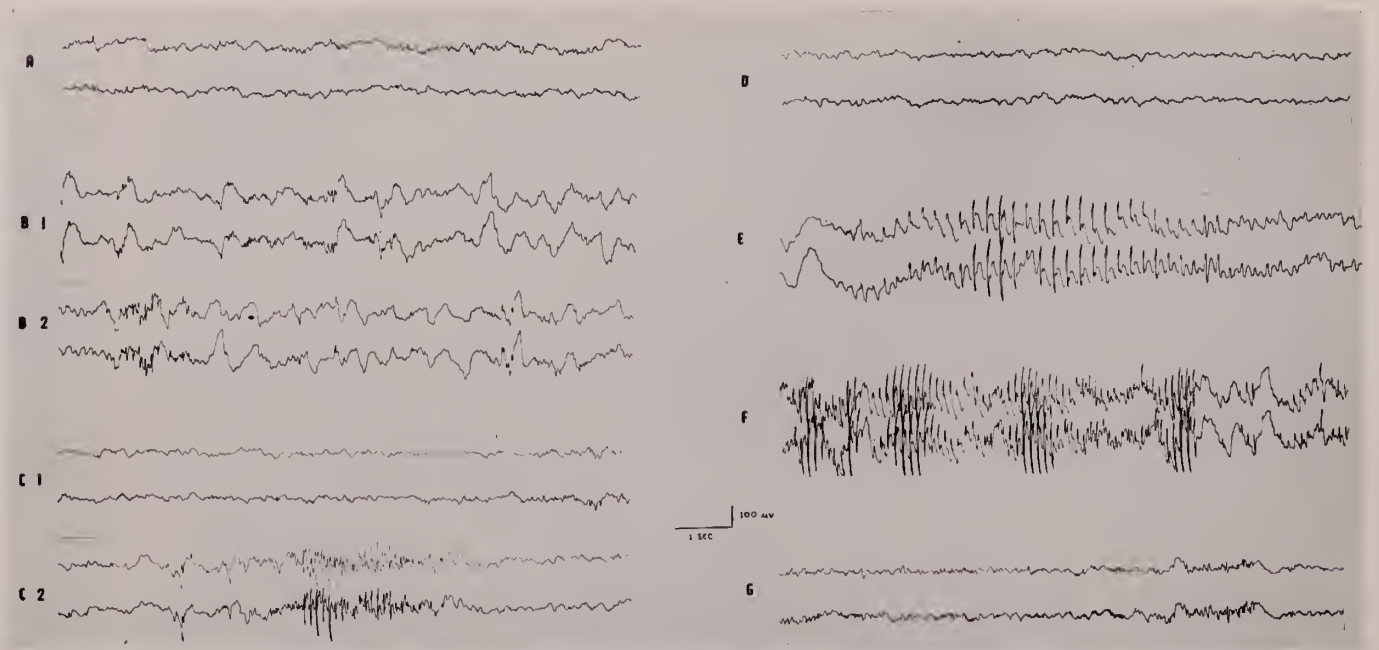

FIG. 3. Changes in EEG patterns during the course of prolonged administration of chlorpromazine (schedule described in text). The upper trace, left occipital to vertex; lower trace right frontal to vertex.

A. Before chlorpromazine administration.

B1, B2. One hour after the administration of 12.5 mgm./kgm. of chlorpromazine I.M. Slow activity is marked.

C1, C2. Four and one half hours after the administration of chlorpromazine. The high voltage slow activity is almost gone. The spiking activity is more marked, comes in bursts and has the appearance of spike and wave activity.

D. Twenty-four hours after the initial dose of chlorpromazine the record appears normal.

E. Three hours after a second dose of chlorpromazine (12.5 mgm./kgm., I.M.) which was administered shortly after the record shown in D was taken. Spike and wave activity is clear.

F. Twenty-four hours after E, and one hour after a third dose of chlorpromazine (12.5 mgm./kgm., I.M.). The spike and wave activity is more marked and appears in more frequent bursts.

G. Twenty-five hours after the final dose of chlorpromazine. The record has not quite returned to that seen in A. It shows somewhat more fast activity and suggestive bursts of sharp waves. The exact time of return to normal was not observed.

That the drug may affect many portions of the nervous system has been shown by various studies. The following are noted as examples. Chlorpromazine's suppression of vomiting has been interpreted as evidence of a selective activity on the medulla (7). Chlorpromazine diminishes the EEG arousal response to electric stimulation of the brain stem reticular formation (8). This drug affects the hypothalamic-pituitary system and may thereby mediate its known endocrine action (9). It also decreases the motor effects of electrical stimulation of the feline cerebrum (10), and has a specific cortical effect in species from the frog to monkey (11).

That the drug mediates its effects primarily by its action on specific structures of the nervous system has been suggested by various studies. For example, there are studies which have singled out the amygdala (12), the brain stem reticular formation (10, 13) and basal ganglia (14–16) as "the site" of chlorpromazine's action.

The reprecipitation of neurologic signs and the appearance of latent defects as described in the present study may be interpreted as concomitants of the depressant action of chlorpromazine which may, we believe, affect any site in the central nervous system. Its similarity in action in this regard to the barbiturates helps to strengthen this interpretation. The neurologic changes may be produced by these drugs in the following manner. If it is postulated that the recovered but partially damaged neural mechanisms function with a lower margin of safety than intact mechanisms, then the former might be more readily and obviously affected by this depressant action. The general depressant action of chlorpromazine may also account for our observations on animals with permanent neurologic deficits, if it is postulated that the damaged part was still capable of functioning and that the observed behavior, therefore, was the resultant of reciprocal activity of both intact and damaged parts. The degree of these deficits suggests structural damage of the appropriate neural mechanism so that it could only be affected minimally by chlorpromazine. The intact mechanisms, however, could be depressed in the expected manner and functions related to their apparent overaction might be minimized. The elimination of this presumed overaction may account for some of the symptomatic improvement observed with chlorpromazine.

That such an explanation involving reciprocal activity of damaged neural structures along with their intact counterparts is feasible, may be inferred from a different type of experiment, pertaining to the result of electrical stimulation of the cortex of monkeys with neurological deficits. Figure 4 shows the effects of cortical stimulation of a cervically transected alert monkey. This animal had a permanent paralysis of gaze to the left, the result of an electrolytic brain stem lesion. Electrical stimulation of the right frontal cortex drove the eyes into their paretic fields, an effect quite similar to that obtained in stimulating the frontal cortex of a "normal" monkey. A possible explanation might be the normal inhibition of the intact pathways accompanied by maximal excitation of the impaired pathways. The result would be to overcome the presumed relative overaction of the intact structures.

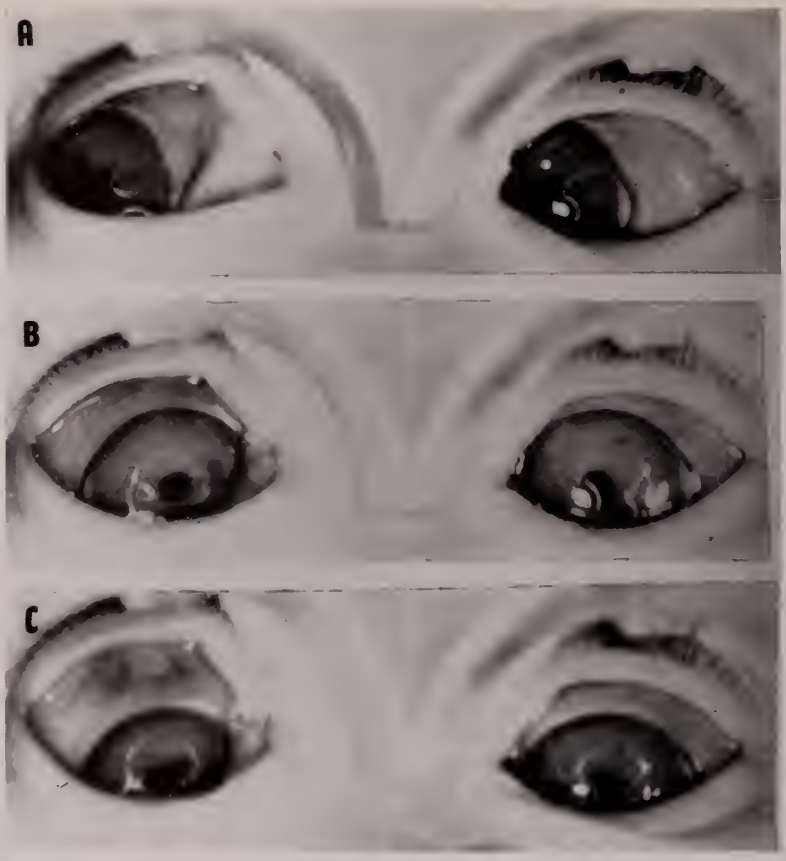

FIG. 4. The effect of electrical stimulation of the frontal cortex of a monkey which had a permanent paresis of gaze following a brain stem lesion. This is the same monkey shown in figure 1. At the time of electrical stimulation it was cervically transected, mounted in a stereotaxic instrument, and responded to visual stimuli. The eye movements were in all respects similar to those prior to transection.

A. The position of permanent right conjugate gaze, the result of the brain stem lesion.

B. Electrical stimulation of the right frontal cortex drives the eyes toward the left. The right eye passed the midline while the left eye, which manifested a sixth nerve palsy, did not move to the midline.

C. With stronger electrical stimulation the right eye moves further to the left and somewhat downward, while the left eye moves to the midline.

It is possible that eye movement into the paretic fields during chlorpromazine intoxication, as well as other actions of chlorpromazine on damaged neural structures, be an example of "sensitization by denervation". That is, the drug may bring about overactivity of the abnormally sensitive damaged pathways and lead to an apparent restoration of normal function.

Our other observations indicate that chlorpromazine may have a selective dedepressant action superimposed upon its generalized depressant effects. These observations include behavioral changes, the production of sustained tremor and rigidity, the appearance of the spike-wave activity in the EEG. The differences between the action of this drug and the barbiturates, on behavior and EEG activity, further suggest this. The relationship, if any, between the spike-wave

patterns following chlorpromazine in one animal and the upper brain stem lesion in this animal may be of significance. However, we do not have enough data to speculate on this point at present. The other EEG observations we have made do not require comment since they do not add to the existent knowledge (see, for example, Dasgupta and Werner (10), Mayr and Leihner (17), Merlis (18), Mauceri and Strauss (19), Bradley and Hance (13)).

SUMMARY

1. The effects of chlorpromazine in normal monkeys and in monkeys with electrolytic brain stem lesions were studied.

2. Chlorpromazine in small doses caused decreased motor activity, decreased responsiveness to all stimuli and a picture suggesting catatonia.

3. Signs of permanent neurological defects following brain stem lesions were rendered less apparent by chlorpromazine.

4. Signs of neurological deficit which subsided following brain stem lesions were transiently reprecipitated by chlorpromazine.

5. Chlorpromazine administered over several days caused tremor, rigidity and EEG changes which included in one animal a spike and wave pattern.

6. The effects of chlorpromazine are compared to those of the barbiturates and to electrical stimulation of the cerebrum.

7. The results indicate that chlorpromazine may have a generalized action on the central nervous system upon which may be superimposed further actions upon specific structures or functions of this system.

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SUCCESSFUL TREATMENT WITH VANCOMYCIN OF SEPTICEMIA FOLLOWING MITRAL COMMISSUROTOMY CAUSED BY ANTIBIOTIC RESISTANT STRAIN OF STAPHYLOCOCCUS AUREUS

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Despite the advent of antibiotics and other chemotherapeutic agents, mortality from Staphylococcus aureus septicemia remains disappointingly high. As may be noted in Table I, an initial dip did take place immediately following the introduction of penicillin into clinical practice, but the present mortality closely parallels that existing in the preantibiotic era.

Although many factors including innate host immunity and concomitant or underlying disease e.g. malignancy, etc., undoubtedly exert a considerable influence in each case, development of resistance by staphylococci to once effective antimicrobial agents has undoubtedly played an important role in this situation.

Vancomycin*, a new antibiotic isolated from strains of Streptomyces orientalis obtained from an Indonesian soil sample, is reported to possess a number of highly favorable properties (4, 5, 6). Among these are its low toxicity, its bactericidal activity in low concentrations against gram-positive microorganisms including many strains of staphylococci resistant to currently existing antibiotic agents, as well as minimal development of experimentally induced resistance after repeated subculture in graded concentrations of the drug. It readily protects laboratory animals against experimental infection with staphylococci, streptococci and pneumococci.

The etiological organism responsible for the case reported upon was found to be resistant to penicillin, streptomycin and erythromycin, but was sensitive to vancomycin. Because of its effectiveness in vitro (7), bactericidal action and minimal toxicity, it was decided to employ vancomycin in this case when the administration of other antimicrobial agents was found to be ineffective clinically. The successful clinical result achieved by its use is the subject of this report.

CASE REPORT

This is the third admission to The Mount Sinai Hospital of a 26 year old white female telephone operator, who entered for surgical correction of mitral stenosis.

The patient was known to have had rheumatic fever at the age of 10 years, which was followed by chorea, lasting 2½ years. Following this, a heart murmur

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* We are greatly indebted to Dr. R. S. Griffith of the Lilly Laboratory for Clinical Research, Eli Lilly & Co., for the generous supply of Vancomycin.

TABLE I

Staphylococcus Bacteremia Mortality

Hospital	Period	Mortality
		%
University of Minnesota Hospitals (1)	Before 1942	75
	1945	28
	1951–1953	54
	1952–1955	80.48
Boston City Hospital (2)	1953	45.4
New York Hospital (3)*	1940–1942	69
	1943–1948	59
	1949–1955	70

* Adults only.

was detected, and the heart was noted to be enlarged. She was asymptomatic, however, until five or six years before admission at which time she began to experience shortness of breath on exercise and occasional abdominal swelling with no evidence of peripheral edema. She was treated by her family physician with occasional injections of mercurial diuretics with relief of the abdominal swelling. This therapy had been continued until three months before admission, when it was noted that she had a slow but progressive increase in exertional dyspnea. The patient never experienced angina, paroxysmal nocturnal dyspnea, or peripheral edema. However, she did have two pillow orthopnea for the past four years. There was no history of hemoptysis or cyanosis. She had never been treated with prophylactic antibiotics.

She was admitted to The Mount Sinai Hospital in November of 1957 for cardiac catheterization. The data thus obtained together with the physical findings and roentgenographic evidence were all compatible with mitral stenosis, and surgery was advised. She was admitted to the hospital for this purpose on January 14, 1958. Blood pressure at the time of admission was 110/70, pulse 76 per minute and regular, respirations 18 per minute and temperature 99.8° F. Examination of the heart revealed it to be of normal size to percussion. The point of maximum impulse was just to the left of the mid-clavicular line in the fifth intercostal space. P_2 was increased and M_1 was loud and sharp. A reduplication of the second sound was noted at the lower left parasternal area. There was a grade III late diastolic apical murmur with a presystolic accentuation. The remainder of the physical examination was within normal limits.

Admission laboratory data was hemoglobin 12.4 grams per 100 ccs of blood; white blood count 9,500 per cubic millimeter; differential: segmented forms 56 per cent, band forms 6 per cent, lymphocytes 33 per cent, basophiles 2 per cent, monocytes 2 per cent; erythrocyte sedimentation rate 10 millimeters per hour. Urinalysis was essentially normal. Blood urea nitrogen, carbon dioxide combining power, chlorides, sodium, cholesterol, albumin, globulin and total proteins were likewise within normal limits.

The patient was treated with Bicillin, 500,000 units daily, orally, starting one week prior to surgery. On January 24, 1958, the patient was taken to the operating room where under general endotracheal anesthesia a mitral commissurotomy was performed by Dr. Ivan D. Baronofsky. She tolerated the procedure excellently. Her entire clinical course in the hospital during this admission is outlined in Fig. 1.

Post-operatively, she was given tetracycline, 400 mg. and streptomycin, 1 gm. intramuscularly daily. On the day following surgery the temperature was noted to rise to 101.5° F. and it continued to rise the following day to 102.8°. At this time, erythromycin, 1 gm. daily was added to the regimen. A chest x-ray taken at this time revealed an infiltrate in the right middle lobe. The white blood count was 25,000 per cubic millimeter, with 71 per cent polymorphonuclear leukocytes and 33 per cent band forms. Chloramphenicol, 2 gms. daily, intramuscularly was added and despite these four antibiotics (tetracycline, streptomycin, erythromycin and chloramphenicol), the patient continued to have a low grade spiking temperature.

On the ninth post-operative day, the patient's temperature rose to 103° F. Bronchoscopy was performed and was negative. For the next four days her temperature rose to 104° F. daily. During these four days, the drain site of the withdrawn thoracotomy tubes was cultured and daily blood cultures were made. All cultures were positive for hemolytic, mannitol fermenting, coagulase positive

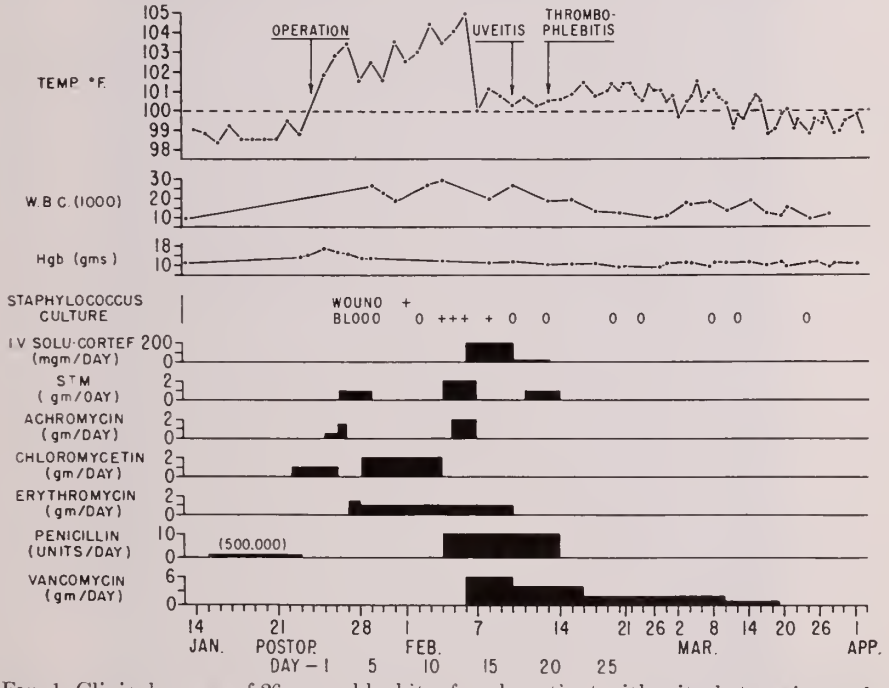

FIG. 1. Clinical course of 26 year old white, female patient with mitral stenosis on whom mitral commissurotomy was performed and who developed Staphylococcus aureus septicemia.

Staphylococcus aureus. Sensitivity determinations showed that the etiological organism was sensitive to vancomycin and ristocetin but resistant *in vitro* to 5 units of penicillin, 10 mcg. of streptomycin and 5 mcg. of erythromycin per ml. The blood cultures remained repeatedly positive despite the administration of 10 million units of penicillin intravenously and 1 gm. of erythromycin orally per day to the patient during this period.

On the 13th post-operative day, the patient's temperature rose to 105° F. and her general condition was one of marked toxicity, the systolic blood pressure falling to 80 millimeters of mercury. Petechiae were present on the right hand and an Osler lesion was present on the right fifth toe. Subungual splinter hemorrhages were also noted. The spleen was palpable just beneath the costal margin. In the conjunctival membrane of the left lower lid, a small white centered petechia was observed. Several petechiae were also noted on the hard palate and the left buccal mucosa. A clinical diagnosis of bacterial endocarditis was made at this time. The patient was started on hydrocortisone, 100 mg., intravenously daily, and the antibiotic regimen consisted of 4 grams of vancomycin and 10 million units of penicillin intravenously and 1 gram of streptomycin intramuscularly daily. On these antibiotics, the temperature fell abruptly over the course of

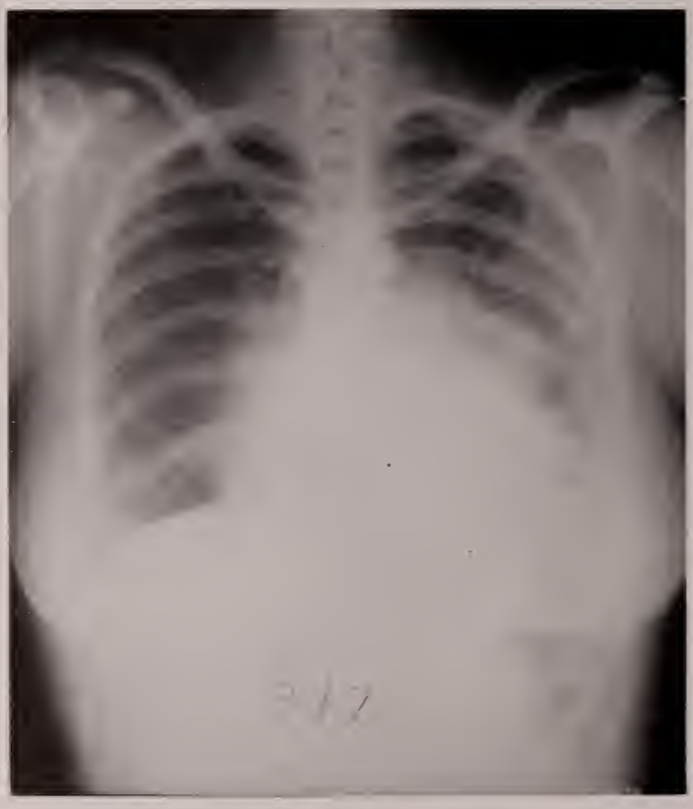

FIG. 2. X-ray of chest taken on the 14th post-operative day, one day after the initiation of vancomycin therapy, showing an infiltrate in the left posterior paracardiac area.

the next 24 hours and never again rose above 101° F. The white blood count dropped to 19,700 per cubic millimeter with 73 per cent polymorphonuclear leukocytes and 14 per cent band forms and remained between 12,000 and 18,000 with a slight shift to the left for the next five weeks.

On the 14th post-operative day, x-ray examination of the chest (Fig. 2) revealed an infiltrate in the left posterior paracardiac area. On the 16th post-operative day, a large oval shaped lucency surrounded by a fairly thin smooth wall was noted in the anterior portion of the left lung field, presumably within the lingular (Fig. 3). The lucency was biloculated and contained two air-fluid levels. The appearance was believed to be due to suppurative bronchopneumonia. By the 18th post-operative day, five days after the onset of vancomycin therapy, the lucencies were no longer identifiable. However, the infiltration of the lung field was still present.

Intravenous steroids were progressively decreased. The penicillin, streptomycin and vancomycin were continued until the 21st post-operative day at which time the dose of vancomycin was decreased to 2 gm. intravenously daily and the other antibiotics were discontinued.

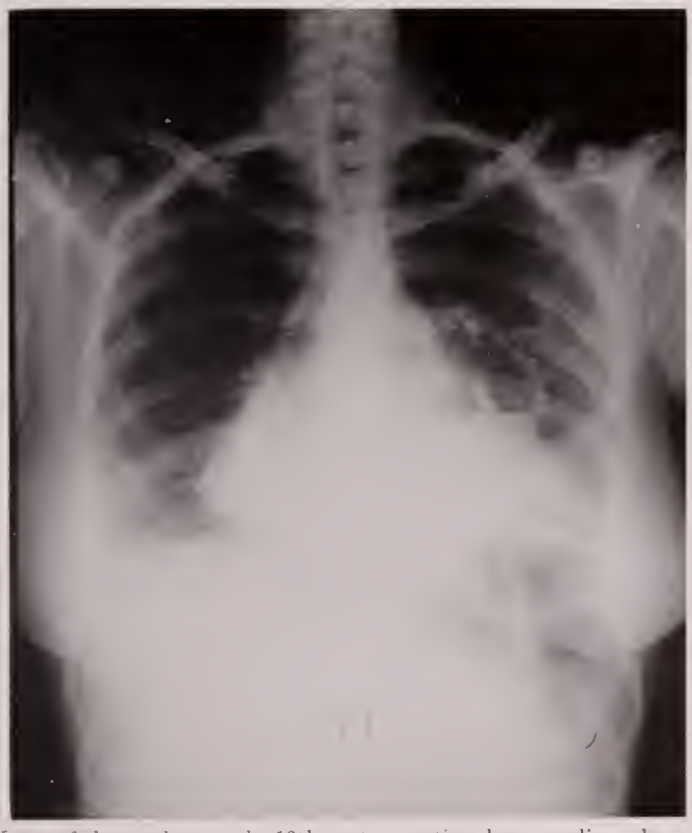

FIG. 3. X-ray of chest taken on the 16th post-operative day revealing a large oval-shaped lucency containing two air-fluid levels and surrounded by a fairly thin, smooth wall in the anterior portion of the left lung field presumably within the lingular. This was interpreted as being due to suppurative bronchopneumonia.

Although the patient had persistently positive blood cultures while receiving large doses of penicillin and streptomycin, all subsequent blood cultures taken after the 3rd day of introduction of vancomycin therapy revealed no growth. Physical findings of endocarditis and/or endophlebitis progressively decreased during the course of the first week of vancomycin treatment, and thereafter, with the exception of a transient uveitis and thrombophlebitis no abnormal physical signs were observable. The infiltration seen by x-ray cleared progressively over the next five week period (Fig. 4) and Vancomycin was discontinued on the 54th post-operative day.

It is noteworthy that during the course of therapy, the patient developed a progressive normochromic, normocytic anemia. The hemoglobin falling from 12.0 gms. on the 12th post-operative day to 7.7 gms. on the 33rd post-operative day. During this period of anemia, mean corpuscular volume was found to be 89 cubic micrograms, mean corpuscular hemoglobin 28.5 micromicrograms, mean corpuscular hemoglobin concentration 32.5 per cent, and the blood bilirubin was normal. Sternal marrow showed moderate eosinophilia and was otherwise within normal limits. There was no evidence of pancytopenia present throughout the

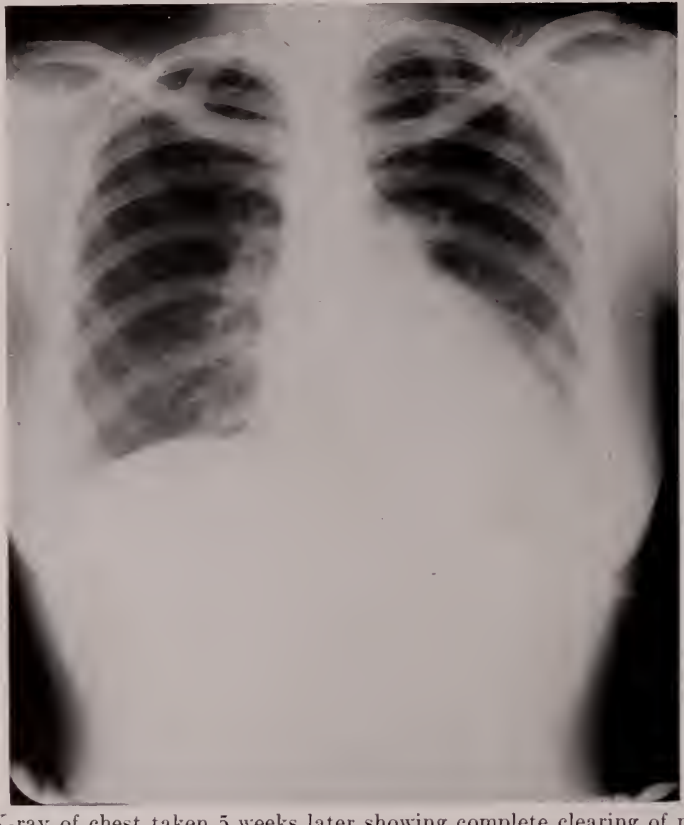

FIG. 4. X-ray of chest taken 5 weeks later showing complete clearing of previous pulmonary infiltration.

course of vancomycin treatment, and it may well be that the relative anemia that occurred was due to "toxic metabolic" reaction rather than any specific hematopoetic depression by vancomycin.

The patient had an uncomplicated convalescence since the first week after the onset of vancomycin therapy. She has remained afebrile and asymptomatic for two months following discharge and at the time of the present writing patient has returned to her normal occupation as a telephone operator.

SUMMARY

A case of Staphylococcus aureus sepsis following a valvulotomy for the correction of mitral stenosis developed bacterial endocarditis, suppurative pneumonia and vascular collapse. The etiological organism was resistant to penicillin, streptomycin and erythromycin but the patient was successfully treated with vancomycin.

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CLINICAL CONFERENCE ON REVERSIBLE RENAL FAILURE

THE MOUNT SINAI HOSPITAL

December 16, 1957

Chairman, Dr. Frederick H. King

Chairman King:

The subject of tonight's discussion is "The Nature and Management of Reversible Renal Failure."

Nothing is more discouraging to the clinician than the recognition by him of the signs of impending and then actual functional failure of the hopelessly diseased kidney. The management of uremia in these circumstances develops into a frustrating attempt at symptomatic relief.

Contrariwise there are few acts in medicine which are more rewarding than the recognition of the reversibility of a state of renal failure, the realization of its cause and dynamics and the institution of appropriate therapy.

The clinician who faces the problem of impending or actual renal failure must quickly survey the possibilities having potential reversibility. These include, as you know, obstructive uropathy, acute pyelonephritis, circulatory insufficiency associated with fluid and electrolyte loss or heart failure, kidney poisoning and intravascular hemolysis.

The exigencies of time prevent a consideration of all these entities. Particularly do we regret the inability to include obstructive uropathy, upon which our colleagues in urology would have had so much to add. Such a discussion would have included a delineation of all forms of uretal obstructions such as calculi, neoplasm, surgical ligation, trauma and bladder obstructions caused by prostatic hypertrophy. This discussion would undoubtedly have emphasized the obvious necessity of relieving the mechanical interruption of urine flow.

We have chosen to discuss the reversible states associated with the subtler derangements of electrolyte patterns and one entity caused by the abnormal elevated calcium contents of the blood leading to its deposition in the renal parenchyma. Finally the condition of so-called "lower nephron nephrosis" pre-

cipitated by a multitude of causes having a common denominator of decreased renal blood flow will be emphasized.

To introduce the subject, we thought it would be appropriate to have one of the clinicians concerned with renal physiology, who has used some of the pertinent physiological principles underlying renal failure in the management of the potentially reversible states. I will therefore call on Dr. Marvin F. Levitt to begin the program with a discussion.

INTRODUCTION

The Function of the Nephron in the Normal and Uremic Subject

Dr. Marvin F. Levitt:

During the past three to four years considerable insight has been gained into the nature of the specific function of the nephron both in the normal and in the uremic patient. Recently, in our laboratory Dr. Marshall Levy and I have become interested in the problem of the concentration and dilution of urine. We have found that an understanding of the physiological principles which are involved prove of real value in helping to manage the patient with renal failure, be that reversible or irreversible failure.

In the next few minutes I would like to present our present concept of the function of the nephron in the normal and uremic subject.

Approximately 180 liters of filtrate are formed per day by the normal kidney. Of this quantity the vast bulk is reabsorbed in the proximal tubule. Somewhere between 80 and even 90 per cent is reabsorbed before the urine reaches the remainder of the nephron. It is believed that the stimulus for this reabsorption is derived from the active trans-cellular transport of sodium. Since this tubule is freely permeable to water, as the solute is actively transported across the membrane, water passively diffuses out concurrently to leave a much reduced volume of tubular fluid of essentially isoosmotic concentration.

If the water lags behind slightly by the end of the proximal tubule the fluid may be slightly hypotonic. However, most of the filtered fluid has been reabsorbed by the time it enters the Loop of Henle.

The role of the Loop of Henle has recently been the subject of considerable discussion. Classically, it was taught that the role of the Loop of Henle was to provide an opportunity for the excess water which had not diffused back in the proximal tubule to diffuse into the renal parenchyma and achieve isoosmolarity. Recently, Berliner has hypothesized that the dilution of the urine begins in the Loop of Henle, and that sodium is actively transported out without the back diffusion of water. In fact, Wirz has argued that this sodium, in hypertonic concentration adjacent to the concentrating apparatus, provides the stimulus for the absorption of water. Whatever the proper role of the Loop of Henle, its delineation is not crucial to our understanding of renal failure.

As the urine reaches the distal tubule, it is now in a lumen distinctly different from the proximal tubule, in that it is far less permeable to water. Consequently, as the active absorption of salt continues, water lags behind. This segment

thus affords an opportunity for the dilution of the urine, and accordingly is properly called the diluting segment.

Recently it has become evident that an important role of pitressin is to render this tubule more permeable to the back diffusion of water. In this view, pitressin acts to limit or prevent the dilution of the urine, rather than actively to concentrate the tubular fluid.

One factor which will determine how much dilution can be achieved is the quantity of iso-osmotic fluid reaching this diluting segment. As that quantity increases, as more fluid is left after passage through the proximal tubule, and as active salt extraction continues leaving water behind, the degree of dilution and free water clearance increases. Thus, how dilute the urine will be, and how much free water is cleared, is not only dependent upon the quantity of circulating pitressin, but the amount of iso-osmotic solute which escapes reabsorption in the proximal tubule.

Further, the distal tubule is important for the exchange of potassium or hydrogen. It is believed that virtually all the filtered potassium is reabsorbed proximally, and that the potassium which appears in the urine is the result of the secretion in the distal tubule. In order for adequate quantities of potassium to be secreted, there must be a considerable quantity of sodium reaching that distal segment to be exchanged for the potassium. In the normal kidney, where very small quantities reach this segment, the secretion of potassium is quite low. The same conditions hold true for the distal transport of hydrogen at which site the urine is acidified, the hydrogen is converted to ammonium, and hydrogen is combined with buffer. The distal transport of hydrogen is likewise dependent upon the availability of the exchanging sodium. The quantity of potassium and hydrogen appearing in the urine are, in part, determined by the quantity of sodium which reaches this distal or exchanging segment.

Finally this variably hypotonic urine reaches the concentrating apparatus which, it is believed, is in the collecting ducts. Here water is extracted without solute, a phenomenon described by Dr. Homer Smith as the outward transport of solute-free water (TcH_2O).

The final concentration of the urine is therefore dependent upon the capacity of this concentrating segment to extract solute-free water. The degree to which the final urine is concentrated is also conditioned by the volume of fluid reaching that concentrating apparatus. As the volume of fluid reaching this concentrating segment increases, the removal of a constant volume of solute free water will tend to have a lessened effect on the ultimate concentration. The actual concentration of the urine is in part determined by the concentration of the fluid reaching the concentrating segment. The ultimate concentration of the urine therefore depends upon the amount of solute free water extracted, upon the quantity of fluid reaching that apparatus and upon the concentration or the degree of hypotonicity of the fluid reaching that concentrating apparatus.

In the normal individual, where most of the filtered load is absorbed proximally, where the distal fluid, particularly in the presence of adequate quantities of ADH, is rendered only slightly hypotonic, and where a small quantity reaches

the concentrating segment, the extraction of relatively small quantities of solute-free water produces a concentrated urine with a maximum concentration four times that of plasma.

Evidence now available suggests that the stimulus for the outward passage of solute-free water in the concentrating segment comes from passing the distal tubular fluid past the hypertonic interstitial fluid of the medulla. In this view, too, the less solute and the less water reaching this site, and the more concentrated the distal tubular fluid, the greater the likelihood for tubular fluid to reach the maximum concentration of the medullary interstices.

With this understanding of the way the normal nephron functions, one can accept the fact that by simply redistributing internally the quantity of fluid acted upon by different segments, we can produce a urine of considerably different composition.

In figure 1, there are represented the characteristic defects which occur in the nephrons of patients with renal failure. It is now believed that in most forms of renal failure, the characteristic defect is a considerable reduction in the number of functioning nephrons. Accumulating evidence suggests that the remaining nephrons are actually functioning quite efficiently but that their number is markedly reduced. The significant characteristic of the patient with renal failure is that as the number of functioning nephrons become progressively reduced and as the quantity of filtered load progressively falls, there is a disproportionate reduction in the quantity which is reabsorbed proximally, and much larger quantities remain behind to be acted upon by the more distal segments. Accordingly, the distal tubule and concentrating segment are overwhelmed with much larger quantities of fluid. As renal failure progresses, the fraction of filtered solute or water which appears in the urine progressively rises. Specifically, in the normal kidney less than one per cent of the filtered solute appears in the urine, but as progressive renal failure develops, a much higher fraction of this filtered load is excreted in the urine.

The theoretical explanation for this difference in the function of the nephron of the patient with renal failure and of the normal nephron is not clear. It is not simply that the tubules have lost their functioning capacity. In part this

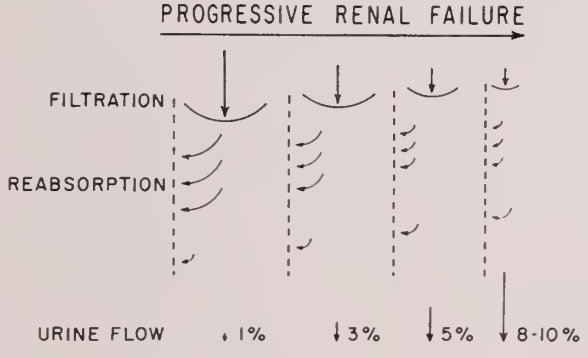

FIG. 1

increased load pouring out in the urine is dependent upon the solute load imposed by the high concentration of urea. In part it also appears to be a manifestation of the fact that the few functioning nephrons in renal failure are nephrons in which the glomerulus tends to overwhelm the attached nephrons. There appears to be glomerular-tubular imbalance in the remaining nephrons of the uremic subject. Much more iso-osmotic fluid escapes reabsorption proximally, so that the distal tubule is presented with a much larger quantity of the original filtered load. Consequently, since extraction of sodium continues to be active and since water tends to lag behind in this segment, the distal tubular fluid tends to be more hypotonic. The urine in the distal nephron of the uremic subject may thereby achieve a far greater degree of dilution or hypotonicity.

Secondly, in uremic patients the potassium and hydrogen exchanging mechanisms in the distal tubule are guaranteed a maximum quantity of sodium with which to exchange. This fact explains the remarkable circumstance that the quantity of potassium excreted per quantity of glomerular filtrate is enormous in a subject with renal failure. Indeed, the first evidences of renal secretion of potassium were obtained by Wirz and later by Sirota in subjects with severe renal failure.

The same holds true for hydrogen, which fact explains why the urine always tends to be acid in renal failure unless there is a specific tubular defect in transporting hydrogen. In the uremic subject, there is apt to be a flow of more dilute urine leaving the distal tubule and the quantity of potassium and hydrogen transported into the fluid per liter of filtrate is increased.

Finally, as this urine reaches the concentrating apparatus, it tends to be overwhelmed with a far larger quantity of dilute urine. As water is extracted in the concentrating apparatus, the urine tends to rise towards iso-osmotic concentrations.

In figure 2 data from the experiments of Mudge et al. (A.J.P. 158: 218, 1948)

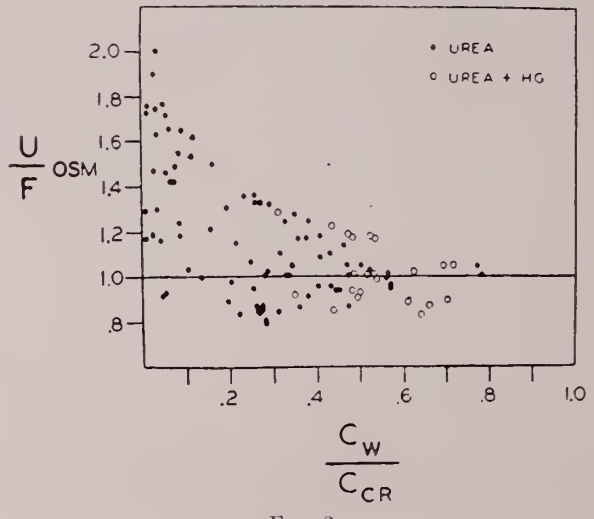

Fig. 2

are presented which demonstrate that as urine flow is increased in the normal dog by a large solute load, the concentration of the urine tends to fall. In other words, when a large solute load reaches the concentrating segment, the reduced effect of the continued extraction of solute-free water becomes apparent and the urine becomes iso-osmotic. This is one of the reasons that the uremic subject is unable to elaborate a concentrated urine.

Let us try to review the advantages which accrue from this redistribution of reabsorption of solute and water in the nephron of the uremic subject. Despite a very markedly reduced rate of filtration, the uremic excretes a considerable quantity of salt and water. Because of reduced reabsorption in the proximal tubule, the uremic is able to excrete almost as much salt as the normal subject. Furthermore, because he presents such a large load to the distal diluting segment, he is able to overwhelm the concentrating apparatus and excrete large quantities of water. The polyuria of the subject with renal failure has been a well-known fact for over four hundred years, and to a very large extent this polyuria is explained by the internal redistribution of solute reabsorption.

The uremic patient secretes a maximum quantity of potassium in view of his marked reduction in filtration rate. Clinically this is apparent in the fact that potassium poisoning rarely occurs as long as there is a fair urine output. Only when urine output falls to oliguric levels does this exchanging mechanism fail to the point that potassium poisoning occurs. The uremic individual is able to secrete relatively large quantities of hydrogen in the face of this markedly reduced filtration rate, again because this exchanging segment is assured of a massive load of sodium upon which to operate.

Finally, because of the fact that a good quantity of dilute urine reaches the concentrating apparatus, the uremic patient is sometimes able to dilute urine and generally bring it towards iso-osmolarity. Now let us consider the tremendous advantages which accrue from being able to bring that urine to iso-osmotic concentrations. I emphasized a few moments ago that the role of pitressin was to prevent the dilution of urine, not to elaborate a concentrated urine. If the uremic subject were forced to secrete a urine of marked hypotonicity, of specific gravity of 1.002, or of 40 mos./liter, it would require about 20 liters to excrete a thousand milliosmoles per day. By bringing the concentration simply up to 1.010 he would be able to excrete that quantity of solute load in about three liters. Thus by raising the concentration from 1.002 to 1.010 he would conserve almost 17 liters of water. If he were able to concentrate the urine further to 1.028 or to 900 mos./liter, he would conserve another two liters of water. The uremic patient has given up that spectrum of his total concentrating ability which is really least important, but he has maintained the capacity to excrete remarkable quantities of sodium, chloride, and water. Of course, as with every situation in which considerable advantages accrue, there are also marked disadvantages and these disadvantages become apparent when the attending physician tries to alter the remarkable balance which is set up by this unusual change in solute reabsorption in the operating nephron of the uremic subject.

The osmotic diuresis under which the uremic patient operates imposes several

limits. Even though he is able occasionally to achieve a dilute urine, his total urine flow is limited by the fact that the filtration rate is markedly reduced. Although he can excrete three and possibly four liters of urine, if his water intake is forced beyond that he begins to retain water and produce hyponatremia. Furthermore, he is unable to handle the opposite extreme, namely the elimination of water from his intake. As water is eliminated from his diet, he continues to pour out large quantities of fluid and rapidly becomes dehydrated. These limits will not permit him to cope with extremes of high water intake or water deprivation. Similarly, although the uremic patient is able to excrete a remarkable quantity of salt and urea because of this system, he cannot excrete as much salt as the normal. Generally, if uremic patients are given high normal salt intakes they may tend to retain salt and develop edema. On the other hand, if salt is eliminated from the diet, such subjects are incapable of producing a sodium-free urine, and so then develop a negative salt balance and the manifestations of salt depletion. This physiological balance which is achieved in the subject with renal failure permits a remarkable capacity to compensate for moderate conditions, but it does not afford the capacity to handle extremes of water or salt intake. I think an understanding of this physiological defect of the uremic subject will help to a great extent in managing the polyuria of renal failure.

Chairman King:

Dr. Levitt has emphasized that there is a tendency to lose electrolytes and especially salt in the polyuric phases of renal failure in general, but there exists a group of cases in whom there is an inordinate loss of sodium chloride in the urine and the usual causative lesions is pyelonephritis. These patients are helped by supplemental administration of sodium chloride.

The first case to be presented this evening by Dr. Arnold Moses will be a case of so-called salt losing nephropathy.

SALT LOSING NEPHROPATHY

Case Report

Dr. Arnold Moses:

This 46 year old female was first admitted to The Mount Sinai Hospital in September of 1955. She had been in good health until four months prior to admission when she noted the onset of progressive weakness and restlessness. Polydipsia and polyuria without pyuria or hematuria developed two months prior to admission, and a month later she noted the onset of fever to 101 degrees F. Several weeks before admission nausea and vomiting developed and became progressively more severe. In the several months prior to admission the patient lost 30 pounds. The patient's past medical history was non-contributory.

Admission physical examination revealed a pulse rate of 110/min., respiratory rate of 20/min., temperature 99 degrees F., and blood pressure of 110/60 mm. Hg. The patient was well developed and in no acute distress. The physical examination was within normal limits except for equivocal skin pigmentation.

The initial laboratory examinations revealed hemoglobin of 12.9 gm%, and a white blood cell count of 20,000/mm^3, with 82% polymorphonuclear cells. Analysis showed one plus albumin and many white cells and granular casts in the urine. The erythrocyte sedi-

mentation rate averaged 40 mm./hr., and the blood urea nitrogen was 82 mgm %. Serum sodium was 102 meq/l., and serum CO2 8.5 meq/l. Serum albumin and globulin values were normal. The serum calcium was reported as 11.7 mgm %, serum phosphorus 6 mgm %, and alkaline phosphatase was 9.8 K.A.U. Urine cultures grew aerobacter aerogenes, enterococcus, proteus vulgaris, and later acid fast bacilli. Chest x-rays revealed old fibro-calcific densities in both apices as well as miliary densities throughout both lung fields. Partial collapse of L1 and paravertebral calcific streaks representing the residuum of old acid fast disease were seen on spine x-rays. The intravenous pyelogram revealed poorly defined densities in the right kidney.

The patient was treated with isoniazid, para amino salicylate, and streptomycin for the acid fast disease. In addition she was given antibiotic therapy including Chloromycetin®, Furadantin®, and Neomycin® for what was considered to be a superimposed urinary tract infection. Additional therapy included several blood transfusions, sodium chloride, sodium bicarbonate, and desoxycorticosterone, the latter in doses of 5–10 mgm per day. The desoxycorticosterone was administered because of the suspicion of adrenal insufficiency. However, the plasma levels of 17 hydroxycorticosteroids were normal, 10 gamma %, and rose to 41 gamma % 2 hours after the intramuscular administration of 40 units of ACTH. Urine 17 ketosteroids were normal as was the glucose insulin tolerance test.

In the early days of the patient's hospitalization a polyuria to the extent of 6000 cc/day was recorded. This represented several thousand cc more than her fluid intake. On a 4 gram sodium chloride intake the 24 hour urine specimen contained as much as 250 meq. of sodium. The effect of desoxycorticosterone on the urine sodium excretion was negligible. Random urine specimens concentrated to no greater than 1.016.

On the prescribed regimen the patient ran a fluctuating low grade fever which gradually subsided after several months. Her symptoms, including the polyuria, concurrently improved. The initial severe chemical abnormalities improved in several weeks. However, later in her hospital course she again developed a transient acidosis when the dosage of the administered sodium bicarbonate was decreased. The urinary microscopic abnormalities gradually cleared but at the time of discharge 5–8 WBC?HPF were still noted along with a urine albumin of one plus. At the time of discharge, 4 months after admission, the blood urea nitrogen was 16 mgm %, serum sodium 141 meq/l., serum potassium 4.1 meq/l., serum chloride 98 meq/l., serum CO2 28 meq/l., and serum calcium 10.6 mgm %.

Five months following discharge the patient presented with hematuria and dysuria. At that time her urine specific gravity was again 1.016. This was associated with a 2 plus albumin, many red blood cells, few white blood cells, and no casts on microscopic examination of the urine. At the time of this admission the patient's blood urea nitrogen and electrolytes were normal despite the fact that she had taken no supplementary sodium chloride or bicarbonate following her initial hospital discharge. The right kidney did not visualize on intravenous pyelogram and the left ureter was dilated. Mechanical dilation of a left ureteral stricture was performed. The patient's third hospital admission followed in five months, at which time the blood urea nitrogen and electrolytes again were normal. During this last admission a left cutaneous ureterostomy was performed.

Chairman King:

We have asked Dr. Gabrilove to discuss this subject since he is interested in this field of endocrinology.

I will ask Dr. Gabrilove to discuss, "Salt Losing Nephropathy."

Discussion

Dr. J. Lester Gabrilove:

This lady came in with the symptoms and signs of dehydration and salt depletion of a rather marked degree including anorexia, nausea and vomiting

and a weight loss of thirty pounds. Upon her admission it was readily apparent that she had tuberculosis and that she also had pyuria. Therefore this patient with tuberculosis and pyuria was studied and it was quickly demonstrated that her serum sodium was markedly decreased and that she was wasting salt.

Ordinarily in patients who come to the hospital and are seen in a state of salt depletion, one has to consider the various causes of salt depletion since many of these are correctable and the patient can be restored to an essentially normal clinical state for quite some period of time if not permanently. The low serum sodium of course is not sufficient of itself to permit one to make a diagnosis of salt wastage. Low serum sodiums are seen in many instances where salt wastage does not occur. It occurs particularly in tuberculosis for reasons which are not clear at the present time. True here is a lady with tuberculosis and a low serum sodium but there is more here than can be explained by the supposition that this is the idiopathic low serum sodium that is often seen in tuberculosis.

Low serum sodiums are seen in the end stages of heart failure, nephrosis and in cirrhosis and at that time presents a particularly poor prognostic sign. It is a type of hyponatremia which ordinarily does not respond to the intravenous administration of salt and indeed the patient is often made worse by this form of treatment. She did not have a hyperlipemia that sometimes is associated with a low serum sodium because of the dilution effect. There was no evidence of water intoxication nor was there a history of the administration of the antidiuretic hormone.

It was therefore apparent that her low serum sodium reflected salt wastage. Now the possible causes of salt wastage, as you known, may be several. We know that the kidney is particularly concerned with guarding the economy of sodium. Patients who vomit can lose sodium. More commonly patients who have severe diarrhea such as occurs in cholera or even milder diarrheal states such as we see in a general hospital may become markedly depleted of sodium. Patients with cystic fibrosis of the pancreas or patients working in extreme heat, both of whom may lose excessive quantities of sodium in the sweat, may be salt depleted.

However, none of these etiologies could be incriminated. Consequently, we had a patient with salt wastage who very likely failed to conserve sodium as a result of renal wastage. It was then a matter of tracking down whether that renal wastage was due to the pyelonephritis, which was apparently present, or to some other renal cause.

Now what can these renal causes be? Well we can readily rule out a few of the more apparent etiologies for failure of renal conservation of salt. We know she had not received mercurial diuretics or diamox both of which agents can induce renal losses of sodium. We may presume she did not have acute tubular necrosis in spite of the fact that she did exhibit some diuresis, since there was no history of the oliguria that one encounters in an acute lower nephron nephrosis. This is particularly important to bear in mind since it is well known that following recovery from acute tubular necrosis there is a marked

loss of electrolytes. We know she did not have the osmotic diuresis that one sees in diabetes mellitus or following loading with osmotic diuretics. Basically the problem therefore resolved itself into one of two etiologies. Did this patient waste salt because the tubules were incompetent to absorb them adequately, as Dr. Levitt explained, or was she wasting salt because she did not secrete those hormones vitally concerned with the renal regulation of salt balance, namely, the salt regulating hormones of the adrenal cortex? The resolution of this problem was a matter of great and pressing importance in order for proper therapy to be administrated.

Fortunately, in both of these instances, one can control the patients for a while with the administration of salt until more definitive diagnostic tests can be performed. The next step indicated was to try to evaluate adrenal cortical function. We evaluated adrenal cortical function not by methods which ordinarily utilize renal function such as the water tolerance test or the renal excretion of sodium because such techniques would not differentiate between an adrenal factor and a renal factor. We could, of course, try a therapeutic trial with desoxycorticosterone. If this agent caused the renal conservation of salt it would establish an adrenal etiology of the salt wastage since a diseased kidney would not respond to the administration of this adrenal hormone. However, a more rapid, if more indirect, method of evaluating adrenal function was desirable.

We therefore tested it in a way by which we could exclude the kidney, namely, by the administration of adrenocorticotropin to stimulate the adrenal cortex and by measuring in the blood a primarily nonsalt-regulating factor secreted by the adrenals, namely, the 17-hydroxycorticoids, or glycogenic corticoids. We found that the adrenal responded quite adequately following the administration of ACTH and was therefore intact with respect to its ability to elaborate glycogenic corticoids. We therefore presumed it was also intact with respect to salt regulating hormones although no attempt was made to estimate the aldosterone content of the urine. It thus became apparent that this woman had a salt wasting nephropathy, not due to Addison's disease, and that she should be treated with salt and bicarbonate of soda. On this regimen she did quite well.

In most instances of salt wasting nephropathy the underlying etiology is usually pyelonephritis. Many years ago Dr. Peters and his group demonstrated that in chronic nephritics there often is mild salt wastage but it remained for Thorn, in about 1944, to demonstrate that the salt wastage may become so extreme at times as to produce a clinical picture resembling that encountered in adrenal cortical insufficiency. In fact, the patient whom he originally described was referred to him because of the suspicion of Addison's disease. These patients occasionally are pigmented for reasons which are not known and they not infrequently have a history of a large oral intake of bicarbonate of soda. They usually are differentiated from patients with adrenal insufficiency by the fact that they have a much higher content of urea nitrogen in the blood than we ordinarily see in adrenal cortical insufficiency. It was perhaps a little

easier than usual to make a diagnosis of salt wasting nephropathy in this patient because she exhibited proteinuria, a finding not commonly encountered in this disorder. The blood urea nitrogen was not greatly elevated in this patient and not of diagnostic significance since it was in the range often encountered in acute adrenal cortical insufficiency. Interestingly enough, at post mortem, the patients with salt wasting nephropathy often have enlargement of the adrenals which we believe probably represents a compensatory hypertrophy of the adrenal cortex as an attempt to overcome the wastage of salt by the kidney.

As we reconstruct this story, this was a patient with tuberculosis and salt depletion. However, the salt depletion was not due to adrenal cortical insufficiency, even though disseminated tuberculosis can involve the adrenal and cause adrenal insufficiency. It was demonstrated that the salt depletion was due to renal wastage and that the salt wastage was due to a pyelonephritic nephropathy partly tuberculous and partly pyogenic in origin. With treatment of the nephropathy by antibiotics specific for tuberculosis and the pyogenic organisms involved, this patient's salt wasting nephropathy improved indicating that at least in her instance the process was still reversible. The lesson to be learned is that this lady was tided over this critical period because it was recognized that she had renal salt wastage and proper therapy was directed to correcting this.

Chairman King:

The syndrome that we are more readily recognizing in recent years is that renal failure may be associated with marked potassium loss, and the recognition of the nephropathy of marked potassium loss is crucial.

We are presenting such a case to illustrate this chemical derangement and its management. It will be presented by Dr. Gerald Weissmann.

POTASSIUM DEPLETION NEPHROPATHY

Case Report

Dr. Gerald Weissmann:

This was the second admission to The Mount Sinai Hospital of a 57 year old white female who entered for investigation of recurring fevers that she had experienced in the six months prior to admission.

Fourteen years before her present admission she had been told by a physician after a routine physical examination that she had rheumatic heart disease. Although she had specifically denied all signs and symptoms of juvenile rheumatism, she did admit to frequent sore throats and pustular tonsilitis. Five years prior to admission she noticed an irregularity of her heart beat that was treated by digitalis, and mercurial diuretics when transient edema developed. This served very well to control her heart failure until six months prior to admission when she was first hospitalized at The Mount Sinai Hospital. At that time she was in congestive heart failure that responded very well to simple measures, and in addition she had mild bronchitis that responded to tetracycline therapy.

After a short course in the hospital she became afebrile and was discharged. At home she had frequent fevers but did not seek medical aid for these. These fevers would come on in the evening, and would be accompanied occasionally by chills. At night her bed sheets would be stained with perspiration.

Finally, she sought admission because of increasing shortness of breath and because of her fever. On physical examination she proved to be a moderately well nourished, well-developed female in slight respiratory distress. Her temperature was 100° and her respiratory rate was 28. Her blood pressure was 130/70 and she was not acutely ill, although she was a bit uncomfortable lying in bed at 30 degrees. There was obvious pulsation of the neck veins above the sternum. There was a visible systolic heave over the precordium and an aortic systolic murmur of grade 3 intensity was heard radiating to the neck. This was associated with a slight dimunition in the intensity of the second aortic sound and a thrill radiating to the neck. In addition a diastolic murmur was heard at the apex. This was a grade 2 diastolic murmur associated with a very loud first sound and a split second mitral sound. There was a positive hepatojugular reflux and pedal edema was noted at the time.

Admission laboratory studies were as follows: the hemoglobin was 15 grams %. Her white blood count was 9,000 with a slight shift to the left. Her sedimentation rate was 36 mm/hr. Her urine showed a specific gravity of 1.018 and contained four to ten white blood cells per high power field but there was no hematuria nor albuminuria.

The serum sodium drawn at that time was 135 meq/l. The potassium was 5.1 and CO2 content 32 meq/l. The blood urea nitrogen was 13 and blood sugar 91 mg %. Albumin equalled 4.3 grams % and globulines 3.3 grams %.

She was admitted on the 24th of June 1955 and was to remain in the hospital until the first week of October. She was placed at bed rest and was observed for a few days. Initially she had a rather febrile course and blood cultures were obtained in the second week of her hospital admission. Four blood cultures proved positive for staphylococcus albus C and she was therefore treated with 20 million units of penecillin per day intravenously, 0.5 gm per day of neomycin intramuscularly and 1 gram of streptomycin per day intramuscularly.

Two positive blood cultures were again obtained after two weeks of therapy, during which her fever did not respond at all ranging from 100 to 101 degrees daily. She was also given albamycin. At no time until the very middle of September was she completely afebrile. Six blood cultures remained sterile thereafter.

A very troublesome symptom plagued the patient after two to three weeks of antibiotic therapy. She began to have frequent loose bowel movements ranging in frequency between two and six a day. These were brown, liquid, copious and did not respond to any therapy. They soon proved quite disabling to the patient and she lost twenty-five pounds, probably on the basis of this diarrhea. At the time that she was losing this weight, she lapsed into moderate cardiac failure so weight loss was even more profound than that recorded.

When antibiotic therapy was discontinued in the middle of August, she again had a rather severe bout of diarrhea. At this point stools were cultured and persistently showed B. Proteus and E. Coli. Sulfadiazene did not reduce the frequency of her stools and through the later part of August and the first few weeks of September she had severe diarrhea averaging six movements a day. On the second day of September she lost fluid to such a degree that she went into a period of mild coma. She had gross muscular twitching and became mildly disoriented. On the second and third of September of 1956, the patient was quite disoriented. The blood urea nitrogen on the fourth of September was 65 mg%. The CO2 content was 32 meq/l, chloride, 77 meq/l, sodium, 131 meq/l and potassium, was 3.5 meq/l.

At that time she was given intravenous doses of potassium in quantities of 240 meq/day once the urinary output was guaranteed. Gradually by the tenth of September her sodium potassium had been raised to 5.2 but more important the CO2 content had declined to 26 meq/l.

On the 24th of September the CO2 was 24 meq/l. The BUN had decreased to 28 mg%, sodium was 134 meq/l, potassium 5.0 meq/l and the chlorides 97 meq/l. She was clinically well with restitution of potassium, sodium and other electrolytes that had been lost.

The urine on the sixth of September during the period of rather severe alkalosis showed a specific gravity of 1.010, but it gave an acid reaction. On the twenty fourth of September the urine gave an alkaline reaction at the time that her plasma CO2 content had fallen. On

the thirtieth of September her urine became normally acid as her serum electrolytes returned to normal limits.

Her clinical picture improved rather promptly after this. She became afebrile and her failure responded well to the usual measures. She was sent to a convalescent home where she again remained afebrile. She has been perfectly well, save for minor episodes of cardiac failure, to the present time.

Chairman King:

I will now call on Dr. Arthur W. Ludwig to discuss "Potassium Depletion Nephropathy."

Discussion

Dr. Arthur W. Ludwig:

In recent years there has been a growing awareness of the importance of the role of potassium depletion in the etiology of renal dysfunction. As a result of studies of renal function in patients with potassium loss, it has become apparent that depletion of this ion is a frequent cause of renal damage, which fortunately is usually reversible. While most of the investigations have been primarily concerned with the physiological effects of potassium loss, we will limit the discussion to the clinical aspects of the subject.

There are many possible causes of potassium depletion. The largest group of patients that has been studied adequately in regard to changes in renal function comprise cases of chronic diarrhea of varying etiology. The patient presented this evening had chronic diarrhea resulting from the administration of antibiotics. There have been reports of renal disease in patients with colitis, and even from excessive enemas. Dr. Dunning, who studied the latter group, demonstrated that with a single enema there may be a loss of 12 to 256 milliequivalents of potassium. Other causes of chronic diarrhea with renal involvement are abuse of laxative ingestion, and the various forms of the malabsorption syndrome. Chronic vomiting and pyloric stenosis have been reported as a cause of potassium depletion nephropathy.

Primary aldosteronism due to adrenal carcinoma has been demonstrated to result in potassium depletion. It was Conn who first pointed out that these patients suffer from hypokalemic alkalosis. Biopsy studies of the kidneys of such cases have revealed the typical changes associated with potassium loss. Thorn reported similar findings in patients with Cushing's syndrome. Patients receiving steroid therapy may suffer significant potassium loss and have been reported to demonstrate renal lesions.

The prolonged use of mercurial diuretics in the treatment of heart failure, particularly after the patient has become depleted of sodium, has resulted in severe potassium loss. Some cases of chronic renal disease, particularly if diarrhea or vomiting are present, have been shown to be depleted of potassium, even though we usually associate advanced renal disease with potassium retention. Respiratory alkalosis and genetic tubular defects are additional causes of excessive potassium excretion.

There are two other groups which are of great clinical importance. First

are the post-operative patients, particularly those who have had gastrointestinal surgery, who are maintained for long periods of time on intravenous fluids containing little or no potassium. This group frequently is subjected to loss of intestinal contents from intubation or vomiting. Such patients have been shown to suffer marked potassium loss. Second, is the group demonstrating the phenomenon of potassium depletion as a consequence of the treatment of diabetic acidosis with insulin.

The clinical features of renal disease secondary to potassium depletion are consistent with those that were mentioned by Dr. Levitt as the most frequent findings in early renal failure, regardless of etiology.

In a summary of 13 cases of potassium depletion nephropathy, Relman and Schwartz found that the most frequent urinary finding was fixation of the specific gravity. None of the patients studied could elaborate urine with a specific gravity above 1.010, and most of them could not go beyond 1.005. With replacement of the potassium deficit, concentrating power was restored to normal in all subjects.

Polyuria was found in only five of their 13 cases; but these patients excreted as much as six liters of urine per day. There was striking impairment of tubular function as measured by phenol red or PAH excretion. There was slight diminution of glomerular filtration, estimated by urea and creatinine clearances. Just why there should be any glomerular dysfunction is strange since pathologic studies indicate normal glomeruli.

Azotemia is rather infrequent, and is usually thought to indicate the existence of an additional renal lesion. As far as routine urinalysis is concerned, there are no significant abnormalities other than occasional slight albuminuria. Some of the patients demonstrate slight to moderate edema, which is probably related to sodium retention.

The pathologic findings were first described by Follis in rats that had been on potassium deficient diets. They have been confirmed repeatedly both in autopsy material and from serial biopsy studies in humans. The lesions are primarily tubular changes, consisting of cloudy swelling with marked vacuolization, and, in the more severe cases, actual desquamation of the tubular epithelial cells. It is the distal tubule which is most severely affected; the proximal tubule less so. The loops of Henle appear to be uninvolved, and the collecting tubules only slightly so. As mentioned earlier, there are no demonstrable glomerular lesions. It is worth mentioning that the serial biopsy studies in the cases with the most marked changes ultimately demonstrated normal renal histology after the potassium deficit had been corrected.

The mechanism by which the depletion of the potassium stores of the body induces renal damage is not clear. Since potassium is primarily an intracellular ion, it has been postulated that the cells of the renal tubule are particularly sensitive to loss of this ion. The anatomical changes reported, as well as the evidence that the renal injury is mainly tubular, tend to support this hypothesis. The physiological studies reported are, however, quite contradictory.

Evans found that in patients who were made alkalotic in addition to being

deprived of potassium, the kidneys can secrete a highly alkaline urine with a low concentration of potassium. Perkins and others have also reported excretion of alkaline urine following potassium depletion.

On the other hand, Berliner has presented evidence that there is a competition between the hydrogen and potassium ions in the renal tubule. In the face of severe depletion of potassium stores, there is an effort to conserve potassium ion, and larger amounts of hydrogen ion are excreted producing an acid urine.

It is difficult to reconcile these reports, but it is suggested that the extent of potassium depletion in the different studies may account for some of the variance. In those subjects with only partial potassium depletion, the kidney may still put out an alkaline urine. This is in accordance with the observations in Cushing's syndrome or hyperaldosteronism where an alkaline urine is usually found. But when there is marked depletion, as well as a restricted intake, of potassium, the need to conserve potassium results in the formation of acid urine. In the case under discussion this evening, you may have observed that she was producing an acid urine, at a time when the blood indicated the existence of alkalosis.

To summarize, the patient presented tonight is an example of severe nephropathy caused by potassium loss secondary to prolonged diarrhea induced by antibiotics. It is somewhat atypical in that azotemia was observed, suggesting the possibility that there was an underlying renal disease either vascular or infectious in origin. However, more typically, she demonstrated fixation of specific gravity, polyuria, and restoration to normal renal function following the administration of potassium ion.

Chairman King:

Renal insufficiency has been known to occur in instances of hypercalcemia associated with hypercalcuria and typical examples of this of course are primary hyperparathyroidism and Vitamin D intoxication.

We thought that the mechanism by which the burden of calcium excretion on perhaps previously damaged kidneys leads to renal insufficiency, is worth illustrating and discussing.

I will ask Dr. David Nash to present what I think is a dramatic case of "Hypercalcemic Nephropathy."

HYPERCALCEMIC NEPHROPATHY

Case Report

Dr. David T. Nash:

A forty year old widow was admitted to The Mount Sinai Hospital for the second time on December 9, 1954 with the chief complaint of anorexia, weight loss and progressive lethargy. The patient also noted left shoulder pains for some time. She had been in good health until the previous July when she experienced aching pains in the left knee with inability to bear weight.

There were no objective clinical or x-ray findings and the patient's pain resolved after

several "vitamin injections." No other joints were involved. Soon after this, symptoms of irritation and epigastric pain appeared and the patient sustained a weight loss of twelve pounds over a two month period. Menometrorrhagia beginning in August necessitated a dilatation and curettage at another hospital. No intrinsic uterine disease was found.

Listlessness became prominent during the last part of the summer and during the two weeks before the first admission in October of 1954, lethargy had progressed to the point where it was found difficult to rouse the patient from her sleep.

Physical examination at the time of her first admission revealed a drowsy obtunded confused white female. The vital signs were normal. The temperature was 100.4 degrees. A non-tender almond size lymph node was found in the left axilla, and a mass believed to be the kidney was found in the left upper quadrant.

Neurological examination at that time revealed a central scotoma and bilaterally depressed ankle and knee jerks.

Laboratory data at that time showed a urinalysis with an albumin of three plus with good concentrating power in the urine. The urinary Sulkowich was two plus. Hemoglobin was 11.7 grams per hundred cc's. There was a normal white and differential count. The sedimentation rate was 92 mm/hr., the sodium 131 meq/l. The potassium was 4.9 meq/l. The chloride was 96 meq/l. Blood urea nitrogen was 48 and creatinin was 2.9 mg%. Total protein was 6.7 gm% with albumin 4.3 and a globulin of 2.4. The calcium at that time was 13.8 mg%, a phosphorus of 4.1 and an alkaline phosphatate of 11.6 K-A units/100cc. The Wasserman and LE tests were negative. The chest x-ray was negative and a bone survey was negative except for a thinning of the posterior clinoid processes of the skull.

The left retrograde pyelogram was done and this revealed dilatation of the renal pelvis. An electroencephalogram done on the day of admission revealed diffuse cerebral signs including diencephalic dysfunction. There was no lateralizing sign. The lumbar puncture showed normal cerebro-spinal fluid without cells and a normal protein content.

At this point a history was obtained of vitamin D ingestion and it was found that the patient had been taking 100,000 units of vitamin D daily for the past six weeks since the onset of knee pain in July. On intravenous feedings and low calcium diet she improved remarkably. A repeat electroencephalogram done on the second day was essentially within normal limits. The blood urea nitrogen increased to 60 mgm per 100 cc. during the first hospital week. It then fell to 24 before discharge.

At the time of her discharge the serum calcium was 12.5 mgm %. The patient continued to do well after discharge until three weeks before her second and last admission on December 29, 1954. Lethargy recurred and this was accompanied by anorexia, constipation, weight loss and pain in her left shoulder.

Physical examination at that time revealed a lethargic woman who appeared chronically ill. The temperature was normal and an irregular freely movable mass, 3 by 7 centimeters was noted in the left axilla. A rubbery lymph node was noted in the right supraclavicular area and the left upper quadrant mass appeared to have increased in size.

The liver edge was palpable one finger below the costal margin. There was tenderness over the lower cervical and upper thoracic vertebrae. The BUN at this time was 25 mg%, the sedimentation rate 91 mm/hour and the hemoglobin 10.5 gm%. The white count at this time was 9,700. There were 51% polys, 24% lymphocytes, 20% normocytes and 5% eosinophils in a peripheral smear. The platelet and reticulocyte count were normal. Serum calcium was noted to be 17.4 mgm %. A phosphorus at the same time was 3.1 mgm %. The alkaline phosphatate was 9.8 King Armstrong units.

X-ray of the cervical and the dorsal spine and the left shoulder were normal. A plain film of the abdomen revealed that the left kidney outline was obscured. On the second hospital day a biopsy of the left axilla was performed. A diagnosis of Hodgkin's disease was made on some of the lymph nodes removed in this fashion.

The patient remained afebrile throughout her hospital stay. Her lethargy continued. On the sixth day of hospitalization, ACTH in dosage of 60 units per day was begun. On the tenth day 100 mgm of cortisone per day was begun. At the same time x-ray therapy was

given to the left axilla, to the left upper quadrant and to the right cervical area. On the twenty first hospital day, the serum calcium had fallen to 10.1 mgm % and the serum phosphorus was 1.9. Her BUN had fallen to 19 mg%.

The patient was discharged on February 4, 1955. At that time the masses in her abdomen and left axilla had decreased in size. However, new lymph nodes were noted in the left cervical area.

She did well for a few weeks after discharge but then became febrile again. Nitrogen muscular therapy was given at home after which thrombocytopenia and leukopenia developed. She died suddenly at home two months after discharge with evidence of cerebral bleeding. No permission for post mortem examination was obtained.

In summary, a forty eight year old white female with lethargy, joint pains, anorexia, and weight loss was admitted to this hospital in 1954. She was found to have hypercalcemia with a serum calcium as high as 17.4 mgm. A diagnosis of Hodgkin's disease was established by lymph node biopsy. The patient's serum calcium was reduced to normal values by the use of steroid therapy.

Chairman King:

Dr. Bernard Schwartz makes all disturbances of calcium metabolism his hobby, so I have called on him to discuss, "Hypercalcemic Nephropathy."

Discussion

Dr. Bernard M. Schwartz:

There are at least eight clinical conditions associated with hypercalcemia. The classical one of course is hyperparathyroidism. The second one is Boeck's sarcoid. It occurs in three malignant conditions: metastic carcinoma either with or without metastases to the bone; in multiple myeloma; and, as we have seen tonight, in Hodgkin's Disease, the newest addition to the list. It also occurs in three, what we might call primarily metabolic conditions: hypervitaminosis D which occurred in our case tonight and which we will have occasion to discuss in a short while. It occurs in what is called Burnett's syndrome which results from the hyperingestion of milk and large amounts of alkali including calcium salts. And finally, it develops in a situation that is called acute osteoporosis which occurs in people who are immobilized and in whom very active bone growth is occurring at the time, such as in growing children with a fracture of the femur, or poliomyelitis, or in elderly patients with Paget's disease. Entirely apart from the diagnosis of the basic disease, the specific recognition of hypercalcemia is important for at least two reasons. One, the patient may experience very disabling and uncomfortable symptoms from the hypercalcemia *per se* and secondly, and more important, any hypercalcemia which is prolonged for a sufficient length of time is accompanied by renal damage, and if this renal insufficiency persists long enough, by irreversible renal failure.

Another reason for attempting early diagnosis of hypercalcemia is that when severe renal insufficiency occurs, the high blood phosphorus which accompanies increasing azotemia will cause a lowering of the previously elevated blood calcium towards normal levels. Further, in the very late stages of the disease the previous hypercalciuria which accompanies the hypercalcemia will be reduced to normal. Thus the presence of a normal calcium in the urine and

a normal blood calcium may mask the fundamental and underlying reasons for the patient's renal insufficiency.

At times, the differential diagnosis of these conditions may be extremely difficult, especially when combinations of them occur. Generally, the various ancillary clinical features that accompany them make the differential diagnosis relatively easy if seen early enough.

Probably more difficult, however, is the recognition of the hypercalcemia, either when it arises de novo or when it arises as a complication of one of the diseases where it is a secondary manifestation. This does not present so much of a problem in a general hospital where many laboratory facilities are available, as in the physician's office.

It therefore would be valuable to review the specific signs and symptoms of hypercalcemia. The first group of symptoms consists of lack of muscle tone, (the reverse of what occurs in tetany with a low blood calcium), lethargy, weakness and obtundation, as we have seen in the patient presented tonight. Even disturbance of gait can occur from the weakness and the lack of muscle tone. All these symptoms may focus the physician's attention on a primary disorder of the central nervous system.

The second set of symptoms revolves about the gastro-intestinal tract. Patients may manifest constipation, occasional diarrhea, but more commonly anorexia, nausea, vomiting. The lack of intake is accompanied sometimes by quite profound weight loss amounting to 20, 30, or more pounds.

The attention of the clinician in this instance is focused upon the gastro-intestinal tract and it is not surprising that these patients have been sent to gastroenterologists.

The situation is further complicated by the fact that in a number of these conditions, it appears that duodenal ulcer is quite common; for example, in hyperparathyroidism. When the diagnosis of duodenal ulcer is made or is suspected, the use of the classic treatment of large amounts of milk and alkali including calcium salts will only aggravate the hypercalcemia.

When calcium is elevated in the blood for a long period, it will tend to be deposited in various organs of the body. In certain situations such as the lung or the mucosa of the stomach and even in the media of the arteries, this does not usually produce clinical symptoms. However, there are two places where the deposits may become clinically evident. One is in the cornea of the eye where the so-called band keratosis or band keratopathy occurs. One usually needs a slit lamp to see these lesions but there have been instances where ocular lesions have been observed with the naked eye.

Finally, the persistent hypercalcemia may lead to renal damage, as we have heard, with polyuria and other symptoms. The hypercalcemia can affect renal functioning in several ways. For one, early in the course it is accompanied by increased rates of calcium excretion in the urine. This will often lead to the precipitation of renal stones. In the wake of renal stones, the urine frequently becomes infected and pyelonephritis may follow.

It is also true that even in the absence of renal stones these patients have a

greater propensity than normal to develop pyelitis, and it frequently is the pyelitis which is the factor that will cause the patient's demise rather than the underlying disease.

The second mechanism is the deposition of calcium in the parenchyma of the kidney, particularly the renal tubule. It is accompanied by what is called an interstitial nephritis, and apparently finally glomerular function is involved so that these people get the classical picture of renal failure with a fixed urinary specific gravity of 1.010, decreased PSP excretion, and elevated blood urea nitrogen.

The time at our disposal doesn't allow us to discuss all the conditions mentioned but I think if we discuss one or two of them, we may bring out some salient points.

A very interesting condition particularly in the light of the keynote of tonight's program, which is reversibility, is the hypercalcemia which accompanies Boeck's sarcoid. In different series it is reported that hypercalcemia occurs in Boeck's sarcoid in from 20 to 45 per cent of the cases. The blood calcium elevation is not usually accompanied by a low blood phosphorus nor elevated alkaline phosphatase as in hyperparathyroidism. It bears no correlation to the degree of bony involvement in Boeck's sarcoid. It bears no correlation with the level of the serum globulin. There are some studies that appear to indicate that very probably, since there is an increased intestinal absorption of calcium and phosphorus from the intestinal tract, there may be a vitamin D like substance created in this disease.

In a recent review of ten cases of Boeck's sarcoid accompanied by hypercalcemia, some important points about therapy were brought out. In every one of the ten cases, each of whom had a fixed urinary specific gravity of 1.010, the administration of steroid hormones resulted in a fall of the blood calcium to normal in a very short period of time, within two to three weeks. In a number of cases there was no further recurrence of the hypercalcemia even though the steroids were stopped after a relatively short course. Some patients were given the drug for other reasons, or perhaps for this reason, for a long period of time; but in many cases where the steroid therapy was stopped there was no recurrence of the hypercalcemia after as long a period as two years. In two other patients, one had a recurrence after eighteen months and another had a recurrence after two years both of which again responded to the steroids.

The response of the kidney function, however, was a little different. In general, one may say that the return of the kidney function was dependent upon the degree of involvement that existed at the time when meticorten was started. In the two patients where the urea nitrogen was already over a hundred, despite the fact that the serum calcium returned to normal, the patients went on to progressive uremia and died.

On the other hand, of three patients with a fixed urinary specific gravity and decreased PSP secretion with only moderate elevation of the urea nitrogen, complete restitution of renal function occured in two. In one, however, it took

three months and in one, two years. There were a few patients with moderate degrees of urea elevation who had some improvement in renal function but who never did return completely to normal.

Another interesting aspect of the Boeck's sarcoid cases, as in some of the other conditions we have mentioned, is their hypersensitivity to vitamin D. Smaller dosages of vitamin D than ordinarily would produce toxicity will cause a great exacerbation of the hypercalcemia in these people, which fact reminds us of the case that was discussed this evening where the same phenomenon occurred. This woman had received 100,000 units of vitamin D for six weeks whereas ordinarily the classical cases of vitamin D intoxication occur only after 150,000 units over much longer periods of time. We may presume here that the tendency for the hypercalcemia in Hodgkin's disease made her hypersensitive to this vitamin.

This patient, by the way, is one of the first two patients to be reported in the literature with the association of Hodgkin's disease and hypercalcemia, as reported by Drs. Kabakow and King of this hospital. It is too early to know whether the hypercalcemia associated with Hodgkin's disease will always be associated with bony lesions or whether as in Boeck's sarcoid and in some of the metastatic malignancies, it will occur with extra-skeletal lesions as well.

As a last word, I might say that in patients with unexplained lethargy, unexplained central nervous system manifestations, unexplained gastrointestinal symptoms, especially with some suggestion of renal involvement, one should bear hypercalcemia in mind. The urine Sulkowich test is one of the simplest tests in medicine and if it is performed, especially in association with a blood calcium where indicated, the results can often be very rewarding.

Chairman King:

I think it is to the everlasting credit of Lucké who is a pathologist at the Army Medical Museum, that he had the clinical insight to appreciate the fact that tubular damage occurred in association with progressive renal failure in the so-called Crush syndrome. He had the perspicacity to realize that many other clinical conditions would cause the same pathological lesions and among them he mentioned transfusions with incompatible blood, sulfonamides, intoxications of various things and various poisonous agents. These were recognized by him early as contributing or causing the same lesions known to be associated with the Crush syndrome. And I think likewise that it is no discredit to Lucké that subsequent investigations notably by Oliver have shown that the pathological lesion is not necessarily localized to the lower nephron. I think, as a matter of fact, it is questionable whether the term "lower nephron nephrosis" is actually descriptive or as a matter of fact is on firm foundation at all.

And yet the term has come to mean certain things to most clinicians, and so for the purposes of this evening, we have retained the term "lower nephron nephrosis". As the last case we will have Dr. Marshall Levy present this case of Lower Nephron Nephrosis which followed transfusion.

LOWER NEPHRON NEPHROSIS

Case Report

Dr. Marshall S. Levy:

This is a case of a 25 year old white woman who, three years prior to her present illness, had had a Cesarian section during which she was given a unit of blood. On December 21, 1956 she was admitted to a local hospital to have a D & C for vaginal bleeding during the third month of her second pregnancy. On the operating table she was given a unit of whole blood. This seemed to be followed by increased bleeding. Following a second unit she developed chills, hemoglobinuria, and eventually severe oliguria. Subsequently, anti-Cellano and anti-Kell antibodies were found in her serum.

During the next week her daily urine output was under 100 cc and her hemoglobin fell to 8.5 gm%. Azotemia began to develop. Despite the fact that her general condition and spirits were good, she was transferred to The Mount Sinai Hospital on the ninth day of oliguria for treatment of her renal failure. Laboratory findings on arrival included hemoglobin 8.2 gm.%, hematocrit 24%, BUN 164 mg.%, and the urine output for the first 24 hours was 200 ml.

On the eleventh day her BUN had risen to 220 mg.%, her hemoglobin was down to 7.4 gm.%, but her urine output was beyond the oliguric phase since she was excreting a liter per day. On the twelfth day her hemoglobin was 6.1 gm.%, and after she had a bout of pallor and vomiting that day a later hemoglobin determination revealed a fall to 4.2 gm.%. This was over a ten hour period.

Antibiotics and Sparine were given at this time and prophylactic Dilantin was started. Despite the severe anemia she produced 1500 ml. of urine that day. On the thirteenth day her hemoglobin was 2.7 gm.%. The clinicians were desperate. They called blood banks throughout the country to find some Cellano and Kell negative blood. On day thirteen her BUN reached a peak 250 mg.% and the 24 hour urine output was 2000 ml. On this day 175 ml. of whole blood was given despite the fact it was demonstrated to be incompatible by the indirect anti-globulin matching method. This was followed by chills and hemoglobinuria. The diuresis was unaffected and the BUN continued to fall. Intravenous hydrocortisone was started.

On the fifteenth day when her BUN had fallen to 200 mg.%, the urine output was almost 4000 ml. and the hemoglobin concentration was 2.2 gm.%. At last the outside requests for compatible blood brought a response. A donor was found in San Francisco, one in London, and two in Boston. Of these four units only one from a 125 lb. Boston woman was compatible. Five hundred ml. of this donor's blood did not produce a measureable rise in our patient's hemoglobin which was down to 1.3 gm.% two days later. The same donor graciously gave another 300 ml. which produced a rise in the patient's hemoglobin to 2.2 gm.%. Urine output at this time was well over 4 liters a day.

On the nineteenth day she developed symptoms of congestive failure and was subsequently digitalized with intravenous Digoxin. The BUN had fallen to 48 mg.%. Her Boston friend was called upon again; she gave another 300 ml. The patient's reticulocyte count had been about 4% up to the nineteenth day. On the twentieth day it was 40% of her 980,000 rbc/mm^3. This was the start of a rapid erythropoiesis.

Hyperkalemia was never a problem. She did develop some fleeting angina with S-T depressions in lead I, II, and the chest leads but this lasted only a few hours. With the onset of the reticulocyte response she rapidly improved over the next three weeks. The BUN was 12 mg.% and the hemoglobin was 7.4 mg.% at the time of discharge.

Concerning treatment, the fluids during the oliguric phase were restricted to the volume she put out as urine plus vomitus, or up to 400 ml. more than that. She developed no edema or dehydration. The fluids given were usually in the form of about a third isotonic saline or sodium lactate; the remainder of the solute was glucose in distilled water. She remained normotensive throughout her illness.

Chairman King:

No mention is made of the donor's hemoglobin.

I call on Dr. Levitt to close this conference with a discussion of lower nephron nephrosis.

Discussion

Dr. Marvin F. Levitt:

You have been so completely harangued by this time that I think we're going to limit our comments to a few relevant ones relating to the therapy of renal failure and to the importance of the ischemia in the development of renal failure.

First, as this patient demonstrates, the conservative therapy of renal failure is simply the replacement of the solute and water which is formed. During the solute diuresis, she was given salt and water in approximately one-third isoosmotic concentration, in a volume comparable to what she was losing. As during the oliguric phase, no attempt was made to force her fluid intake. The fluid output was defined by the fact that nephrons were beginning to operate, and this quantity was simply replaced, with the understanding that this urine contained large quantities of solute because her tubules were not absorbing salt. Salt and water were replaced in a volume equivalent to what she was losing.

Another very important consideration that I think this patient demonstrates so clearly is the problem of correcting the anemia. I think it should be reassuring to see this fabulous polyuria occur in the face of a mean hemoglobin concentration under three grams per cent. And I think I'm understating it when I say her mean hemoglobin concentration was under three. It was probably under two grams per cent, but I would like to emphasize that anemia per se does not produce any untoward effect on renal function. Possibly this remarkable resistance of the kidney to anemia is a consequence of the fact that the kidney has the lowest oxygen extraction ratio of any organ in the body. The kidney has not one fraction of the vulnerability to anemia that characterizes the heart and to some extent the brain.

The indications for the use of blood in the management of renal failure should largely be the development of symptoms due to the anemia per se. The organ which fails most quickly when the anemia becomes severe is the heart. Generally, it is the manifestation of heart failure or angina which conditions the need for blood. Actually there was only one tense night with Lorraine when she had a hemoglobin somewhat under $1\frac{1}{2}$ grams per cent, and she complained of a little pain in her chest. Of course the fact that her coronary arteries were widely patent proved helpful.

This type of renal failure represents a form which is precipitated by reduced renal perfusion. Dr. King, earlier in the evening emphasized that the one common denominator which underlay the development of "lower nephron nephrosis" is a variety of different etiological factors reducing renal perfusion. Whether that factor be a reduced cardiac output, or a reduced circulating volume, or

hypotension or the release of free hemoglobin, or the sudden development of hypotension due to heart disease or pulmonary embolism, the one underlying factor which tends to destroy kidney functions is ischemia. Although a patient like this is a very dramatic one, and represents the sudden development of renal failure in a previously normal patient, this development of ischemia is far more important when it is superimposed in patients with renal disease.

The subject with renal disease is exquisitely sensitive to any superimposed ischemia. Any factor which will reduce his renal blood flow, be it a coronary thrombosis, reduced cardiac output, a retrograde pyelogram, salt depletion, or possibly infection; any such factor, in a patient with underlying renal disease, makes him vulnerable to the superimposition of a picture of lower nephron nephrosis.

In the management of patients with renal failure, a vital factor is the avoidance of any stimulus which will reduce the level of renal blood flow. Although a dramatic incident like the one presented here would demonstrate how ischemia can produce lower nephron nephrosis in a perfectly normal woman, this phenomenon is far more relevant and frequent in patients with underlying renal disease.

Radiological Notes

Edited by

BERNARD WOLF, M.D.

THE USE OF A FRACTIONAL FOCUS FOR SPOT RADIOGRAPHY ENTRANCE AND EXIT DOSES AT "HIGH KV"

(With the Assistance of Sergei Feitelberg, M.D.)

In a previous note, the usefulness of the so-called fractional focus (0.3 mm. x 0.3 mm.) for spot ("aimed") radiography of infants and young children, especially during barium meal and barium enema examination was described. The detail achieved under these circumstances was easily comparable to conventional radiography. It was pointed out that extension of the technique to adults (except in the chest) presented difficulties because of the relatively low output of the x-ray tube. The effort was nevertheless made to extend the technique by making the following changes: (a) The voltage applied to the tube was increased from the maximum conventional peak kilovoltage of 90 to 125; (b) a "wave smoothing" device was incorporated into the circuit in order to approach constant voltage; (c) the milliamperage was increased to 30 milliamperes; (d) more sensitive, fast screens and x-ray film were used. Unfortunately, to obtain satisfactory contrast at 125 KVP, it was necessary to use the equivalent of a 14 to 1 grid. Moreover, the use of fast screens and fast film to some degree viciates the increased detail obtainable from a fractional focal spot. It was found nevertheless that more satisfactory films could be obtained with the fractional focal spot but that the time of exposure had to be increased in general by about 50%. It is therefore not feasible to obtain films in the abdomen of heavy adults in oblique or lateral positions without prolonging the time to a point where motion, particularly of the duodenum, produces undesirable blurring. In this investigation, the added aluminum filtration in each case was 2 mm. of aluminum and for comparison, conventional spots taken at 90 kvp, 190 milliamperes and 8 to 1 grid were used.

The utilization of higher kilovoltages and more constant potential for spot radiography should also make possible a decrease in the radiation exposure of the patient for equivalent radiographic results. This was investigated with a masonite phantom 6½ inches thick. With a field size of about 10 inches square, the entrance and exit doses were measured with a 25 r Victoreen condenser r-meter as a function of various thicknesses of added aluminum filtration. The results of these experiments are indicated in Fig. 1. The findings indicate that approximately the same exit dose was required in order to obtain spots of similar quality but that the entrance dose could be reduced to two-thirds. These figures refer to the factors quoted above used for comparison of the radiographs, that is, 125 kvp, 30 milliamperes and a 14 to 1 grid was used while at 90 kvp, an 8 to 1 grid and 190 milliamperes were used. At this latter milliamperage, the wave smoothing device has little if any effect. Fig. 1 also demonstrates that a slight further decrease in radiation exposure can be obtained by increasing the added

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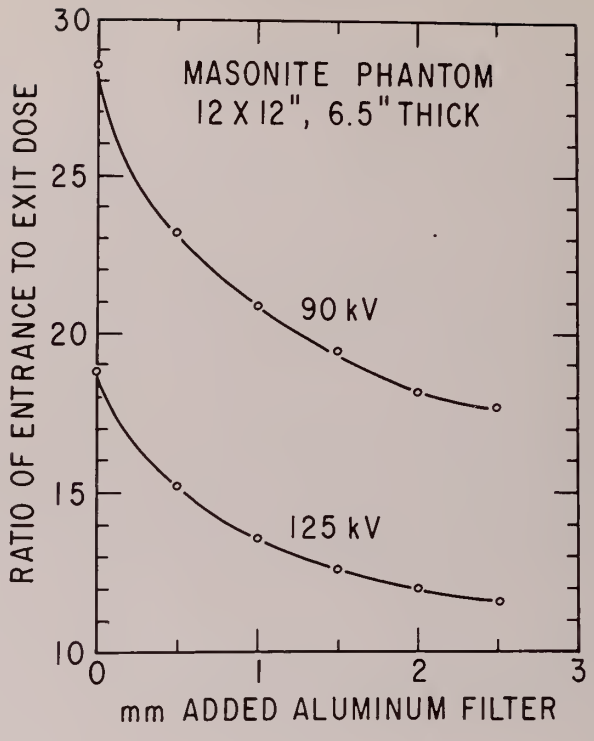


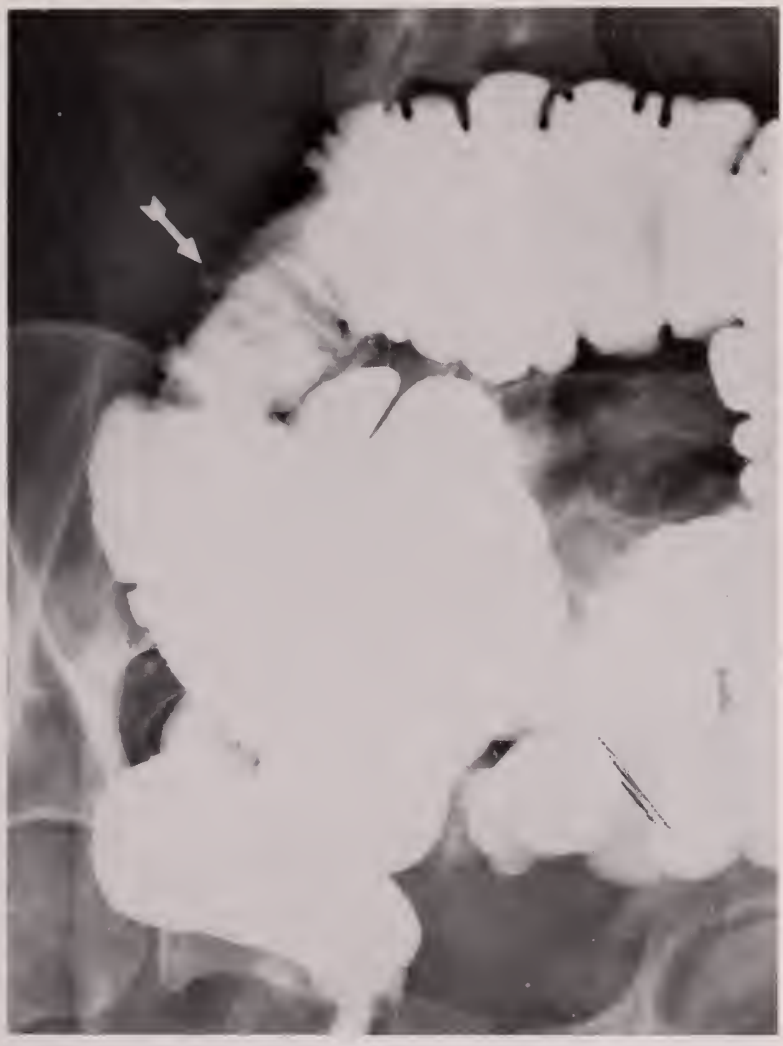
Fig. 1

aluminum filtration to 2½ or 3 mm. It was also of interest that the entrance to exit dose ratio with the fluoroscopic factors used, that is 90 kvp, 3.5 milliamperes, 2 mm. aluminum, with the wave smoothing device in the circuit, was 15, that is, about midway between the curves of figure 1. The actual table-top output (with backscatter) was 9.4 r per minute; target-table top distance was 18 inches, field size (exit) about 8 by 8 inches.

CASE NO. 48

Barium enema examination (Figs. 1A, 1B) on a 39 year old female was performed without incident and demonstrated a segment 2 to 3 inches in length in the ascending colon with limited distensibility and a markedly ragged contour, particularly posteriorly on its medial aspect. The transition between this area and adjacent portions of the colon appeared to be fairly abrupt. A normal haustral pattern was not evident but instead transverse folds and multiple haustreolae were demonstrated. The area did not appear to be rigid and there was no associated intraluminal filling defect or any remarkable spasm. On close examination of the films (Fig. 1B), it could be noted that barium had entered the appendix which was directed upwards behind the colon; the tip of the appendix was not definitely visualized but had to be located in the region of the involved segment of colon.

The history on this patient in combination with the roentgen findings was



Case 48, Fig. 1A. Film from the barium enema examination with the patient prone in the right anterior oblique position shows a segment 2 to 3 inches in length in the ascending colon with limited distensibility and a markedly ragged and irregular contour posteriorly. The normal haustral pattern is absent but fairly thick transverse folds can be seen traversing the lumen. This segment appears to begin and end rather abruptly but there are no overhanging edges. An intraluminal filling defect is not present and there is no remarkable spasm. Arrow points to a markedly shaggy mucosal pattern without ulceration or rigidity, indicative of mucosal congestion and inflammation.

diagnostic. Three weeks prior to admission, she began to complain of right lower quadrant pain which had increased progressively in severity. In the two days prior to admission, temperature had been between 101 and 103°. There was no history of nausea, vomiting or diarrhea. On physical examination, a grapefruit size mass was palpable low on the right side of the abdomen. Rectal and pelvic

Case 48, Fig. 1B. Film taken after evacuation of the barium and injection of air shows limited distensibility of the medial aspect of the involved segment in the ascending colon. Small haustra or haustreolae are present along the lateral contour of this segment but the medial contour is jagged. The arrow points to the filled appendix located behind the ascending colon and directed towards the involved segment. Incidentally, the "fat" lines of the abdominal wall adjacent to the involved region of the colon are indistinct but the significance of this is difficult to judge.

examinations were negative. Blood count prior to admission was 20,000 but came down to 7,200 with 76% polyps at the time of admission. With antibiotic therapy, the patient improved and the mass decreased in size. The patient was discharged to return for interval appendectomy.

Three months later, laparotomy was performed. The appendix was found to be retrocolic and its tip was adherent to the ascending colon. At this site, there were remnants of a previous abscess with yellowish granulation tissue adherent to the colon. Appendectomy with drainage was performed.

Final Diagnosis: APPENDICEAL ABSCESS INVOLVING THE WALL OF THE ASCENDING COLON.

CASE NO. 49

Barium meal examination on a 47 year old female showed no evidence of any intrinsic lesion of the stomach or duodenum. However, (Fig. 1) the duodeno-jejunal flexure appeared to be lower than usual and moreover was straightened and horizontal instead of showing the usual graceful curve convexity upwards. This area appeared to be abnormally fixed since it remained in the same location in all positions of the patient. The mucosal pattern of this segment was intact and there was no evidence of any delay in the passage of barium.

This patient complained of episodes of abdominal pain for 8 months prior to

Case 49. Fig. 1. Film from the G.I. series with the patient prone shows the duodeno-jejunal region (arrow) to be depressed, compressed and abnormally straight and horizontal. The mucosal pattern in this area is intact and there was no evidence of any delay in the passage of barium through this site. Comparison of films taken in different positions showed that there was no mobility of the duodeno-jejunal flexure.

admission. An x-ray examination taken elsewhere was said to have demonstrated a gastric ulcer. The patient improved somewhat on an ulcer regime and a repeat G.I. series showed no evidence of gastric ulceration. The pain nevertheless recurred, mostly on the left side of the epigastrium, and radiated to the back. The patient also began to complain of anorexia and lost 12 pounds in weight.

On admission, the positive finding was a mass to the left of the epigastrium. At exploratory laparotomy, this was found to be in the body of the pancreas and biopsy was reported as adenocarcinoma.

The case is presented to emphasize the importance of visualizing the duodenojejunal flexure routinely in barium meal examinations. This may be difficult in cases in which it lies high behind the stomach. In such instances, the left anterior oblique position or right posterior oblique with the patient on his back may be useful.

Final Diagnosis: Carcinoma of the body of the pancreas depressing and compressing the duodeno-jejunal flexure.

CASE NO. 50

This was the first admission of a 65 year old, white female who was admitted with the chief complaints of abdominal pain, anorexia and a weight loss of 20 pounds. The pain was located near the umbilicus. Several months before admission, the patient began to have black stools almost daily. Barium meal examination done prior to admission suggested the possibility of an antral gastritis. Physical examination and laboratory findings were not contributory except for persistent 4 plus stool guaiac and hemoglobin of 7 grams.

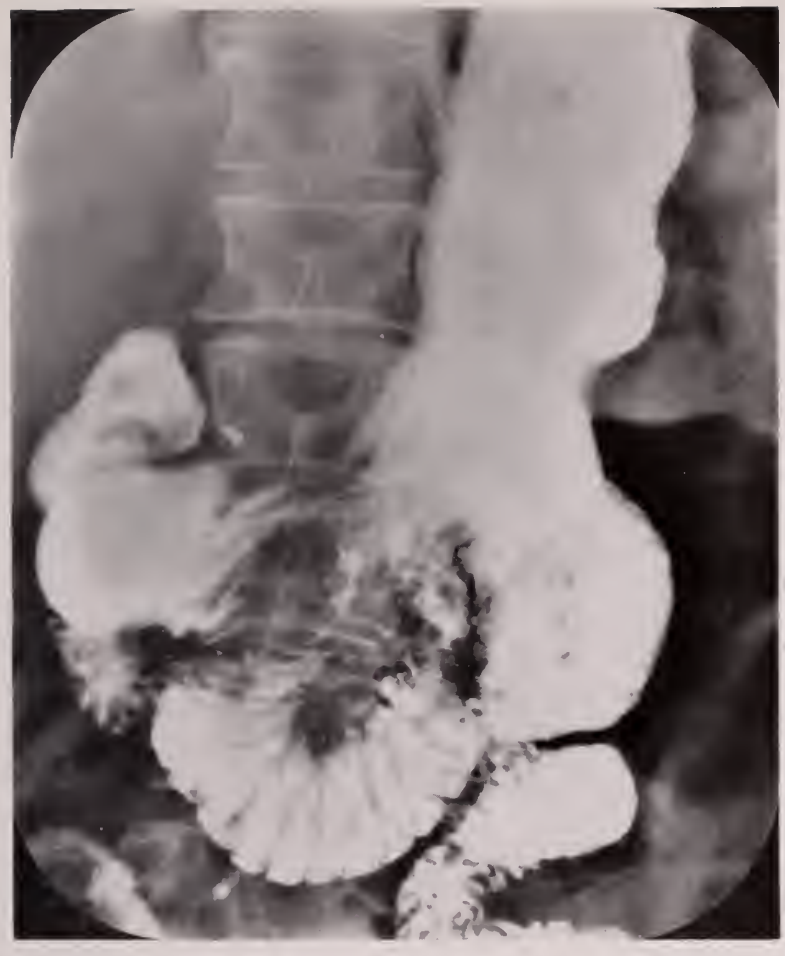
Barium meal examination demonstrated no abnormality in the esophagus, stomach or duodenum. Immediately distal to the duodeno-jejunal angle, two adjacent segments of jejunum were markedly narrowed although the mucosal pattern appeared to be intact. Evidence of a mass in the same area was indicated by the fact that, with the patient prone, a pad-like defect was present on the body of the stomach anterior to the spine. There was no delay to the passage of barium through the duodenum or jejunum. The roentgen impression was that of an infiltrating neoplasm, not primary in the small bowel, but due either to a metastatic carcinoma or carcinoma of the pancreas.

On exploration, an infiltrating tumor was found involving the lower portion of the body of the pancreas and extending into the base of the mesentery as well as the adjacent portion of the jejunum, located about 2 inches distal to the ligament of Treitz. Many retroperitoneal nodes were present around the origin of the superior mesenteric vessels. Frozen section was reported as infiltrating adenocarcinoma.

Final Diagnosis: Carcinoma of the body of the pancreas infiltrating two loops of proximal jejunum.

CASE NO. 51

Barium meal examination on a 40 year old female (Fig. 1A) showed no evidence of an intrinsic lesion in the stomach and barium went through the duodenum into



Case 50. Fig. 1. P-A, prone; film from G. I. series. Two segments of jejunum in adjacent loops immediately distal to the ligament of Treitz are markedly narrowed. The mucosal pattern does not appear to be destroyed. There is evidence of a mass surrounding this region as indicated by pressure on the body of the stomach in front of the spine ("pad sign").

the jejunum without difficulty. However, a peculiar distortion of the fold pattern apparently associated with a filling defect was noted in the last portion of the duodenum immediately proximal to the duodeno-jejunal flexure. The patient was re-examined and spot films of this area (Fig. 1B) confirmed the presence of an eccentric defect with the superior margin flattened, rigid and the folds obliterated over about $^2/_3$ of the diameter of the lumen. The fixed irregular contour and the effacement, if not destruction, of the fold pattern as well as the discrete nature of the lesion indicated that it was neoplastic. From the roentgen point of view, however, it could not be determined whether this was a primary lesion, or the result of direct extension from a carcinoma of the pancreas, or of metastatic nature.

Case 51, Fig. 1A. Barium meal shows a peculiar localized distortion of the fold pattern surrounded by an arcuate streak of barium (arrow) immediately proximal to the duodeno-jejunal flexure.

This patient was admitted because of weakness of 5 months duration and marked anemia. One year prior to admission, the patient had undergone a hysterectomy and salpingo-oöphorectomy for an endometrial carcinoma which had been followed by radiotherapy to the pelvis. On admission, the hemoglobin was 5.4 grams. The only other positive finding was persistently positive guaiac stools. Except for the lesion described above, no other abnormality was noted in the gastrointestinal tract.

At exploratory laparotomy, a large tumor was found in the region of the duodeno-jejunal flexure which had produced an ulceration about 1½ inches in diameter in the posterior wall of the duodenum. The tumor had extended beyond the wall of the duodenum and was fixed to the lumbar spine and the left side of the aorta. A portion of the tumor including adjacent small bowel was resected and a duodenojejunostomy performed as a palliative procedure. The pathology

Case 51, Fig. 1B. On re-examination, a spot view of the same area demonstrates effacement of the mucosal pattern and a rigid, irregular, flat border superiorly (arrow). These findings are indicative of neoplastic invasion.

report was that of an infiltrating adenocarcinoma similar in histology to the original endometrial carcinoma.

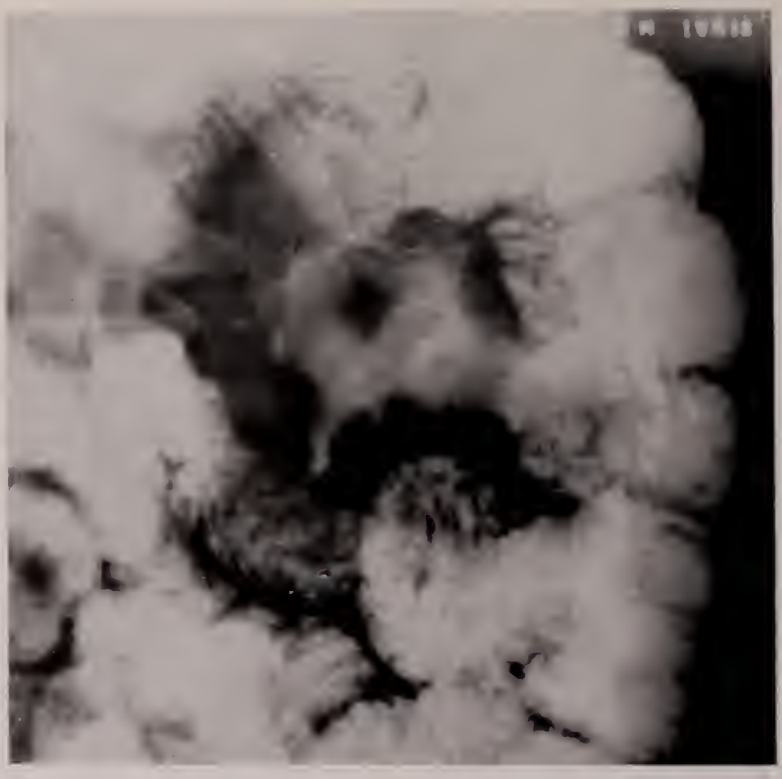
Final Diagnosis: METASTATIC ENDOMETRIAL CARCINOMA TO THE DUODENO-JEJUNAL FLEXURE.

CASE NO. 52

This was the first admission of a 40 year old white male with a two year history of abdominal pain, at first intermittent but rather constant during the 7 months prior to admission. The pain was described as burning in character and apparently had responded to symptomatic therapy on several occasions. On two occasions, barium meal examinations had been performed and were said to have been negative. The patient had lost 40 pounds in a period of about 6 months and his hemoglobin was reduced to about 8 grams. On physical examination, there was a question of a mass in the upper abdomen to the left of the umbilicus.

A barium meal examination immediately prior to admission demonstrated a lesion of the upper jejunum. This was repeated (Fig. 1) and demonstrated an irregularly ulcerated mass in the jejunum with soft tissue extension beyond the bowel displacing the adjacent loops of ileum. There was no evidence of obstruction to the passage of barium.

At exploratory laparotomy, a large, obviously malignant neoplasm of the jejunum was resected. The report from the Pathology Department was "a large



Case 52, Fig. 1. Irregularly ulcerated mass in the proximal jejunum. The mucosa is destroyed. Surrounding the central ulceration, there is a globular soft tissue mass which displaces the adjacent loops of bowel. There was no obstruction to the passage of barium.

infiltrating adenocarcinoma of the small bowel without involved lymph nodes. The possibility of metastatic carcinoma cannot be ruled out".

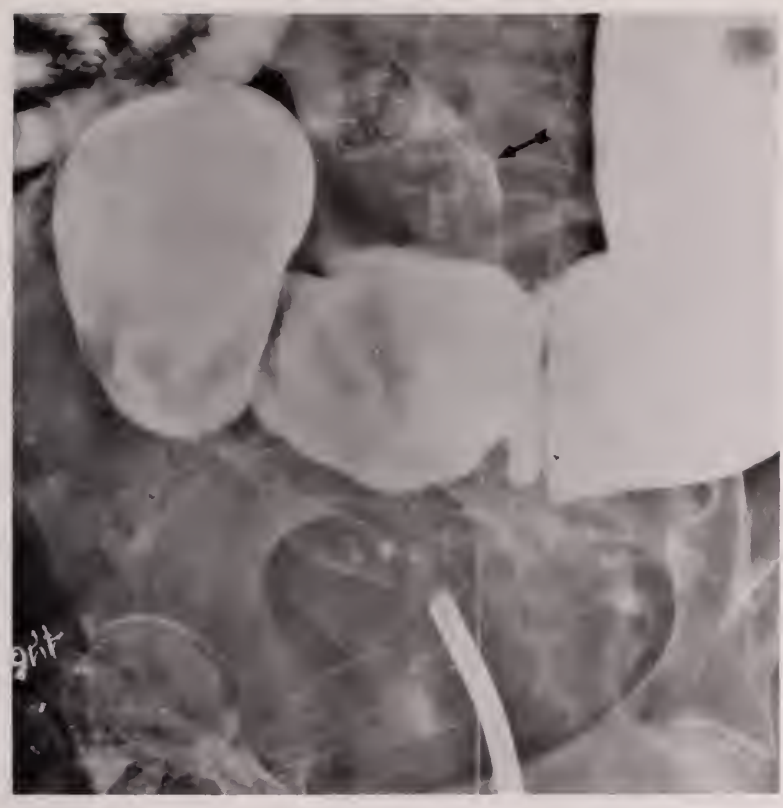
Twenty-two months after operation, this patient returned to the hospital with a carcinoma of the rectum. This appeared to confirm the suspicion of the Pathologist that the original jejunal lesion was metastatic.

The case is presented to emphasize (a) the difficulty in the detection of lesions of the small bowel and (b) the difficulty in differentiating primary from metastatic carcinoma to the small bowel, particularly the jejunum.

Final Diagnosis: LARGE ULCERATING ADENOCARCINOMA OF THE JEJUNUM—PRIMARY OR METASTATIC?

CASE NO. 53

Barium enema examination was requested on a 67 year old white female who had suffered from chronic ulcerative colitis for many years. Multiple operative procedures including finally a resection of the right side of the colon and terminal ileum with ileosigmoidostomy had been performed. She had been relatively well

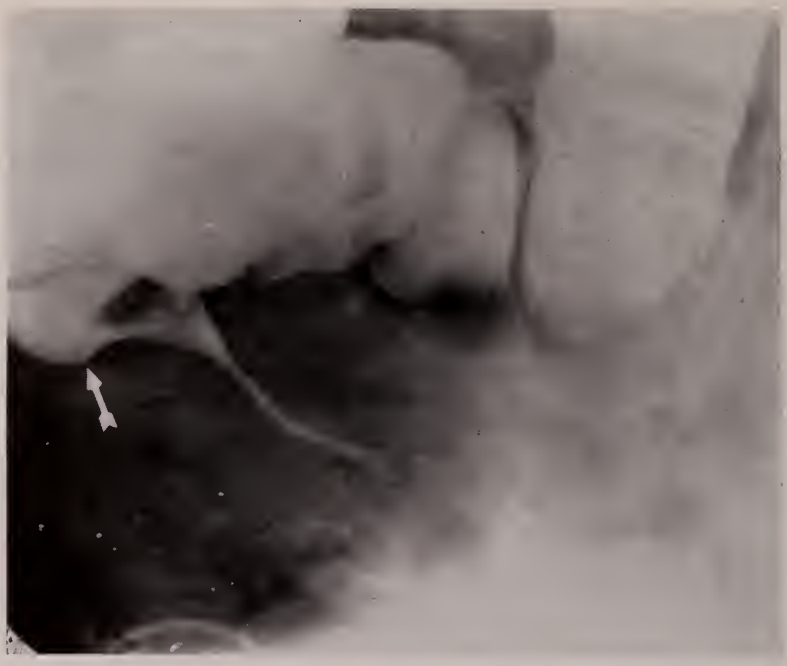


Case 53, Fig. 1A. The rectum extends upward and towards the right from the tip of the enema tube. Over a distance of about 3 inches, there is marked narrowing with an effaced mucosal pattern. The margins of this segment appear sharp and quite straight. The colon proximal to the rectum is unusually distensible and contains inspissated fecal material. A small amount of barium entered the anastomotic loop of ileum (arrow) which is narrowed or compressed on its right aspect.

for several years but two years prior to admission, diarrhea had recurred and she began to complain of rectal pain. She developed a rectovaginal fistula and became progressively emaciated.

Barium enema was done with considerable difficulty because of inability of the patient to retain barium but it was possible to demonstrate a long, rather smooth, completely strictured rectum. The bowel proximal to the stricture was dilated and contained inspissated stool; barium entered the anastomatic loop of ileum which also appeared eccentrically narrowed. At sigmoidoscopy, the rectum was markedly stenotic and said to be "typical of chronic ulcerative colitis". Biopsy was taken 5 inches from the anus and was reported, surprisingly, as adenocarcinoma.

At operation, metastatic implants were found in the abdomen. A palliative ileostomy was performed and the patient improved considerably.



Case 53, Fig. 1B. Spot film of the rectum shows very marked narrowing with funneling toward the distended colon proximally. There is a suggestion of a mass behind the rectum displacing it forward in a convex fashion. The funneling is not smoothly tapering —there is an abrupt reversal of the curvatures (arrow) at the junction of the lesion with normal bowel ("point of inflexion"). A point of inflexion of this type is characteristic of a neoplasm with marked thickening of the wall—a subtle variety of "overhanging edge."

This patient is presented to emphasize (a) the delay which often occurs in the recognition of a carcinoma of the colon in a patient who has chronic ulcerative colitis and (b) the fact that on roentgen examination, differential diagnosis from a stricture of benign or inflammatory character is difficult. It is also of interest that the correct diagnosis was not made at sigmoidoscopy confirming the spreading intramural type of growth so common in these cases.

Final Diagnosis: Diffuse spreading carcinoma of the rectum in a patient with long standing chronic ulcerative colitis.

Clinico-Pathological Conference

Edited by

FENTON SCHAFFNER, M.D.

A 31 year old white married female commercial artist was admitted to The Mount Sinai Hospital on October 28, 1957 with shortness of breath, fever and a cough.

In 1952, during a routine examination, a pulmonic diastolic murmur was heard. Fluoroscopy revealed a large pulmonary artery. While in Colorado a year later, the patient first noted shortness of breath and palpitations. At that time a left vocal cord paralysis was discovered. During the next year, the patient did well and underwent a tonsillectomy for recurrent tonsillitis. Two years prior to admission, her shortness of breath gradually increased. She coughed persistently and on one occasion coughed up about an ounce of bright red blood. Later that year her liver and spleen became palpable and a transient homonymous hemianopsia developed. In May 1956, spontaneous ecchymoses were seen. At that time a platelet count was normal but a tourniquet test was positive. The patient complained of chest pain and ankle edema three months before coming to the hospital. The diastolic murmur was louder and an apical systolic murmur had appeared. On October 1, 1957 she experienced fever, muscle aches, increasing dyspnea and ankle edema. She had a positive hepatojugular reflux and was treated with penicillin, Mercuhydrin® and, for the first time, digitalis. She improved until three days before admission when she again noted fever, muscle pains, cough productive of yellow and bloody sputum, severe shortness of breath and weakness. She was treated with penicillin, streptomycin and mercurial injections without improvement. Throughout this febrile illness, examination of the lungs was normal.

Family history: In 1952 the patient's mother was admitted to The Mount Sinai Hospital because of shortness of breath, edema and abdominal swelling. The mother's symptoms dated back four years when she first experienced shortness of breath on exertion. These symptoms progressed and by the time of her admission she had anasarca. Six paracenteses were performed during the months prior to her admission. Two Papanicolaou smears of the ascitic fluid were reported positive for malignant cells but cell blocks were repeatedly negative. On admission the mother had distended neck veins with a positive hepatojugular reflux and systolic pulsations of neck veins and liver. Her heart was markedly enlarged. P2 was accentuated. A2 and M1 were normal. Faint systolic murmurs were heard over the pulmonic and aortic areas. The abdomen was tense with ascitic fluid. After paracentesis the liver was felt a handbreath below the right costal margin. No other organs or masses were felt. Pelvic examination was normal. The significant abnormal laboratory data during the mother's hospitalization were as follows: A/G ratio 3.0/3.5, bilirubin 1.7 mg%, urine urobilinogen 1:80, alkaline phosphatase 32 KAU, cephalin flocculation 2+, prothrombin time

From the Department of Pathology, The Mount Sinai Hospital, New York, N. Y.

17.5 13 seconds (patient control), thymol turbidity 8.0 units, BSP 43 per cent, and venous pressure 240 mm with a rise over the top of the manometer with right upper quadrant pressure. Circulation time was 23 seconds arm-to-tongue. Electrocardiogram showed right ventricular hypertrophy. Chest x-ray revealed the heart to be considerably enlarged and globular with a prominent pulmonary artery, the configuration suggesting the possibility of an inter-atrial septal defect. Paracentesis fluid was negative for tumor cells. The mother experienced chest pain and hemoptysis, leading to shock and death five days after admission.

Physical examination: The patient was a well developed, well nourished, young white female in acute distress owing to a persistent brassy cough, shortness of breath and orthopnea. Temperature 103°; pulse 104, regular but weak; respirations 32; blood pressure 85/70 in both arms. Cyanosis of the lips and nail beds was present. The head, eyes, ears, nose and throat were normal. The neck veins were distended. A markedly positive hepatojugular reflux was seen with systolic pulsations of the neck veins. The chest wall and diaphragms moved well. The lungs were clear to auscultation and percussion. The PMI was palpated in the fifth intercostal space 2 cm. left of the midclavicular line. A forceful systolic impulse was felt midway between the apex and the left parasternal border. There was a gallop rhythm. P2 was markedly accentuated; M1 and A2 were normal. A grade III blowing apical systolic murmur, a grade II soft prolonged pulmonic diastolic murmur, and a grade II soft pulmonic systolic murmur were heard. The liver was felt one fingerbreadth below the right costal margin. All peripheral pulses were palpable and no edema was seen.

Laboratory data: Hgb. 14.6 G., WBC 21,600, segmented neutrophils 57%, bands 16%, lymphocytes 21%, monocytes 4%, atypical lymphocytes 2%, BUN 42 mg.%, blood sugar 95 mg.%, A/G ratio 3.2/3.4, antistreptolysin-O titer 166 units. Influenza hemagglutination titers were as follows:

Group A	NY-3 (1953)	1:160
	Denver (1957)	Neg.
	MSH-1 (1957)	1:160
	Far East (1957)	Neg.
	R.E. MSH	Neg.
Group B	B-G1	Neg.

Electrocardiogram showed marked right ventricular hypertrophy. X-ray of the chest showed an increase in the prominence of the pulmonary vessels. At the level of the third right interspace, there was a band-like density. The heart was enlarged with rounding of the ventricular contour. The aortic knob was small. The right atrium seemed prominent as in an interatrial septal defect.

Course: The patient was treated with Chloromycetin®, streptomycin, penicillin and digoxin. She continued febrile. Her respiratory distress and cyanosis increased and she ceased breathing 48 hours after admission.*

Dr. Charles Friedberg: This is apparently a two-in-one case. The major prob-

* This case and that of the mother will be published in greater detail by Dr. Joseph Kuh.

lem is concerned with a 31 year old white married female commercial artist who was admitted with cough, shortness of breath and fever. The date, October 28, 1957, may have some bearing because of the prevalence of respiratory diseases, especially influenza.

During a routine examination at the age of 26, a pulmonic diastolic murmur was heard and fluoroscopy revealed a large pulmonary artery. Some findings have a bearing out of proportion to anything else that is stated. Such a finding is the one about a pulmonic diastolic murmur, which may imply pulmonic valvular insufficiency in the sense of intrinsic valvular disease, but is extremely rare. As a rule, this finding denotes pulmonary insufficiency associated with pulmonary hypertension.

We then have to determine the nature of the pulmonary hypertension and whether it is primary, or secondary to congenital heart disease with left-to-right or combined shunts, or to intrinsic pulmonary disease such as sarcoidosis or to pulmonary vascular disease.

In 1953 a left vocal cord paralysis was noted. While that can be due to a variety of causes, in this instance where we already have reason to suspect pulmonary hypertension, we have to assume that a very large pulmonary artery is compressing the recurrent laryngeal nerve supplying the left vocal cord.

She noted a persistent cough and on one occasion coughed up about an ounce of bright red blood. In the absence of anything to suggest a febrile infectious disease, this could possibly denote a pulmonary infarction or some other pulmonary vascular obstructive lesion. Recurrent thrombosis of the pulmonary vessels or recurrent embolism also may be responsible for pulmonary hypertension. Furthermore, thrombosis indirectly can be part of the syndrome of pulmonary hypertension and narrowing of the vessels.

In 1956 spontaneous ecchymoses were seen and one asks whether that denotes some hematologic disease for which we have no additional data. Pulmonary hypertension can occur as a result of thrombosis due to schistosomiasis in the lungs. We have no evidence that this was seriously entertained or investigated.

Three months before admission, the patient complained of chest pain and ankle edema. Examination revealed that the diastolic murmur was louder and an apical systolic murmur had appeared. We might then begin to wonder whether we are now dealing with heart failure with a functional tricuspid regurgitation accounting for the systolic murmur.

On October 1, 1957 she experienced fever, muscle aches, increasing shortness of breath and ankle edema. We now come to the final illness of a few weeks before her admission to the hospital. She was treated with penicillin, Mercuhydrin® and, for the first time, digitalis; in other words, a combination of drugs for infection and for congestive heart failure.

She was admitted with what sounds like some pulmonary infection, possibly pulmonary infarction, at a time of the year when pneumonia is prevalent, in addition to a suggested pulmonary hypertension.

The family history is of interest. We have a story that the mother had evidence

of right heart failure and with an accentuated P2, perhaps something related to the type of disease we are encountering in the daughter.

The significant abnormal laboratory data during the mother's hospitalization were hypoalbuminemia and moderate hyperglobulinemia with reversal of the A/G ratio, elevation of serum bilirubin and urinary urobilinogen, increased alkaline phosphatase, BSP retention and an elevated venous pressure which rose over the top of the manometer with right upper quadrant pressure.

All this evidence of right heart failure and abnormal liver findings theoretically could mean intrinsic hepatic disease. In the presence of advanced right heart failure, there is no reason to invoke liver disease because all these findings could result from an extremely congested liver in a patient who has sufficient heart failure to cause tricuspid insufficiency.

The heart was described as considerably enlarged and globular with a prominent pulmonary artery, suggesting the possibility of an interatrial septal defect.

We must assume that this is only a suggestion because the configuration of the heart associated with an atrial septal defect can look very much like that associated with other conditions. The point of interest here is that again we have a picture which suggests to us that the same kind of pulmonary hypertension which we are predicating in the daughter was present in the mother.

The ascitic fluid was negative for tumor cells. The mother experienced chest pain and hemoptysis, leading to shock and death five days after admission.

I am not clear whether shock occurred as a result of the paracentesis, in which case we might not attach any specific diagnostic importance to it. On the other hand, sudden death as a result of very minor procedures is almost characteristic of primary pulmonary hypertension.

The patient, the 31 year old daughter we started with, had acute distress with a persistent brassy cough, shortness of breath and orthopnea, and not only a low blood pressure but a low pulse pressure. Whether this is due to the acute pulmonary infection or whether this is an additional evidence of the type of disease we are postulating in the pulmonary artery is difficult to say.

There was cyanosis of the lips and nail beds. Ordinarily we would have to lay more stress on the significance of the cyanosis because in cases with intrinsic or primary pulmonary hypertension, if cyanosis occurs at all, it is more likely to be of the peripheral type due to the diminished blood flow and tissue anoxia, and not to a shunting of blood as occurs in congenital heart disease with severe pulmonary hypertension. In this instance, however, the clinical history strongly suggests that the patient may have had pneumonia and, therefore, may have had some cyanosis of the lips due to that disease.

The positive hepatojugular reflux with systolic pulsation of the neck veins indicates tricuspid regurgitation due to right-sided heart failure, and such pulsations may occur in cases of pulmonary hypertension.

The fact that the lungs were clear to auscultation and percussion is quite a surprise in the light of the rest of the story because, on the basis of her cough and expectoration of bloody sputum and a fever, one would ordinarily think that at this time of the year the patient had some respiratory infection and, more specifically, pneumonia.

If these findings are correct, she probably had a lesion which was chiefly or exclusively interstitial, and perhaps this accounts for the absence of more findings.

The forceful systolic impulse midway between the apex and the left parasternal border also suggests an increase in the size and pulsation of the right ventricle, a finding associated commonly with pulmonary hypertension. The gallop rhythm is not specific but may very well indicate failure of the right ventricle, a finding encountered frequently in cases of primary pulmonary hypertension.

The white blood count was 21,600. At this time of the year, with influenza prevalent, I would have predicated that she had a viral pneumonia, which usually we expect to be associated with a normal or a low white count. This high white count makes us wonder whether this is just an exceptional finding or whether some complication exists such as a secondary staphylococcus or streptococcus infection.

The electrocardiogram showed marked right ventricular hypertrophy with the sharp peaked P waves, so-called pulmonary P waves, which are commonly found in cases of right ventricular hypertrophy and congenital heart disease. Lead V_1 shows a very prominent R, also indicative of a right ventricular hypertrophy.

The suggestion has been made, at least with the mother and perhaps also in this patient, that the x-ray film suggested the presence of an interatrial septal defect. The electrocardiogram associated with this condition is characterized by a pattern that looks like an incomplete right bundle branch block, that is, with an RSR' pattern, which is absent in this case.

X-ray films of the chest showed an increase in the prominence of the pulmonary vessels. At the level of the third right interspace, there was a band-like density.

Dr. Rabin will say a word about it.

Dr. Coleman Rabin: In the axillary region there is a triangular density which seems to occupy a small part of the lateral part of the anterior segment of the right upper lobe.

The heart is enlarged with rounding of the ventricular contour. Most striking is a prominence of the left pulmonary artery. There is apparently an increase in the vascular markings that extends almost to the periphery. Most of this is probably due to venous congestion. The periphery of the lung is not highly vascular as one might expect in instances of interatrial or interventricular septal defect. The aortic knob is small. The right atrium seems prominent.

Dr. Friedberg: In summary, the case is that of a young woman in her 20's and early 30's with pulmonary hypertension of a severe degree. That this pulmonary hypertension is not secondary to some other cause seems apparent from the absence of other findings. Interatrial or interventricular septal defects, which might give this type of x-ray finding, may be associated with concommitant pulmonary hypertension, do not seem to be likely here because of the other physical findings. For example, we might have expected that long before there was a pulmonary diastolic murmur, she would have a murmur suggesting a ventricular septal defect. It was not heard early or late although before death additional murmurs had appeared. Some of the evidence indicating that this was probably not an interatrial septal defect was discussed. There was no murmur to suggest a patent ductus although, at the stage in which the shunt is reversed,

the murmur may be atypical. Nothing is present to suggest that this patient had sarcoidosis, nor is there anything to indicate a long history of intrinsic pulmonary disease. On the other hand, we do have a woman in the age group in which this disease is most common, with a history that is very suggestive of primary pulmonary hypertension.

We do not have a story to suggest primary embolic disease which then produces pulmonary hypertension. Perhaps many of the cases we call primary pulmonary hypertension are of this kind.

Now, for the more immediate history, I think that some kind of a viral pneumonia with perhaps secondary infection to account for the marked leukocytosis was present, despite the absence of pulmonary findings on physical examination. Interstitial pneumonitis is a possibility, but that is not what the x-ray film denotes.

Before we go on with the pathology, would you say a word, Dr. Aronson, about the findings on bacteriological or immunological examination?

Dr. Betty Aronson: This patient had a hemagglutination-inhibiting antibody titer of 1:160 against the New York 3 and the Mount Sinai 1 strains of Influenza A. These are strains which have been present in the population since 1953, and approximately 65 per cent of the adults who have been tested during the current epidemic have antibody titers against these particular strains. Therefore, she is entitled, on the basis of her age and length of residence in this area, to have antibodies against the New York 3 strain.

We also received a fairly fresh lung specimen from this patient and we failed to isolate influenza from her lung. All the evidence seems to indicate that, within 24 hours after death due to influenzal pneumonia, the chances of recovering the virus from lung is very high, and this was, I believe, a 10-hour post mortem specimen. I must add that her lung suspension appears to be pathogenic in tissue culture and we have not yet been able to identify the source of this cytopathic tendency. It is non-bacterial. Even if we isolate a virus that can be identified, whether that has any etiological relationship to the disease, I cannot say.

Dr. Friedberg: Does the 1:160 antibody titer with New York 3 and Mount Sinai influenza strains mean that there was infection with these viruses?

Dr. Aronson: Yes. The patient at some time in the past four years had experience with these strains.

Dr. Friedberg: Do you find these increased antibodies in many cases?

Dr. Aronson: Yes. About 65 per cent of adults have demonstrable antibody titers.

Dr. Friedberg: Dr. Rabin, did this patient have pneumonia on the 8th day?

Dr. Rabin: In the x-ray film made at that time, the heart was seen to be enlarged to the left, but much of this is caused by the right ventricle. The pulmonary artery is large and some branches are still large, but toward the periphery there are no large pulmonary branches. On the left side, except for the main artery, all other vessels are small. This is what is seen in patients who have hypertension of the pulmonary circuit and who have diminished blood flow through the lungs.

The remainder of the picture, as far as the vessels themselves near the root are concerned, is identical with that which you will find in interatrial septal defect.

The triangular lesion in the right upper lobe is largely due to atelectasis with perhaps some consolidation of the lung. This indicates that the patient had a bronchopulmonary infection.

Dr. Richard Bader: I think that this patient had pulmonary hypertension, the cause of which is unknown. The cyanosis can be explained on one of two bases, first, on a peripheral basis, and, secondly, and only theoretically, because of the right-sided hypertension, on a right-to-left shunt. Patients can experience chest pain with enlargement of the pulmonary arteries, as occurs in pulmonary emphysema, asthma, and any congenital lesion which enlarges the pulmonary artery.

Dr. Hans Popper: At the autopsy we are interested first to examine the skeletal muscles to see if vascular changes could be demonstrated, and the vessels in the skeletal muscles were entirely normal. We saw no significant change in the bone marrow.

To paint the background for the actual disease which we are discussing, we turn first to the abdominal organs. In the colon an extensive circumscribed hemorrhage was seen which may or may not have been the result of congestion or some manifestation of shock.

Grossly, the kidney appeared entirely normal except for severe passive congestion. The vessels in the medullary portion showed acute congestion. The spleen was enlarged to more than 200 gms. with congestion and slight degenerative vascular changes.

The liver was moderately enlarged to almost 1600 gms. On the surface, congestion was seen which was not severe. The lobular architecture in general was still well preserved. Liver cells had disappeared around the central vein because of marked passive congestion but in the portal areas not too much congestion was present.

Death occurred from cardiac failure with acute and not yet chronic congestion. The heart weighed 420 gms. It had a globular appearance with a soldier's patch anteriorly. In the left heart some blunting of the apex was noted but the valves appeared entirely normal. No septal defect was found and the aorta contained no arteriosclerosis. In the myocardium there was some circumscribed or interstitial fibrosis. The right heart was markedly enlarged, thick walled and dilated. The heart muscle was of extreme thickness with flattening of the papillary muscle. Histologically, leukocytic infiltration was seen and a few cells accumulated in the vessels and were in the process of escaping from it. This is called a nonspecific type of an interstitial myocarditis in a hypertrophic heart. The right atrium was tremendously dilated. The auricular appendage was large and the tricuspid valve incompetent. The right and the left ventricles were almost equal in thickness. The pulmonary artery was dilated and revealed arteriosclerosis. On section it was very fatty with excessive fibrosis, narrowing of the muscular layer and some disappearance of elastic fibers, and appeared as though it were taken from an arteriosclerotic aorta.

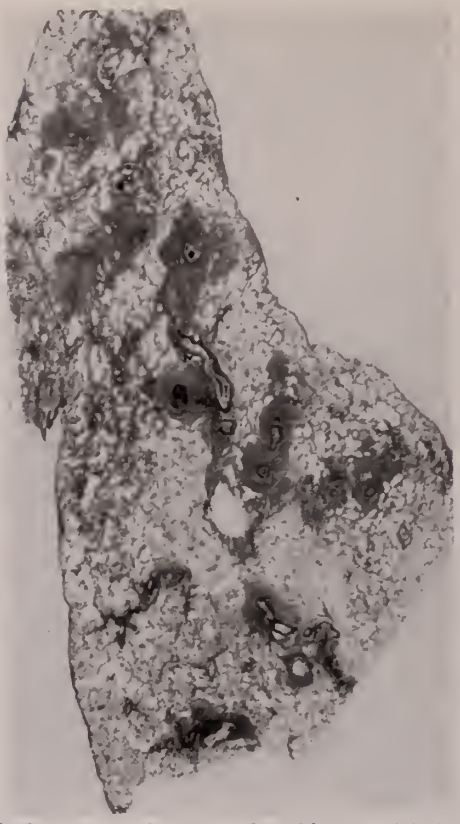


FIG. 1. Nodules in the lung parenchyma produced by arteritis (8×—chromotrope aniline blue stain).

The lung showed few changes grossly. The pleura was normal. Some emphysema was seen in the periphery. The tracheobronchial lymph nodes were somewhat enlarged. Some fat was apparently deposited within, having been drained from something which had broken down. On cut section of the lung, distinct nodularity was seen (Fig. 1). The nodules varied in size and we suspected that most of the nodules were related to vessels. In the left upper lobe, two old and probably tuberculous scars were found. The lesions in which we were most interested were the vascular ones. The round nodules were extremely thick, muscular pulmonary arteries. Smaller arteries, but still muscular, were completely fibrosed (Fig. 2).

Some arteries showed intraluminar proliferation with distinct inflammation, a severe arteritis (Fig. 3). In any other organ this would be called a polyarteritis nodosa. However, the only organ in which periarteritic changes were found was the lung and, therefore, this is pulmonary polyarteritis.

The arterial muscle fibers were disintegrated. The whole wall of the pulmonary arterial branch in some areas had fallen to pieces. Around these arteries were edema and cellular infiltration. The inflammation and fibrosis extended outward

FIG. 2. Fibrotic occlusion of small pulmonary arteries with surrounding emphysema (60×—H & E).

from the arteries into the interalveolar spaces. Such a pulmonary polyarteritis is a counterpart of polyarteritis in other organs not only in its similar histologic appearance but possibly also etiologically. We know that some instances of polyarteritis are unquestionably hyperergic, but in these instances there is involvement of the peripheral arteries and veins (1). We separate this hypersensitivity angiitis in the periphery from the real periarteritis or polyarteritis nodosa, which we now assume is not the result of hypersensitive reaction but something else. Some polyarteritis in the periphery is doubtlessly the result of increased systemic arterial hypertension.

We may have the same situation in the pulmonary circulation. In proven increased pulmonary hypertension, as in a mitral stenosis or secondary pulmonary hypertension, this picture can be produced (1, 2). In this case we have a primary pulmonary hypertension because we were unable to find any changes in the heart to explain it, and it, therefore, must originate in the lungs.

In a later stage of the lesion, near a bronchial artery, many vessels were seen between the pulmonary arteries and the bronchial arteries. These vessels came partly from granulation tissue and were probably not newly formed around the

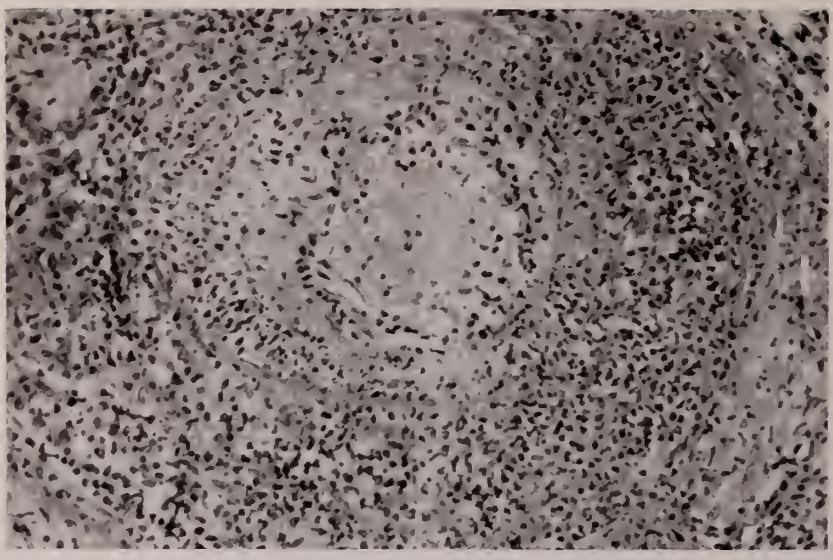


FIG. 3. Acute pulmonary arteritis similar to peripheral polyarteritis with periarterial inflammation (160×—H & E).

artery but were dilated bronchial artery branches (3, 4). Therefore, part of the inflammation became a collateral or compensatory hyperemia of bronchial vascular origin.

In the branches of the original pulmonary artery, these vessels were markedly proliferated and they have been described under the name of plexiform capillaries with glomus-like formation because they resemble the glomus in the periphery (4, 5).

In summary, the following changes were present in the vascular system: an arteritis in the pulmonary arterial branches, dilatation of pulmonary veins, dilatation of the bronchial arterial branches, and changes in the bronchial artery vascularization.

In the polyarteritic granulation tissues, new vessels from the bronchial artery grew around and into pulmonary vessels, and capillaries connected with the pulmonary artery. The extensive arterial anastomoses may have been the result rather than the cause of pulmonary hypertension (3, 5).

In the literature, some claim that the anastomoses are arteriovenous (6) while others state that they are between the pulmonary and bronchial arteries (3, 4, 5). The multitude of vascular anastomoses partly obstructs the blood flow and partly leads to shunts within these vessels. As the process becomes clear, severe fibrosis of vessels develop which makes the pulmonary hypertension permanent. The arterial elasticity is destroyed. In the presence of this pulmonary hypertension, arteriosclerosis in the middle-sized pulmonary branches and even in the larger pulmonary branches is secondary to the increased pressure.

As to the cause of death, in the base of the right upper lobe there were yellow areas of consolidation. Some central necrosis was found in the consoli-

dated areas. The arteritis extended into the inflammatory changes which occur in the alveolar system around the artery, and a chronic non-resolving type of pneumonia had developed, although whether this came from the arteritis is uncertain. In addition to being non-resolving, the pneumonia was also fibrosing. In some areas the non-resolving pneumonia broke down and abscesses formed, especially the small pneumonic foci which form close to the arteritis. In view of the diminished or absence of a defense mechanism, breakdown was probably due to infection with some pyogenic organism.

At this point we would like to leave this case. We had the somewhat unusual opportunity to have the autopsy material of the mother and, just as Dr. Friedberg said, we have two cases in one. The mother, 56 years of age at her death, had exactly the same history although the pulmonary hypertension lasted five years.

The lung grossly looked almost the same as the daughter's lung. Pulmonary arterial dilatation and pulmonary arterial sclerosis were present. Similar vascular changes and fibrosis were seen except that they were somewhat older (Fig. 4). Even very small vessels were involved in the fibrotic change but acute arteritic changes were missing. In this case, much nicer glomus-like formation was found (Fig. 5). Arteries have apparently become recanalized and led to the communicating shunts.

The hepatic changes were far more advanced. The sick daughter apparently died in a much more acute stage, probably from the arteritis associated with pneumonia and the circumscribed lung abscess. The mother lived long enough to die from cardiac failure, and the liver then was already transformed into cardiac cirrhosis (Fig. 6).

In summary, this was primary pulmonary hypertension with idiopathic arteritis and not pulmonary pressure arteritis. Arterial spasm resulted in the pulmonary hypertension. The pulmonary arteritis developed and led to vascularization and, since there was obstruction, bronchial arterial compensatory hyperemia resulted. From this and the surrounding arteritis, anastomoses developed connecting the bronchial arteries with the pulmonary artery and pulmonary vein. The pulmonary pressure rose and a vicious cycle started which led to pulmonary arteriosclerosis.

The fact that the mother lived to be somewhat older than the daughter, but died with a similar picture, suggests a hereditary factor as in essential arterial hypertension of the periphery.

The primary reasons for presenting the case were not only the arterial changes but also the rather unusual feature that mother and daughter died from exactly the same disease, primary pulmonary hypertension.

Dr. Joseph Kuh: The etiology of primary pulmonary hypertension has been said to be simply a congenital communication between the bronchial arteries and the pulmonary arteries; and I think this case points that out very nicely.

It would be very hard to postulate an arteritis as the reason for having communications between the bronchial arteries and the pulmonary arteries. You do not see these shunts so frequently in typical polyarteritis, and there would be no

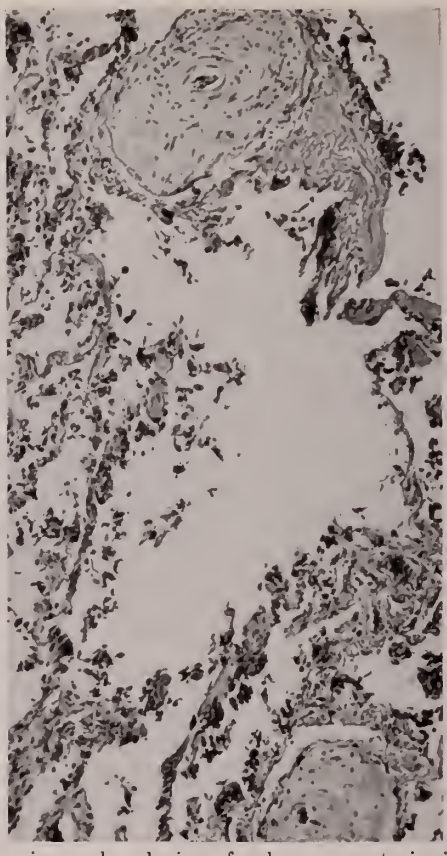


FIG. 4. Fibrous thickening and occlusion of pulmonary arteries in the lung of the mother (160×—H & E).

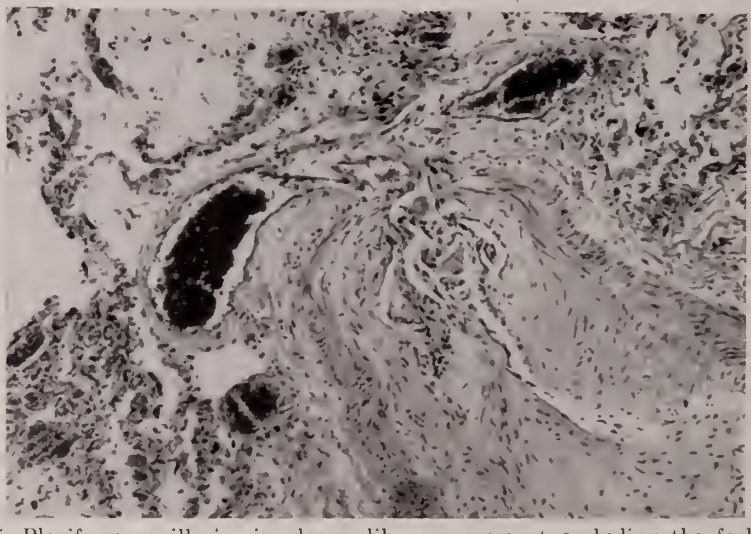


FIG. 5. Plexiform capillaries in glomus-like arrangement occluding the forking of a pulmonary arterial branch (60×—H & E).

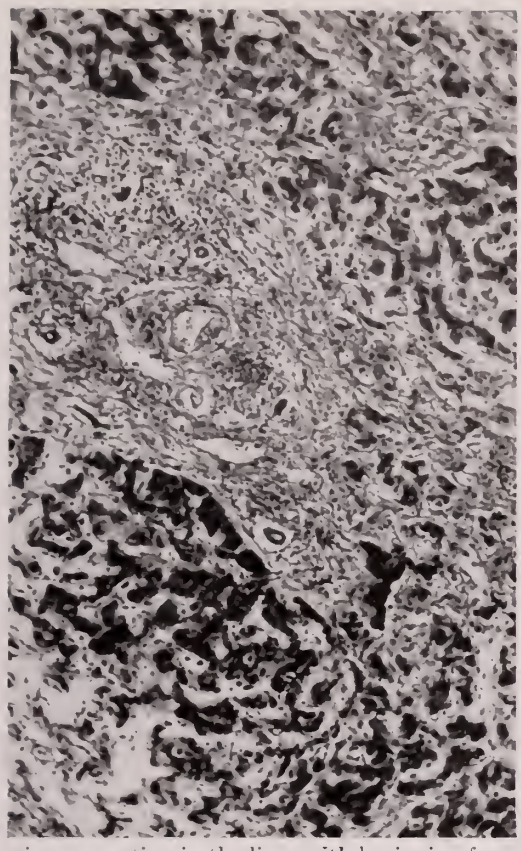


FIG. 6. Severe passive congestion in the liver with beginning formation of regenerative nodules and septa connecting the portal tracts and central veins (160×—Masson trichrome stain).

reason to expect them to develop. However, if you started with communication between the bronchial arteries and the pulmonary vessels, then you could get a picture that would explain all the autopsy findings in these two cases. It certainly would explain the findings in the case of the mother, and the only thing that it might not explain to Dr. Popper's pleasure perhaps, is the apparent periarterial inflammatory reaction in this case.

I can only say that clinically we were without hesitation in making a diagnosis of an influenzal process, and I think that this might explain the presence of the inflammatory reaction in the septa and about the bronchi and bronchial arteries.

I would like to suggest that the periarteritis is secondary, or else is an inflammatory process due to the infection, and it is not a real so-called primary polyarteritis nodosa. It has none of the other characteristics of peripheral polyarteritis, and it is not present in the mother. Where you have a mother and a daughter with the same disease, I think that the theory of congenital communication between the bronchial arteries and the pulmonary arteries explains the picture better.

Dr. Popper: Two problems have been raised: one, the question of whether an initial pulmonary bronchial arterial anastomosis is the cause of the entire disease and, two, that influenza might be the cause of the periarteritis which we found in the lung.

As to the first point, I cannot completely deny it because definite evidence that this is not the case could only be obtained by an injection preparation and we have not made this. After a long search I could find no existing larger bronchial anastomosis and I believe that anastomosis takes place at the level of very small vessels. I must concede, however, in the absence of injection preparations that I am not quite happy to accept pulmonary to bronchial arterial fistulas as the primary cause of the disease and that they produce a primary pulmonary hypertension. I am uncertain of how that functionally would raise the pulmonary pressure to a degree that such a severe arteritis could have developed.

On the second point, I believe that I have the right to be dogmatic. If there were an influenzal lesion in the lung, we should have found it. Besides, we can see all stages from beginning arteritis to a very late stage, and this very late stage, relying on our information from the peripheral lesion, can be accepted as probably old.

I would be hesitant to assume a year-old influenzal arteritis as being present in the lung. Therefore, while I must be broad-minded about your first suggestion, I do not think that an arteritis of this type could either be secondary to hypertension, as it would have to be, or that it could be due to influenza.

Now as to the question of the mother. The mother has no acute arteritic lesion but definitely had scars of one. Therefore, I am a little bit inclined to feel that the mother also had arteritis once but no longer had the active changes.

Dr. Arthur M. Grishman: I have another family with this primary pulmonary hypertension. I think these are the only two families known.

Dr. Friedberg: It is possible that the number of cases reported form a very small percentage of those that are seen, and in a few years we will probably see more extensive reports which might enable us to say whether it is or is not common.

Dr. Kuh: The changes that you call scars in the mother might possibly be simply secondary to the sustained pulmonary hypertension.

Dr. Popper: Yes, but I cannot find the same lesion in the mother and in the daughter, and in the daughter I can trace every step from arteritis to scarring. As far as the mother is concerned, there is only very strong circumstantial evidence.

Dr. Friedberg: Are there not many instances of these arteriovenous and pulmonary-bronchial arterial communications in a variety of pulmonary diseases in which there is no primary pulmonary hypertension?

Dr. Popper: Yes, there are anastomoses of a fistulous type. The glomus, however, occurs only in pulmonary hypertension.

Dr. Richard P. Lasser: This patient and also the mother had chest pain which is very common in pulmonary hypertension. If this pain resembles the anginal

syndrome, one might see subendocardial fibrosis and necrosis. Was a study made of the muscle types?

Dr. Popper: In the daughter's case, we looked at the papillary muscle and found only interstitial fibrosis on the left side. There was none on the right.

Doctor: Pain in pulmonary hypertension is like angina in its location or intensity but it increases with respiration associated with dyspnea and is not relieved by nitroglycerine. The pain is thought not to be related to right ventricular ischemia but more likely due to distention of the pulmonary artery.

Dr. Friedberg: The term primary pulmonary hypertension has to be used with a little caution because, in the first place, it is not precise etiologically or even anatomically. All we are saying is that the increase in pulmonary resistance is located somewhere in the small arteries of the pulmonary system and that this is not due either to pulmonary disease or to disease outside of the lungs. But we begin to see that cases we label primary pulmonary hypertension may differ in the anatomical appearance within the small pulmonary arteries and also in their etiology.

Many of you are familiar with the experimental work as well as clinical correlations indicating that if fibrin clots are injected into animals, embolic lesions are produced that look very much like those seen in primary pulmonary hypertension. Here and in other cases we have instances of inflammatory lesions of the small vessels with closure.

From the physiological point of view, the basic disturbance is obstruction or increased resistance due to obstruction, plus vasoconstriction in the pulmonary arteries, thus far, cause unknown. I think this is the difficulty that leads us to uncertainty as to which comes first.

We agree that the atherosclerotic and the intimal proliferative lesions in the larger vessels are secondary to the pulmonary hypertension. It is quite possible that some of the lesions, particularly the necrotic ones in the smaller arteries in the pulmonary system, as in the systemic system, may also be secondary to severe pulmonary hypertension, but what we do not know is how much of the closures of vessels is due to arteritis, to organizing thromboembolism, to local thrombosis, or perhaps even to primary spasm. Injections have been made into the pulmonary artery of parasympatheticomimetic drugs which sharply reduce the pulmonary pressure by diminishing the pulmonary arterial resistance for a brief period. This only tells us that there is some degree of vasoconstriction but not whether this is primary or secondary.

Final anatomical diagnosis: Idiopathic pulmonary artery arteritis with pulmonary hypertension and cor pulmonale. Unresolved pneumonia with pulmonary abscesses.

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In Memoriam

DR. H. EVANS LEITER

1906–1958

The sudden death of Hy Leiter during the night of September 11, 1958, struck his family, friends, confreres and countless patients with profound emotional impact. In the very prime of his life, having reached the summit in his chosen field and at a time when he was enjoying the fruits of his many years of hard work productive of magnificent accomplishments, he was suddenly stricken and removed from our midst. The personal attributes of the man, his professional stature, his innate sympathy for the suffering of his fellow-men, his devotion to his calling and the sincerity of his personal and professional relationships amply explained the high esteem in which he was regarded by everyone who came in contact with him.

Dr. Leiter was born in humble surroundings in New York City on November 4, 1906. After preliminary education in the public schools, he entered the College of the City of New York and received his B.S. degree in 1923. He later entered The New York University Medical School. In spite of great financial and physical hardship, he was graduated in 1930 with membership in the Alpha Omega Alpha honorary fraternity and in possession of the Alpha Omega Alpha prize.

He started his combined medical and surgical internships at Mount Sinai Hospital in July of 1930. During the succeeding four years of his training period, the high calibre of his work and his intense application promised a bright future. It was during this latter period that he chose urology as a surgical specialty and after he was graduated, began his long association with that master urologist, Dr. A. Hyman. In the succeeding 15 years, Leiter's collaboration with Dr. Hyman both in private practice and on the urological service at The Mount Sinai Hospital brought into full bloom all the professional capabilities which were recognized in ever enlarging circles.

Soon after the completion of his formal training at Mount Sinai, he was appointed adjunct surgeon at The Hospital for Joint Diseases, a position he held until 1938. In the same year, he received his appointment as assistant attending surgeon at The Mount Sinai Hospital and during the succeeding twelve years gave devoted and distinguished service to the surgical and urological services. All of us on the attending staff soon realized that Leiter was a young man with unusual capabilities and watched his subsequent rapid progress with admiration and deep satisfaction. As he matured, the three distinctive attributes of the outstanding surgeon began to crystallize, excellent diagnostic ability, sound surgical judgment and superlative technical skill. This unusual combination was soon recognized by the medical fraternity in New York and, when he terminated his association with Dr. Hyman in 1949 and opened his own office, his practice increased at an unprecedented rate so that at the time of his death he was one of the busiest urologists in New York City.

H. EVANS LEITER
1906–1958

In 1948 he was appointed Chief of the Department of Urology at The Hospital for Joint Diseases where he served with distinction for the next ten years. In the spring of 1958, he was chosen by Beth Israel Hospital as Attending Urologist, an appointment of which he was rightly proud. During the afternoon of the day he died, he discussed with me his plans for the reorganization of his service and the high hopes he entertained of making this one of the most important urological services in the city. From our knowledge of his warm personality, his high scientific standards and executive ability, these hopes would surely have been realized.

Dr. Leiter was a Fellow of The American College of Surgeons, a Diplomate of The American Board of Urology and a member of The New York Urologic Association, American Urologic Association and The New York Academy of Medicine. He was the author of many surgical papers, mainly devoted to his chosen field. One of his most important contributions was concerned with the development of the open direct-vision suprapubic prostatectomy operation with meticulous hemostasis of the prostatic bed and primary closure of the bladder. Here his previous training in general surgery came to the fore and this new method will undoubtedly replace the older blind and traumatic operation.

The Mount Sinai Hospital has lost a distinguished alumnus. He will be sorely missed but will be remembered for his genial personality, his superlative technical ability, his concern for his patients' welfare, and the sincerity of his professional and personal relationships.

To his lovely wife, Babette, and his two fine sons, James and Robert, all of us extend our most heartfelt sympathy.

JOHN H. GARLOCK, M.D.
for
The Editorial Board

CONSIDERATIONS IN SURGICAL MANAGEMENT OF ATYPICAL MUSCULO-SKELETAL MALIGNANT TUMORS*

ALBERT J. SCHEIN, M.D.

New York, N. Y.

The treatment of a sarcoma of bone or adjacent tissues should be by wide resection or excision if it is located in the trunk or head and if the location and lack of vital structures involved lend themselves to such a procedure. If the tumor is in an extremity, amputation at a level well above the tumor is usually the treatment of choice. Excision of the regional nodes is also sometimes advisable, along with supplementary radiation therapy. Even with such radical methods, the mortality rates are high and the incidence of cure is only 15 to 20 per cent. Some types of disseminated sarcoma which are notably radiosensitive may be treated primarily by radiation therapy.

In long bones, a selected group of sarcomas of the lower grades and relatively small size, preferably contained within the bone, may be treated by extensive resection of the involved bone and adjacent soft parts and repair by bone grafting. Phemister (1) has recommended such therapy especially in some chondrosarcomas, giant cell sarcomas, and reticulum cell sarcomas. Higinbotham and Coley (2), among others, have reported on treatment of bone tumors by resection. These were chiefly in the humerus and fibula and only occasionally elsewhere in fifteen cases.

In spite of all considerations—grading of the tumors, careful selection as to size, encapsulation and location—it is still very difficult to choose which ones may be successfully treated by local radical excision as compared to still more radical limb ablation, often including interinnominoabdominal and interscapulothoracic amputations. The purpose of this communication is to show a group of five cases of less common musculo-skeletal tumors in which a relatively local radical resection was done in preference to possible more radical ablation of the part or parts (with the possible exception of case #3 where such ablation was impossible).

CASE REPORTS

Case #1

W. S. (#245631), a ten year old girl, gave a history of a fall and an injury to the left scapula about six months before admission. Three weeks later she noted a mass and pain in this region. At the time of the above incident an x-ray taken at another hospital was stated to be negative. The mass increased in size until the time of admission.

Examination showed a 6 cm. x 4 cm. smooth, rounded, somewhat tender mass occupying the infraspinatous portion of the left scapula. It moved with the scapula and was not

From the Departments of Orthopedic Surgery, The Mount Sinai Hospital and the Bronx Hospital, New York, N. Y.

* Presented before the Orthopedic Section of the New York Academy of Medicine, March, 1957.

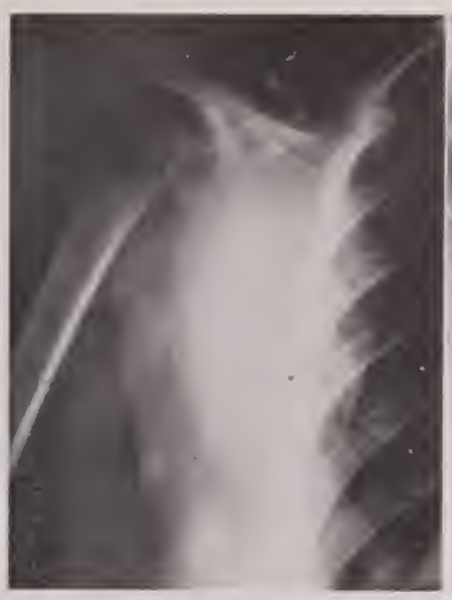

FIG. 1A.

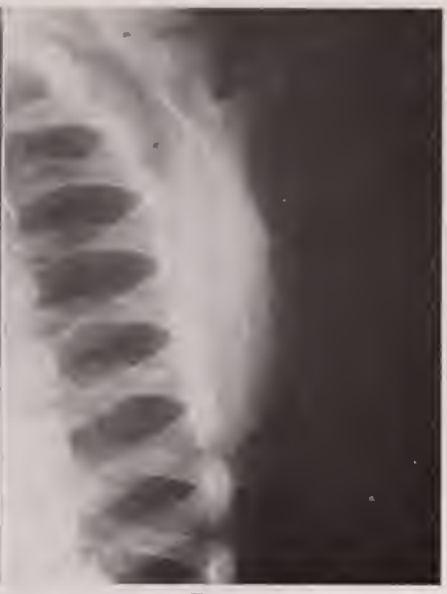

FIG. 1B.

FIG. 1A. AP view of left scapula, after admission to hospital, 1/7/52. FIG. 1B. Tangential view of left scapula, 1/7/52.

attached to overlying normal appearing skin. There was no limitation of shoulder motion. No glands were palpable in the left axilla. The general examination was negative.

Laboratory studies including blood count, urine analysis, blood calcium, phosphorous and alkaline phosphatase were normal.

X-ray on 1/7/52 (figures 1A and 1B) showed irregular bone destruction in the lower ⅔ of the left scapula with expansion of the bone and thinning of the cortex over the medial posterior portion. There was cortical thickening of the lateral border and anterior surface of the scapula. At one point there was a suggestion of discontinuity of the cortex and possible breakthrough in the medial posterior portion. Diagnosis was lytic bone tumor, possibly malignant. Skeletal survey, chest, ribs and skull were normal.

Biopsy was done on 1/10/52. Reddish brown, soft tumor tissue was found. The cortex of the scapula was broken through at the site of the exploration. Pathologic report was a highly cellular osteogenic neoplasm which destroyed and replaced most of the normal bone. The tumor was composed of numerous large, irregularly shaped, pleomorphic, darkly staining cells, most of which were arranged about numerous tiny fragments of poorly formed bone, consisting of little more than calcified cartilage or osteoid tissue. Many multi-nucleated tumor cells were present with bizarre shapes. The neoplastic trabeculae were in a matrix of loose, highly vascular connective tissue. Diagnosis was osteogenic osteosarcoma.

Dr. H. Jaffe saw the slides and felt that this was a rare type of osteoid, osteoblastic tumor such as he had described in a metacarpal with Dr. Leo Mayer and that it was not truly a malignancy (7). This influenced me toward conservatism. In fact he felt that it was quite benign rather than malignant.

On 1/28/52 excision of the infraspinous portion of the left scapula was performed. The glenoid was left with the spine of the scapula and the supraspinous portion. The subscapularis and serratus muscles were uninvolved and separated extra-periosteally as were the other scapulo-spinal muscles at the medial border. The infraspinatus, teres major and teres minor muscles were excised with the scapula. The previous biopsy site was excised *in toto* with the large resection. The attachments of the infraspinatus and teres muscles to the

humerus were left intact. The entire tumor was contained in the resected mass. Closure was done by suturing the remaining muscles to each other from the anterior, medial and lateral and posterior aspects with chromic catgut. These included the latissimus dorsi, serratus anterior, rhomboids, serratus posterior and subscapularis and the remains of the teres and infraspinatus laterally.

Final pathologic report gross: The specimen was the resected part of the scapula, 14 cm. x 8 cm. x 4 cm. The under surface of the scapula was convex instead of concave. There was no cortical perforation there. Infraspinatus was attached closely to the dorsal surface. The upper cut surface showed sclerotic but normal bone and ultimately proved to be beyond the tumor section. After sawing through longitudinally, the tumor was 6 x 5 cm. in diameter, oval in shape and somewhat sclerotic. It reached the vertebral border of the scapula but did not perforate it. There was a margin of intact bone 2 cm. superiorly and 2.5 cm. laterally. The bone around the tumor was sclerotic and dense. The center of the tumor was softer than the rest, crumbly, but not very vascular. Several areas were hemorrhagic and necrotic. Perforation of the tumor had occurred only dorsally into the infraspinatus muscle. The cortex at the lower tip of the bone, although thin, was intact.

Microscopic pathology: There was no extension of the tumor beyond the cut edge of bone. The tumor was, as described previously, composed of numerous closely packed, poorly formed, interlacing masses of trabeculae composed chiefly of osteoid tissue with occasional

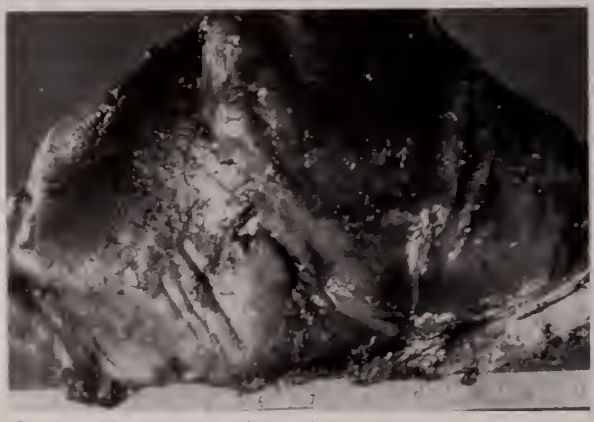

FIG. 1C. Resected gross specimen, infraspinous part of the scapula.

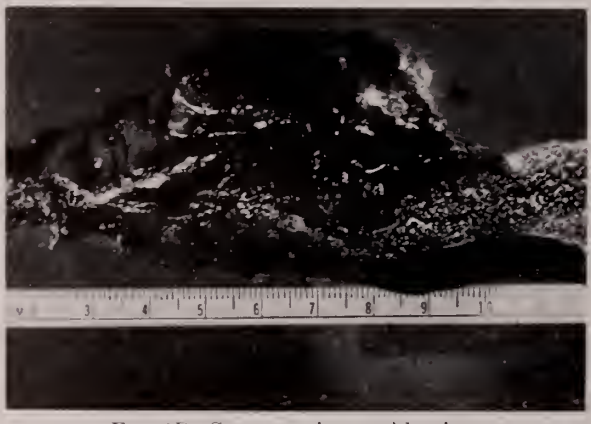

FIG. 1D. Same specimen, side view.

calcific deposits in a matrix of fibrous connective tissue. Numerous large pleomorphic neo plastic osteoblasts were present at the periphery of the trabeculae growing into the trabeculae without definite arrangement, and even into the fibrous connective tissue. Many of the nuclei were large and vesicular with prominent nucleoli. Others showed marked hyperchromatism and multi-nucleated forms were seen distinct from the osteoclasts. Diagnosis was low grade osteogenic sarcoma of the scapula.

The post-operative course was uneventful. Wound healing was clean and primary and she was discharged on 2/8/52, eleven days post-operative. Repeated chest x-rays had been negative pre-operatively and post operatively. She has been followed to date and has remained entirely well. Function of the left shoulder joint in motion, strength and utility has approximated that of the normal right, with slight weakness and restriction when used above should level. She has had no complaints. Repeated chest studies remained negative. There was some periosteal regeneration of irregular plaques of bone in the old scapular bed by x-ray. When last seen in orthopedic clinic in December, 1957 she was well without any sign of recurrence and living a normal life, even having become a mother.

Summary: This is a case diagnosed by one group of pathologists on biopsy as an osteogenic sarcoma of low malignancy, and by another pathologist as a rare benign osteoid-producing tumor. It could have been treated by total scapulectomy, interscapulo-thoracic amputation, or as it was actually treated, by local partial scapular resection. The latter

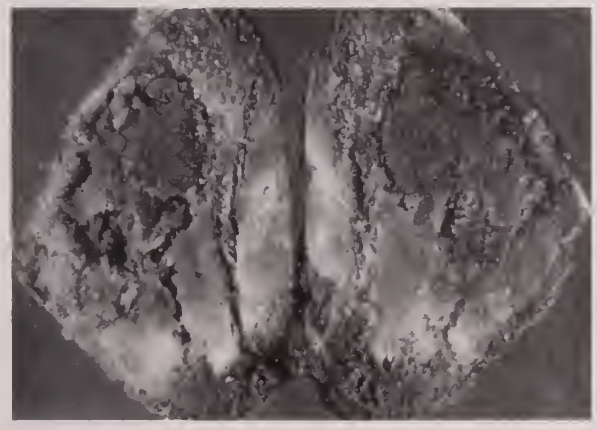

FIG. 1E. Cross sections, vertical, of gross specimen, opened out.

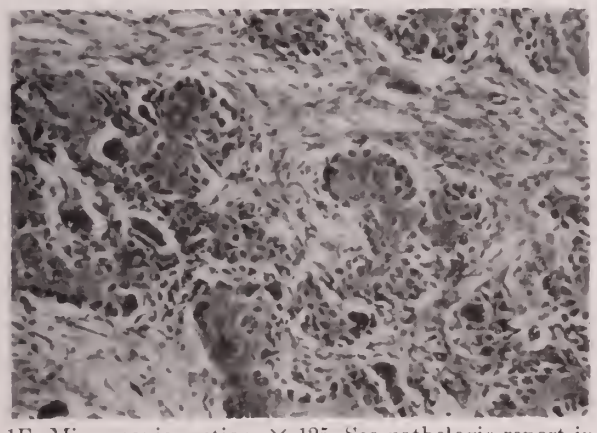

FIG. 1F. Microscopic section, × 125. See pathologic report in text.

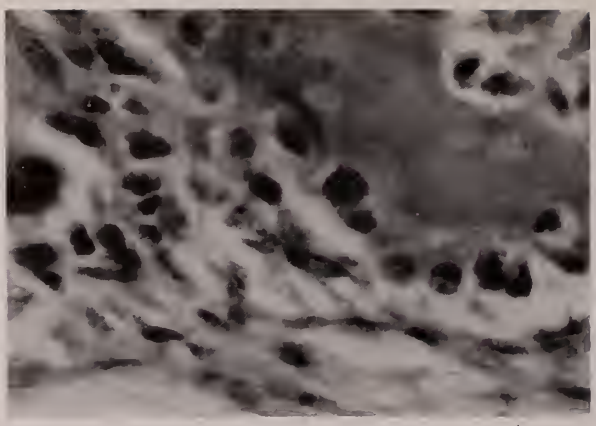

FIG. 1G. Higher power microscopic section, × 500.

was decided upon because of doubt as to true malignancy and the "low grade of malignancy" in the various reports, and because it proved entirely resectable at operation without destroying function of the shoulder or upper limb. The subsequent course and apparent cure have borne out this reasoning. It was agreed that other therapy such as radiation and chemotherapy offered nothing.

Similar cases have recently been reported by Golding and Sissons (4), and by Kirkpatrick and Murray (5) as osteogenic fibroma of bone. While all of these have been considered benign, it must be agreed that this one resembled an aggressive tumor and that the biopsy, according to one group of pathologists was an osteosarcoma, albeit low grade. This indicates the need for extremely careful pathologic study by the most competent pathologists with frequent and multiple consultation as indicated before arriving at a clinical decision as to how radical to be in surgical therapy.

Case #2

M. F. (#210516) was a five month old female child at the time of admission. There was apparently a sudden onset, noted by her mother, of a swelling over the right upper pectoral region on 2/25/54, the day of admission. No known injury was elicited. Swelling was seen by the family physician and then by an orthopedist. X-rays of the chest, right upper limb and shoulder girdle were negative. There was no fever. Aspiration withdrew 8 cc. of gross blood and a hemorrhage was considered the diagnosis. She was then admitted to the hospital.

The positive physical findings were in the right upper pectoral region only (figure 2A). There was an orange-sized tense mass, not involving skin, freely moveable in or with the pectoral muscles. It was well localized, extending from the anterior axillary fold to about ½ inch from the border of the sternum and from the clavicle to the level of the nipple. It was not very tender and did not interfere with function of the right upper extremity. The axilla was clear of nodes and the cervical spine and supraclavicular region appeared normal. Peripheral pulses were normal. There was no bruit or auscultatory abnormality.

Developmental history and general examination were entirely negative.

Biopsy on 2/27/54 showed a large tumor underlying the pectoralis major muscle, friable, white, formless and stringlike and part of this was removed piece-meal. Because of bleeding the wound was partially packed open.

Laboratory studies showed RBC 3,080,000 per cubic mm., WBC 8,200, Hgb. 52%, normal differential and normal bleeding and clotting time.

Transfusion was given via cut down intravenous infusion during the biopsy and afterwards

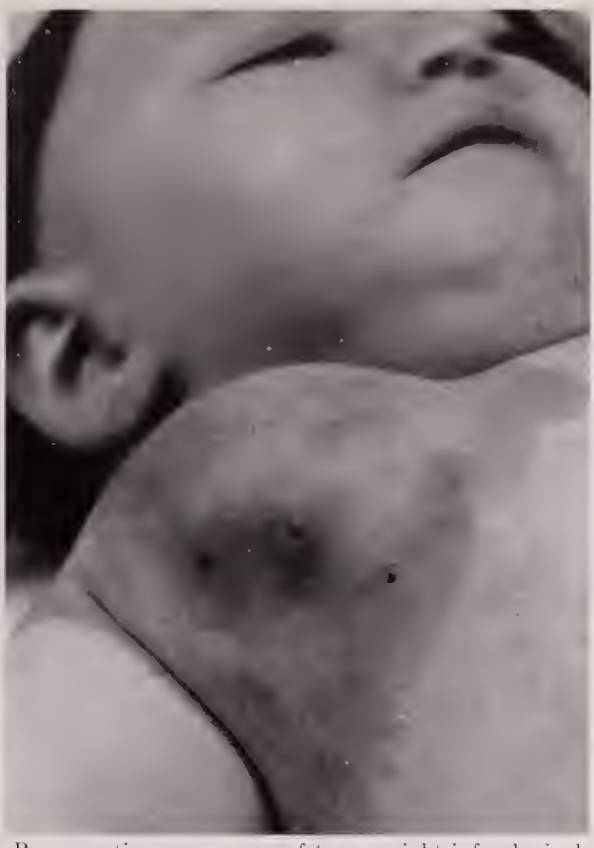

FIG. 2A. Pre-operative appearance of tumor, right infraclavicular region.

Biopsy pathologic report (figures 2B and 2C) showed a highly cellular neoplasm with uniform appearance throughout. The tumor was arranged in closely packed masses of cells which formed tufts of varying sizes and even solid sheets of cells. Within them were irregular spaces or clefts, some of which were quite large and contained blood elements. A few of the cells were arranged in bundles or fasciculi. The nuclei were oval in shape, closely crowded and many showed pointed ends. There were frequent mitosis and nuclear hyperchromatism. Some of the tumor showed hemorrhage or liquefaction necrosis. Diagnosis was sarcoma, probably synovial type, or malignant synovioma. Sections were shown to Dr. A. P. Stout who agreed with the diagnosis of probable synovioma or possibly mesenchymoma, highly malignant, with poor prognosis and probably radio-resistant (9).

Operation was done on 3/8/54 with a view to radical resection with interscapulothoracic amputation in mind if necessary. Removal of the outer $^2/_3$ of the clavicle was done leaving only the sterno-mastoid attachment. The pectoralis major was freed from the chest wall along with the pectoralis minor. The brachial plexus, sub-clavian artery and vein were identified and dissected free of all surrounding fat, lymphatic tissue etc. as in a radical breast operation, preserving only the thoracodorsal and long thoracic nerves. As the dissection proceded from medial to lateral, it was seen that the entire lesion could be removed without performing a fore-quarter amputation. The entire axilla was dissected and the pectoral muscles completely excised except the remnants of the coracoid and humeral attachments. The previous biopsy wound with the cavity of the tumor tissue and adjacent infraclavicular and supraclavicular contents were removed with adequate surrounding skin

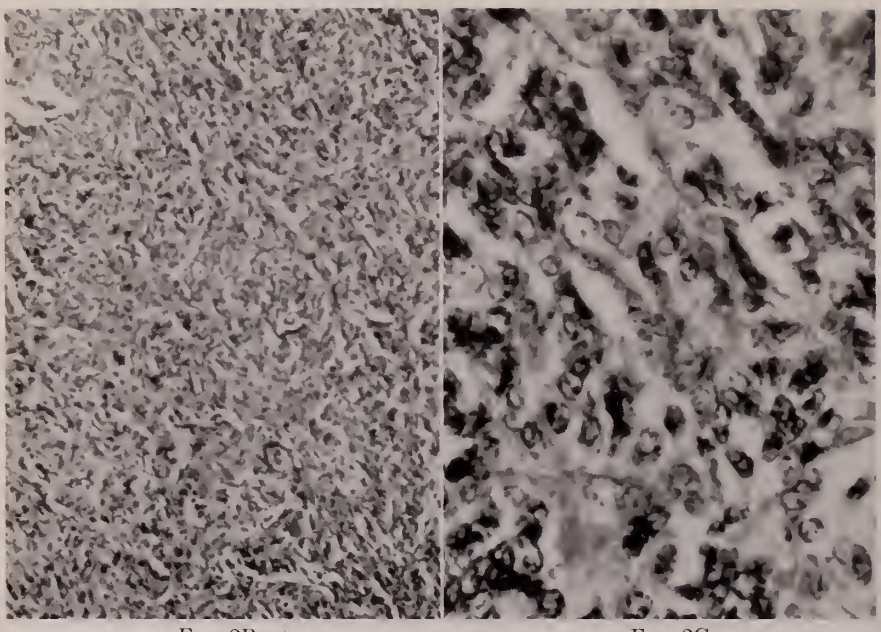

FIG. 2B. FIG. 2C.

FIG. 2B. Microscopic section of biopsy specimen, × 125. FIG. 2C. High power microscopic section, × 500.

FIG. 2D. Resected gross specimen.

so that the mass was not entered during this radical dissection. The skin flaps remaining, which had been formed well away from the previous wound, were closed with some difficulty and a drain placed through a stab wound in the dependent part of the axilla. No definite site of origin of the tumor could be found. It did not involve the shoulder joint or the coracoid process.

Final pathologic report gross: The resection included a tumor, skin, subcutaneous tissues, muscle and clavicle. In the center of the skin the previous biopsy wound was noted, closed with silk sutures. The mass included apparently the entire tumor since when inspected externally the tumor could not be seen superficially, not having been entered at the time of the second operation. The specimen was 3.5 inches x 2 inches x 1.5 inches. The tumor itself was about 2 inches in diameter. The mass was not particularly hemorrhagic except at one pole where a circumscribed area 1 inch in diameter was noted, containing brown pigmentation, and somewhat necrotic, friable and hemorrhagic. The tumor otherwise was grayish-white, spongy, without fluid or cystic material.

Microscopic: It was a highly cellular, malignant pleomorphic celled tumor containing many mitoses, irregular clefts throughout with intermingling of leucocytes, erythrocytes, histiocytes and fibroblasts. Diagnosis was malignant synovioma.

Post operative course was relatively uneventful. The drain was removed in 48 hours. There was a mild wound separation after sutures were removed and further healing occurred by granulation. There was no infection. She had received penicillin for one week. By 3/28/54 the wound had healed down to a small granulating area and she was discharged.

She has been followed to date and remains perfectly well without sign of recurrence (four years). Repeated chest x-rays and local examination and x-ray study have remained negative for tumor. No irradiation was given. She has developed normally. She even has maintained fairly good function of the right arm and shoulder (figure 2E). The scar has

FIG. 2E. Post-operative function of the right shoulder and arm.

produced no trouble although it is somewhat indented. The resected clavicle has not regenerated except for some sub-periosteal bone formation in irregular plaques. There have been no complaints nor symptoms and she has gained weight normally in accordance with her age. No lymphadenopathy has ever been noted.

Summary: This was a highly malignant tumor of mesenchymal origin called by one pathology department a synovioma, and by a consultant mesenchymoma and by a third, undifferentiated spindle cell or round cell sarcoma. It had grown so rapidly in a young infant that the odds were against survival by any treatment. Radiotherapy was considered useless as was chemotherapy. After the diagnosis was made by biopsy, the choice was as to local wide excision, or additional interscapulothoracic amputation. It was felt that the lesion was so malignant that neither was likely to be successful. Fortunately at block resection operation, the major nerves and arteries to the upper limb were not compromised and a radical block dissection and excision was accomplished outside the boundaries of the tumor. It is questionable whether amputation would have made the excision any more complete. The result thus far has borne out this judgment in that the child is well four years later, without recurrence and with good function of the right upper limb and shoulder.

Case #3

E. F. (courtesy of Dr. E. Blumenfeld) was a 14 year old girl who was seen for the first time on August 30th, 1954. She had developed spontaneous pain in the left shoulder four weeks before. There had been no definite injury. The pain was sharp and steady. She had been first examined by a physician for this condition on August 16th, 1954. A mass had been found located below the nape of the neck, to the left of the midline in the upper dorsal parascapular region. Increased local heat was present. A preliminary diagnosis of hematoma was made and heat and medication advised. Aspiration withdrew no blood. A blood sedimentation rate on 8/26/54 was 52 mm./hour (Wintrobe).

Previous history was non-contributory. There had been no weight loss, malaise, or other systemic manifestations of illness.

There was an obvious swelling, tense, in the seated and somewhat forward flexed attitude, less so when she lay prone. The mass was to the left of the midline in the cervicodorsal,

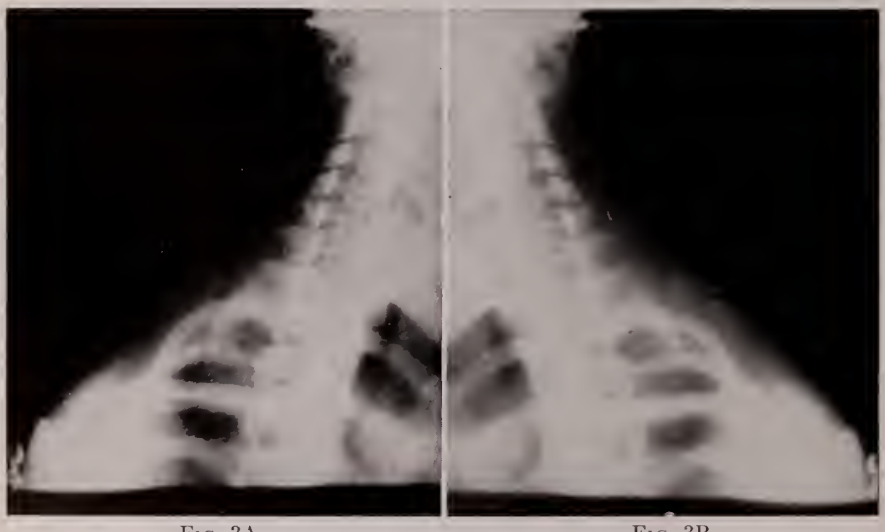

FIG. 3A. FIG. 3B.

FIG. 3A. Oblique view left cervicoscapular region, preoperative. FIG. 3B. Additional oblique view, same region, preoperative.

parascapular region, between the medial border of the left scapula and the spine. It was about the size of a peach. Over it was considerable edema. It was hard, immobile, markedly tender and felt warmer than the surrounding skin. Extension of the neck increased her pain but there was no limitation of motion of the neck or upper limbs. All other findings were normal.

Secondary anemia and a rapid sedimentation rate were demonstrated. Blood count and urinalysis including Bence-Jones protein test were normal. Tuberculin tests were negative. The temperature ranged between 100.5 degrees and 101.5 degrees.

X-ray demonstrated an oval calcified mass (figures 3A and 3B) about 1.5 cm. x 3 cm. in the left parascapular, paravertebral region just behind and lateral to the transverse process of D1. No evidence of origin from or communication with the underlying spine or ribs could be demonstrated.

Biopsy: Predominant opinion was that the lesion was an extraskeletal osteogenic sarcoma, although diagnoses of fibrosarcoma and atypical myositis ossificans were also entertained. The tumor was firm, finely granular and light tan in color. It contained a calcified zone, partly spongy and partly more solid. Part of the specimen was semi-gelatinous.

Microscopic findings revealed a variable and bizarre picture. In some regions, dense fibrous tissue bands were noted with atypical proliferating cells (figure 3C). These bands coursed along looser type of soft tissue in which were many dilated vascular spaces and a loose faintly basophilic mesenchymal-like stroma. There was extensive formation and destruction of osteoid and osseous tissue (figure 3D). The great number of osteoblasts were indicative of the simultaneous processes of bone formation and destruction. The bony trabeculae were more formed and more calcified in the periphery but looked like osteoid in the central zones. These bony trabeculae lay within dilated spaces in the midst of a loose connective tissue. The cells varied from an elongated spindle form to a bizarre giant shape (figure 3E). Some of these cells had vacuoles displacing the nucleus eccentrically and others had multiple nuclei with prominent nucleoli. Many of the nuclei were densely hyper-

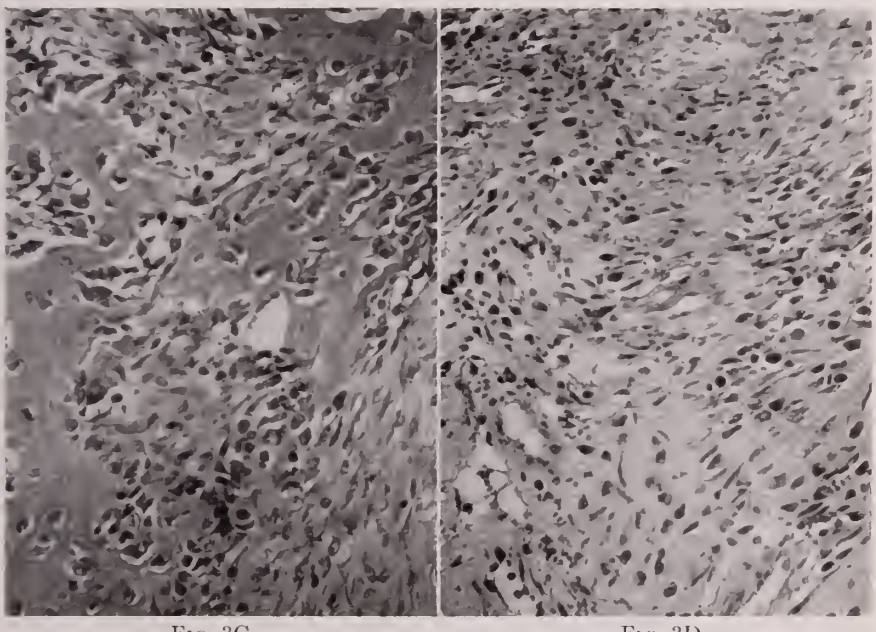

FIG. 3C. FIG. 3D.

FIG. 3C. Microscopic appearance, × 125, soft tissue portion. FIG. 3D. Microscopic appearance, × 125, bony trabeculae with malignant cells.

chromatic and occasional mitoses were seen. This tumor was a sarcoma comprised of several components, the predominant one being osseous.

The biopsy wound healed per primum and she was then re-admitted to the hospital for wide excision and block dissection of the area. At this time, chest x-ray showed a periosteal reaction about the left first rib posteriorly.

On 9/17/54 radical resection was done. The tumor was not attached to the underlying ribs and appeared to arise from and lie within the serratus posterior muscle as far distally as its tendon of insertion which was cut to remove it. The resected specimen included a 13 x 3 cm. portion of skin and subcutaneous tissue including the previous biopsy wound. The muscle tissue resected was 15 x 10 cm. in size and in the depths of it was an irregular 6 x 4 cm. thick walled cavity, the site of the previous excision and biopsy. The wall of this felt thick, firm and almost cartilaginous. The deep portion of the specimen was covered by a thin layer of normal muscle. About 6 x 2 cm. of rib was also removed.

Final pathologic report: The sections revealed sarcomatous tumor tissue which had largely replaced muscle. There was variation in the degree of cellularity. Some nuclei were round or oval and others elongated and spindle shaped. There was an abundance of fibrillar cytoplasm with a tendency to form whorls. In many areas the tumor contained trabeculae of osteoid tissue with calcification but this tissue was irregular in appearance and poorly formed. There appeared to be a zone of loose connective tissue separating the tumor from underlying muscle. The rib bone sections showed periosteal new bone but no neoplastic tissue and were otherwise normal. Diagnosis was extraosseous osteogenic sarcoma.

Course: Up to the end of 1957, the patient has remained well. There is a fullness of the left posterior upper chest in the upper left parascapular and suprascapular region. This feels bony and apparently part of the rib cage. This is non-tender and has not changed in three years. There has been no sign of tumor recurrence. Complaints are of minimal discomfort at the operative site with some discomfort extending into the left arm and elbow

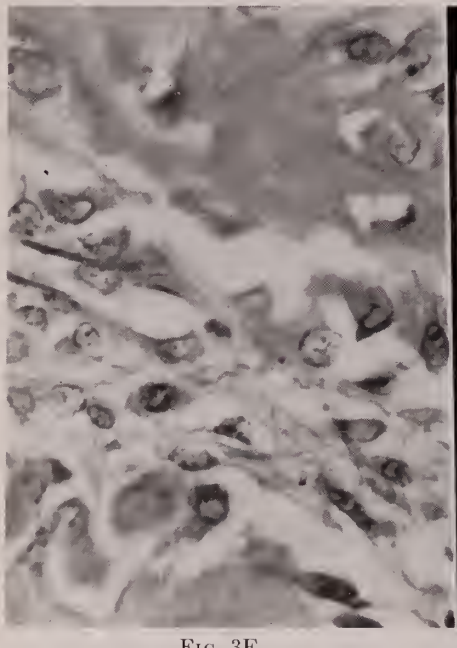

FIG. 3E.

FIG. 3F.

FIG. 3E. Higher power microscopic appearance, × 500. FIG. 3F. Function of left shoulder and arm, postoperatively, after healing.

region as well as the upper right cervical region. Weight has been maintained and there is no tumor mass. A mild left upper dorsal scoliosis is noted (figure 3F).

Summary: This was a case of a sarcomatous tumor reported as osteogenic sarcoma by two different departments of pathology even though it did not originate in bone. It formed bone and osteoid tissue. In this case, radiation and chemotherapy were considered unlikely to be helpful, and amputation was not possible by the location. Fortunately, radical block resection was possible without involvement of vital structures and without sacrificing much function of the upper limb, shoulder or cervicothoracic junction. The clinical cure after 3½ years is very encouraging although further follow-up will be indicated.

Case #4

A. C. (#2895-1952), 25 year old Puerto Rican male, entered with complaints of a swelling in the right forearm of five months duration—intermittently painful. There was no loss of weight, no weakness nor general symptoms.

Mumps with bilateral orchitis and parotitis in 1954 was followed by pleural effusion and pulmonary embolism and thrombophlebitis of the left calf.

The right forearm showed a non-tender swelling 4 to 5 cm. in length fixed to the ulna at its mid portion. The left leg was noted to be larger than the right with pitting edema of the upper tibial region. There were distended veins in the left leg as a result of the old phlebitis.

X-ray (figure 4A) showed sclerotic and periosteal change along the radial border of the mid shaft of the ulna but this did not involve the ulna itself completely. Blood urea, sugar, calcium phosphorous and alkaline phosphatase, total protein, uric acid were all normal. The urine was normal.

Biopsy: Excisional biopsy was done on 5/4/56 of a walnut-sized fleshy mass, easily separated from the surrounding muscles and fascia. It was attached to the ulna which was exposed sub-periosteally above and below. It was excised with "a generous amount of bone" and a plaster sugar-tong splint was applied.

Pathologic report was fibrosarcoma of low grade malignancy. Rare mitoses were seen with little cell atypism (figures 4B and 4C). It was recommended that a wider local excision be done because the lesion extended to the margins of the biopsy specimen.

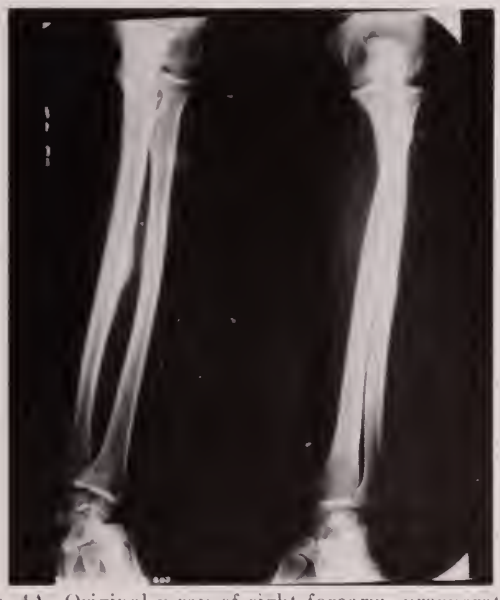

FIG. 4A. Original x-ray of right forearm, preoperative.

Re-operation was done on 5/23/56 with resection of 3½ inches of the middle of the ulna with wide excision of the adjacent tissues, muscle and fascia, especially in the interosseous space. A solid iliac graft 3½ inches long was inserted to bridge the ulnar gap, and held in place by a long Vitallium plate (figure 4D). The forearm was placed in a circular cast. This specimen showed no gross tumor but fibrous tissue at the center adjacent to the previous resection. The interosseous membrane was excised over to the adjacent radius. There was later loss of abduction power of the right thumb and some weakness of thumb extension due to removal of part of these muscles in the procedure. The specimen unfortunately was lost so that there was no later pathologic report.

The wound healed per primum. Post-operative x-ray (figure 4D) showed the bone graft in place bridging the defect in the ulna held in place with three screws above and two below. The patient was followed in the orthopedic outpatient department. The plaster was changed at intervals. Healing was excellent at the distal end with fusion of graft to the ulna. The graft revascularized. Non-union took place at the proximal end causing some posterior angulation.

Second admission took place on 1/28/57 for the purpose of revising the non-union and re-grafting.

Laboratory studies: Hgb. 15.7, WBC 9,000, normal differential, urine negative. The patient seemed well.

Operation was done on February 6th, 1957 to repair the non-union of the upper end of the graft to the ulna. This was done by use of iliac slivers and chips and the old plate replaced by a longer one permitting good bridging and immobilization from the proximal to the distal original ulnar fragments. No sign of recurrent tumor was detected along the ulna at either end or along the entire length of the previous iliac graft which was found intact and viable and exposed full length on its posterior surface.

Summary: This was a periosteal fibro-sarcoma reported to be of low grade malignancy with few mitoses and little cell atypism, probably arising from the interosseous space or the

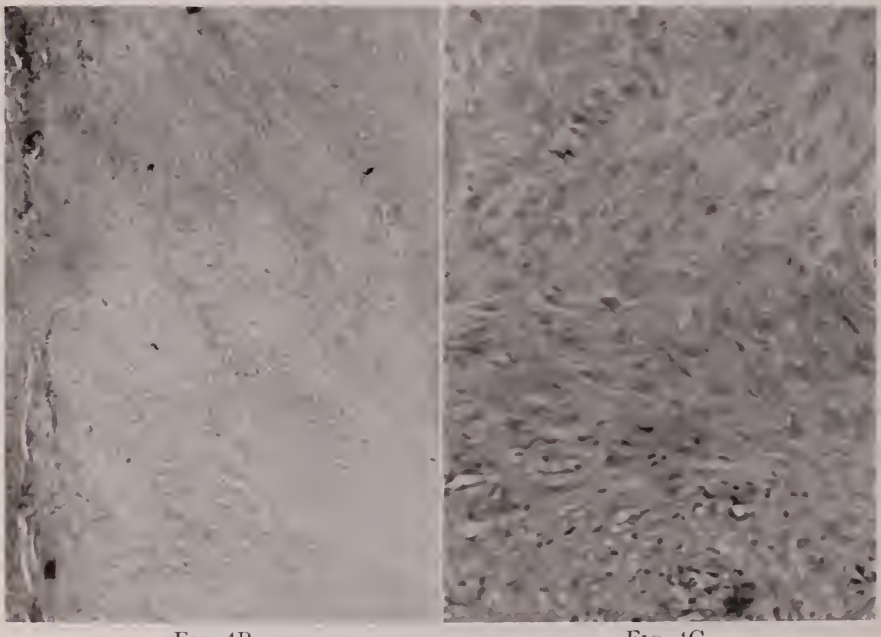

FIG. 4B. FIG. 4C.

FIG. 4B. Low power microscopic view of biopsy section of 5/4/56. FIG 4C. High power view of same section.

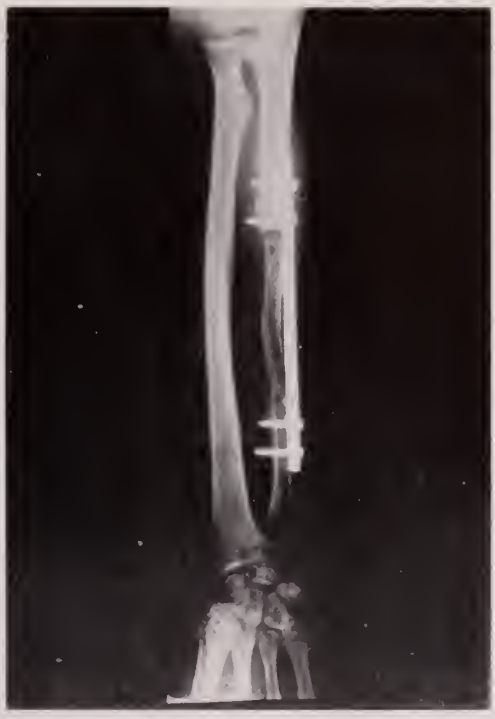

FIG. 4D. X-ray of right forearm a few months postoperative resection and graft.

periosteum of the ulna on its radial surface. The alternatives here were amputation above the elbow or attempt at radical local excision. Because of the nature of the pathologic report and the atypical roentgen findings, the local resection and excision were performed as radically as possible removing the entire involved portion of the ulna with grafting. Subsequently no sign of recurrence has been evident in the interval but the period of follow-up is too short to be certain. At re-operation to perform additional grafting, no sign of tumor tissue was in evidence. It is now two years since the original operation.

Case #5

The patient was a 45 year old woman with a history of six months of pain in the upper third of the right leg, worse in the past three months. A mass was noted on the medial aspect of the upper third of the tibia for about 1½ months. She was admitted to the hospital on 8/15/51.

The medial anterior aspect of the upper third of the right tibia presented an irregular, tender, soft tumor expanding and perforating the tibia, about the size of a lemon, not adherent to the skin. There was softness at the center.

Laboratory studies were negative except for the x-ray findings and pathology. X-ray (figures 5A and 5B) showed localized enlargement of the tibia at about 5 inches below the knee joint. There was a lesion in the marrow cavity 3 inches long, sharply circumscribed superiorly, inferiorly and laterally by a calcific rim about 3 mm. in diameter. Medially there was destructive change for a distance of about 2 inches with periosteal reaction of horizontal spiculation. The cortex in this lytic area was replaced by the mass. There was a suggestion of an old benign lesion which had undergone malignant change.

Biopsy was done on 8/17/51. The periosteum on the medial side was intact but bulging. A large plug was excised. Skeletal survey and chest x-ray on 8/17/51 were negative for

metastases. Pathologic report was central fibrosarcoma—said to be a very low grade malignancy in a pre-existing fibrous dysplasia (figures 5C and 5D). Blood chemistries were negative, blood counts normal. Sedimentation rate 8/16, 37; 8/27 post-biopsy, 52 mm.; 9/4, 79 mm.; 9/26, 42 mm.

Operation was done on 9/29/51 by cylindrical resection (figure 5E) of the tibia with removal of the entire lesion plus ½ inch above and below with 1 inch of shortening. Bridging of the gap was accomplished by a free autogenous intramedullary graft of 5 inches of fibular shaft and an onlay graft from the bone bank plus reverse L-shaped blade plate fixation piercing the short upper fragment and covering the bank bone graft (figure 5F). The previous biopsy soft part wound and the skin wound were excised with the bone via an elliptic incision not exposing tumor at the site of cortical perforation. Instruments were changed after removal of the bone tumor. Cancellous bone fragments from the bone bank were also packed in and around the fibula and between it and the large onlay graft of bank bone and between the ends of the tibia.

The section of tibia removed was 3¼ inches long. The final defect was 2¼ inches. A long leg cast was applied and 1,500 cc. of blood given. The procedure was done under tourniquet—thrice released hourly. The post-operative course was uneventful. The wound healed by primary union.

The patient was followed in the out-patient department with regular monthly films which seemed to show healing and vascularization of bone grafts filling in the defect.

One week prior to readmission x-ray showed a lytic area with destruction of the tibial cortex about one of the screws (figure 5G). There was also recurrence of pain and a soft tissue mass was noted just below the knee anteriorly. There was 1 inch of shortening. X-ray of the chest was negative.

Operation: Mid thigh amputation was done after prior biopsy (figures 5H and 5I) on 9/19/52. Pathologic report had shown recurrent fibrosarcoma (figure 5J). A large tumor

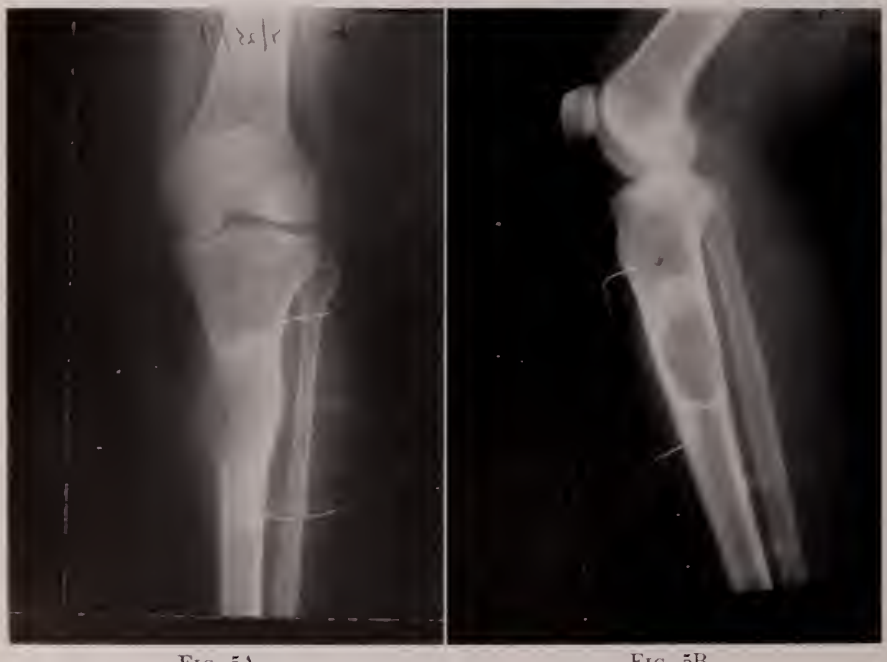

FIG. 5A. FIG. 5B.

FIG. 5A. Original tumor of right tibia, AP, taken 8/26/51 postbiopsy but pre-resection. FIG. 5B. Lateral view, same time, same lesion.

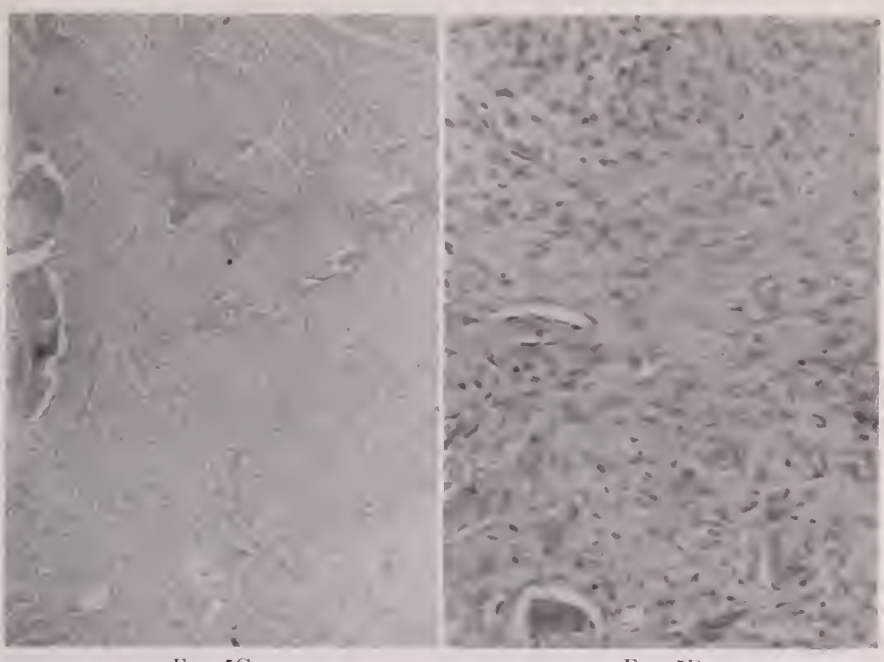

FIG. 5C. FIG. 5D.

FIG. 5C. Low power microscopic view of original biopsy specimen. FIG. 5D. High power view of same biopsy specimen.

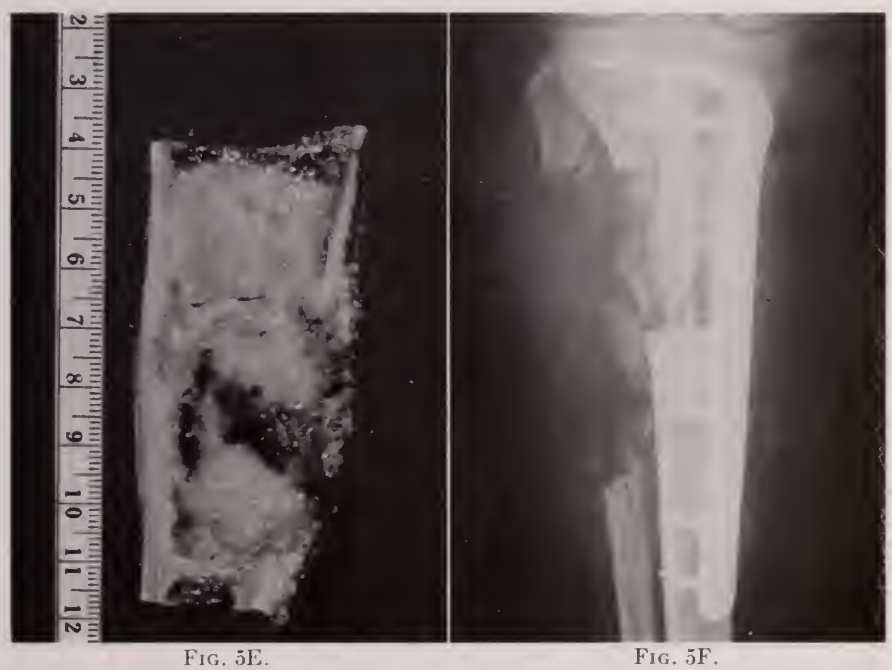

FIG. 5E. FIG. 5F.

FIG. 5E. Resected gross specimen, including bone above and below tumor. FIG. 5F. Post-resection x-ray, 8/29/51, OR control film.

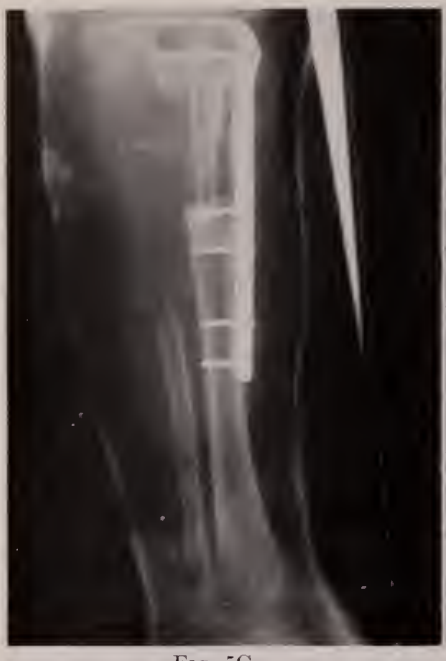

FIG. 5G.

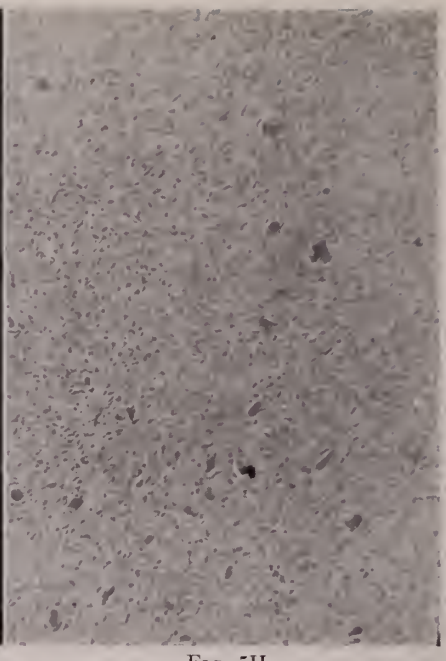

FIG. 5H.

FIG. 5G. Partial healing of grafts, rarefaction about a screw in the tibia 9/10/52. Fig. 5H. Later biopsy specimen removed 9/19/52, low power microscopic view.

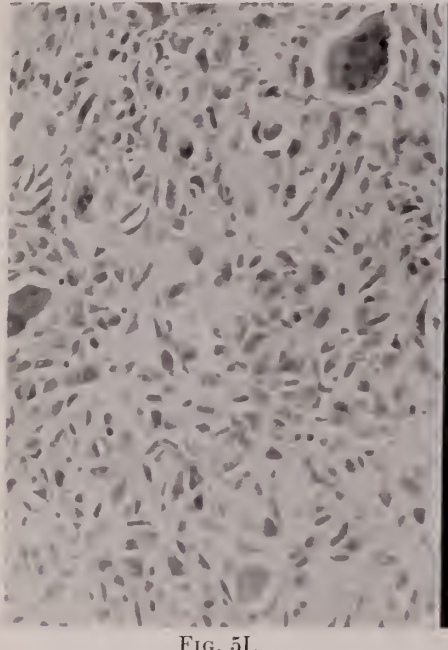

FIG. 5I.

FIG. 5J.

FIG. 5I. High power view, microscopic section of same biopsy specimen. FIG. 5J. Gross amputation specimen showing the recurrent tumor in the upper tibia.

mass 6 cm. in diameter, had replaced the origin of the tibialis anterior and also extended postero-laterally. The bone grafts were all united and well vascularized. Both bank bone and fibular grafts were united above and below. Tumor tissue filled the marrow cavity of the tibia and extended into the soft tissues of the interosseous space. It was attached to the periosteum of the head of the fibula. A branch of the popliteal and posterior tibial artery were noted within the mass.

Post-operative healing of the amputation was uneventful.

Four weeks prior to the third admission on 2/28/53, there was cough and pain in the right posterior chest at the 9th and 10th interspaces with tightness in the chest antero-superiorly. Three weeks before there was dyspnea on exertion and orthopnea. The cough was associated with flecks of blood in the sputum. On admission she was acutely ill with fever, tachypnea and, cough.

Sedimentation rate was 84 mm. Sternal marrow aspiration was negative for neoplasm. X-ray on 3/2/53 showed several large nodular densities in both lungs and a large right pleural effusion indicative of metastatic disease. Hemoglobin tested on 4/13 was down to 8.9 grams.

The patient had four chest aspirations producing serosanguinous fluid up to one liter each. No tumor cells were found in the fluid. X-ray therapy was suggested by radioactive gold to stop the accumulation of fluid. The patient was discharged unimproved.

Summary: This was a case of fibrosarcoma apparently arising within a pre-existing osteitis fibrosa cystica, or similar benign lesion, but coming to attention when it became painful and perforated through the subcutaneous cortex of the tibia. Because of the original pathologic report of low grade fibrosarcoma with extremely few mitoses, and the apparently localized nature of the lesion radical excision locally and bone grafting with internal fixation was attempted, instead of the obvious mid thigh amputation ordinarily indicated in a malignant sarcomatous tumor of a main weight bearing bone of a lower limb. Although the grafting procedure seemed to be successful and bony union was well under way a year later, recurrence of the tumor destroyed the result. Late amputation, even though no metastases were evident, proved unavailing and she died of metastatic pulmonary and pleural disease. Thus, the diagnosis of low grade fibrosarcoma was not borne out by the results, indicating the difficulties in judgment in a case of this type.

DISCUSSION

Table I summarizes the diagnosis, indications for therapy, biopsy reports, final pathology and results in these five cases. Four of the five cases could have been treated by more radical measures than were actually employed. The choice of the less radical procedure was done with intent. The criteria in each case were somewhat different. These included low grade, atypical or even questionable malignancy as determined by pathologic study of a sizeable biopsy specimen (four out of five cases), possibility of apparently complete resection due to lack of involvement of vital arteries, nerves, and other structures (all five cases); lack of infiltration into surrounding tissues so that a line of demarcation could be found outside which the resection could be done; absence of involvement of weight bearing bones requiring extensive plastic repair by bone graft with its long convalescence (four out of five cases). The synovial sarcoma, mesenchymoma or spindle cell tumor in the infant was considered so highly malignant that it was felt little additional benefit would result from ablation of the limb.

This serves to indicate in reverse the limitations of local resection. In general, malignant tumors which have already perforated through the cortex of long, weight bearing bones, especially infiltrating growths such as osteogenic sarco-

TABLE I

Case	Age	Sex	Duration	Location	Radical Resection vs.	Biopsy Pathologic Report	Final Report	Result	Follow Up
1	10 yrs.	F	6 mo.	Left scapula infra-spinous	Infraspinous scapulectomy; total scapulectomy; interscapulothoracic amputation	Osteogenic sarcoma, low grade osteogenic, osteoid producing fibroma	Same	Well; good function of lt. shoulder and arm	5 years
2	5 mo.	F	3 da.	Rt. pectoral & infraclavicular region	Interscapulothoracic amputation	Highly malignant synovial sarcoma, mesenchymoma	Same	Well; no recurrence; good function of right arm	3 years
3	11 yrs.	F	4 wks.	Left cervicoscapular region, upper dorsal paravertebral		Fibrosarcoma, extraskeletal osteogenic sarcoma	Same	Well; minor complaints in lt. shoulder and arm; no recurrence; good function of shoulder & arm	2½ years
4	25 yrs.	M	5 mo.	Right forearm, mid-ulna & soft parts	3½ inches of ulna removed; iliac graft vs above elbow amputation	Fibrosarcoma, very low grade malignancy	?	No recurrence at rebone graft	10 months
5	45 yrs.	F	6 mo.	Right tibia	Cylindrical resection 3¼ inches, fibula & bank onlay grafts vs thigh amputation	Central fibrosarcoma of low grade malignancy engrafted on pre-existing fibrous dysplasia	Recurrent fibrosarcoma	Recurrence locally; amputation Metastatic lung lesions	1 year 2 years

mata, or higher grades of malignancy in fibrosarcomata, chondrosarcomata, rhabdosarcomata etc. which are peripheral enough should be treated by amputation. It must be emphasized that these presented cases are the exceptional cases to be carefully selected since the risk of failure is always great and failure usually means fatality. In this series, the indications are that the result is or will be successful in four out of five cases. In the one failure, it is possible in retrospect that in addition to the perforation antero-medially, there may also have been another not detected pre-operatively on the deep or lateral surface of the tibia as shown by the location of the recurrence. It serves to emphasize the danger of such treatment in long, weight bearing bones where perforation of the cortex has already occurred. The need for complicated grafting procedures, wide dissection and prolonged time required for bone consolidation enough to permit free function in weight bearing are additional reasons for caution in considering resection of major weight bearing bones. It also indicates that pathologic grading of the tumor as of very low malignancy is no guaranty of success in local resection, although very important in considering and planning the type of surgery.

CONCLUSIONS AND SUMMARY

1. The ordinary treatment of musculo-skeletal malignant tumors of the extremities remains proximal amputation where feasible.

2. Exceptions are: a. Unusually radiosensitive tumors likely to be multicentric (such as Ewing's tumor, reticulum cell sarcoma etc.) b. Some atypical tumors as in the five cases presented in this paper.

3. In the latter, radical resection, local, may be done instead of amputation but the cases must be carefully selected.

4. Some factors in the selection include: a. Size of the tumor and its degree of localization so that it is contained within a particular bone or muscle. b. Resectability without sacrifice of vital structures which would render the limb useless or devitalized. c. Encapsulation or regional localization so that excision is possible in toto without entrance into the mass and inclusive of the biopsy site. d. Degree of malignancy as indicated by the histological study of the biopsy and clinical invasiveness. Especially if there is difference of opinion among competent pathologists as to the presence of malignancy or if there is agreement as to the low grade of malignancy of the tumor, local resections may be considered. e. High grade malignancies may also be considered for such therapy if proximal in the limb so that the difference in certainty of excision is not great as between amputation and resection, each case to be judged individually. f. Large tumors of weight bearing bones, involving complicated grafting replacement, prolonged convalescence and consolidation time for useful function should not be treated this way except in very special, otherwise favorable cases from all the above standpoints. g. Perforation of such malignant tumors through the bony cortex, especially of a long bone, indicating aggressiveness in the growth, renders local recurrence extremely likely despite what may appear a low grade malignancy on histologic study of the biopsy. Ordinarily, this should favor therapy by amputation rather than by local resection.

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FIVE YEAR SURVIVAL AFTER PANCREATODUODENECTOMY FOR CARCINOMA OF THE HEAD OF THE PANCREAS

Case Report and Review of the Literature

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The prognosis of primary carcinoma of the head of the pancreas treated by any method is poor. A survival time of longer than five years has been reported occasionally in patients with islet cell carcinoma and cystadenocarcinoma of the head of the pancreas (12, 13). On the other hand, patients with other untreated malignant neoplasms of the head of the pancreas ordinarily survive less than eighteen months, (6, 10, 11, 20), with a usual survival time of three weeks to six and a half months (8, 10). Patients treated with palliative biliary-intestinal anastomosis survive under 29 months (10), with a usual survival time of four to fourteen months (8, 9, 11, 20). Only pancreatoduodenectomy has resulted in prolonged survival times, with averages ranging from 10 to 26 months (8, 9, 10, 21).

Since the report of Whipple in 1935, pancreatoduodenectomy with various modifications has been extensively employed for all tumors in the region of the head of the pancreas (14). To our knowledge, despite its extensive use, there have been only 13 documented cases of primary carcinoma of the head of the pancreas which have survived the operation five years or more, again excluding cases of cystadenocarcinoma and islet cell carcinoma (Table I). Because of the rarity of prolonged survival of carcinoma of the pancreas, the following case is presented.

CASE REPORT

A 70 year old woman was admitted to The Mount Sinai Hospital for treatment of diabetes mellitus and evaluation of her status following pancreatoduodenectomy performed for carcinoma of the head of the pancreas five and a half years previously. The patient was well until July 1950, at which time she noted epigastric pain made worse by food intake. In April 1951, she noted anorexia, persistent nausea, loose stools and progressive weakness. Several weeks prior to admission to Memorial Hospital in New York in June 1951, she noted jaundice, light stools, dark urine and pruritus. There was a loss of 13 pounds during the preceding three months.

On physical examination, she was found to be icteric; the liver was enlarged four centimeters below the right costal margin; the gall bladder was palpable and non tender.

Laboratory findings prior to the operation were: Hemoglobin, 11.8 gm. per 100 cc.; white blood cell count, 5,300 per cu. mm.; eosinophiles 8 per cent and shift

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TABLE I

Author	Year	Survival of Patient	Remarks
Cattel, R. B., Warren, K. W.[1]	1953	5 years	Died
		6 years 5 months	Living and well
Dennis, C., Varco, R. L.[2]	1956	9 years 9 months	Died of heart disease
		6 years 5 months	Living and well
		5 years	
		5 years	
Pratt, J. H., Welch, U. S.[3]	1956	8 years	Living and well
Miller, E. M., Clagett, O. T.[4]	1951	5 years 3 months	Living and well
Brunschwig, A.[5]	1952	7 years	Living and well
Clifton, E. E.[5]	1952	5 years 5 months	Died. Probable metastatic carcinoma
		6 years 3 months	Living and well. Primary site of carcinoma questionable
Muir, E. G.[7]	1955	5 years	Living and well 3 years after resection of colonic carcinoma
Senff, A.[30]	1951	5 years	
Ginsburg, S. M. (this report)	1957	6 years 8 months	Died. Metastatic adenocarcinoma

to the left of the differential count. Platelet and reticulocyte counts were normal. On several occasions, transient glycosuria was noted. Fasting blood sugar was 172 mg. per 100 cc.; blood urea nitrogen was 23 mg. per 100 cc.; serum bilirubin, 8.8 mg. per 100 cc.; direct bilirubin, 6.3 mg. per 100 cc.; indirect bilirubin, 2.5 mg. per 100 cc.; cholesterol, 204 mg. per 100 cc.; cholesterol ester, 109 mg. per 100 cc.; cephalin flocculation and thymol turbidity, negative; alkaline phosphatase, 9.6 Bodansky units; prothrombin time, 17.6 seconds (control 13); urine urobilinogen, 6.4 Ehrlich units. X-ray studies of the chest and of the gastrointestinal tract (barium enema and gastrointestinal series) were reported to be normal. The clinical diagnosis was obstructive jaundice due to carcinoma of the pancreas.

At operation at Memorial Hospital, performed by Dr. George Pack, in June 1951, the gall bladder was found to be distended to three times normal size with a two centimeter cholesterol stone in its fundus. The common duct was dilated to one and a half centimeters in diameter and the wall was moderately thickened. Located in the head of the pancreas was a nodular firm mass, which measured approximately two centimeters and was ill defined. There was evidence of induration and fat necrosis in the body and the tail of the pancreas. There was no gross involvement of lymph nodes and none on later microscopic examination. A partial pancreatoduodenectomy was performed and included resection of the head of the pancreas, the distal three centimeters of the stomach, the entire duodenum, and proximal five centimeters of the jejunum (Figure 1) as well as choledochojejunostomy and gastrojejunostomy. The end of the pancreas was closed without anastomosis to the intestinal tract.

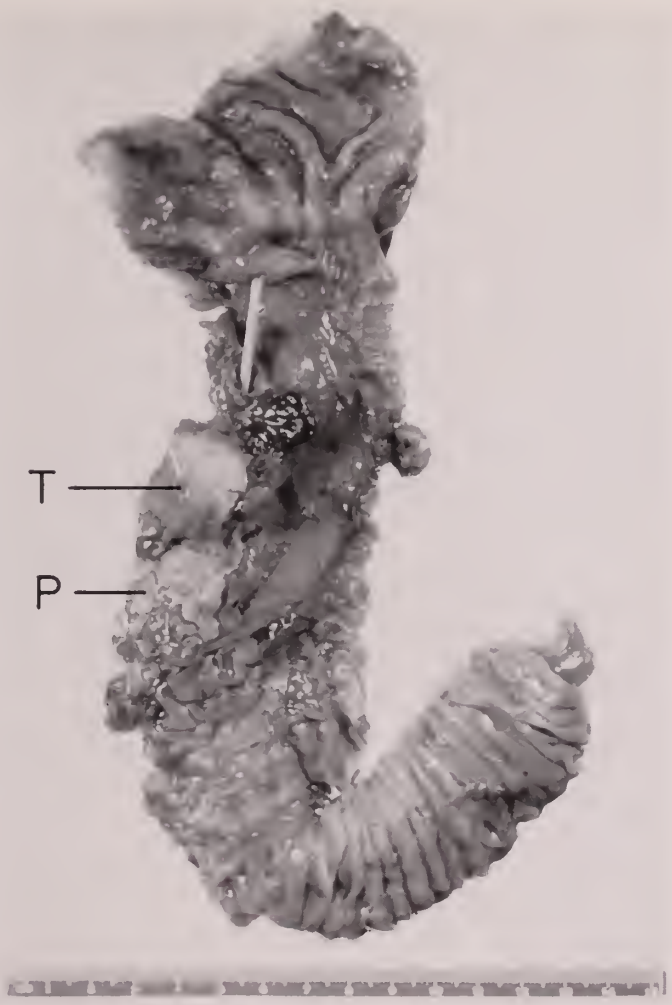

FIG. 1. Posterior view of opened resected specimen. Note common duct with inserted probe, distal to it the pancreatic tumor (T), and below it normal pancreatic tissue (P).

The pathological report was adenocarcinoma, grade II, of the head of the pancreas infiltrating the muscularis and submucosa of the duodenum. There was invasion of the perineural lymphatics in the head of the pancreas. There was no invasion of the common duct by tumor.

The patient's postoperative course was complicated by a hypokalemic alkalosis, which responded to potassium therapy, and a febrile episode which was treated with antibiotics. No postoperative fistula developed. Her bilirubin fell to 1.7 mg. per 100 cc. At the time of discharge on the twenty-seventh hospital day, she was doing well on a high protein, low fat diet, supplementary vitamins, relatively small amounts of pancreatic extract, and 20 to 25 units of protamine zinc insulin for control of glycosuria. With excessive fat intake, or after discon-

tinuation of the pancreatic extract, there was mild diarrhea of four loose bowel movements a day. Her weight had been constant at 110 pounds from July 1951 to November 1956, when she was admitted to The Mount Sinai Hospital.

The patient's family history was significant in that her sister had diabetes mellitus.

Physical examination: The vital signs were normal. The blood pressure was 140/65 mm. Hg. She was a well developed thin woman appearing in good health. Funduscopic examination showed no diabetic retinopathy. The heart and lungs were within normal limits. A right upper quadrant scar was present. The liver was palpable two centimeters below the right costal margin. The spleen was not palpable.

Laboratory findings: Urinalysis was normal except for glycosuria. The hemoglobin was 13.2 gm. per 100 cc.; red blood cell count, 4,400,000; hematocrit, 40.5 per 100 cc.; white blood cell count, 5,200 with 62 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes, 4 per cent eosinophiles, and 4 per cent monocytes; platelet count, 198,000 per cmm.; reticulocytes, 2.2 per cent. The sedimentation rate was 38 mm. in 1 hour. The fasting blood sugar was 251 mg. per 100 cc.; blood urea nitrogen, 17 mg. per 100 cc.; albumen, 4.0 gm. per 100 cc.; globulin, 2.7 gm. per 100 cc.; bilirubin, 0.7 mgm. per 100 cc.; cholesterol, 161 mg. per 100 cc.; alkaline phosphatase, 23.2 King Armstrong units; cephalin flocculation, negative; prothrombin time, 15 seconds (control 12 seconds); sulfobromophthalein test, 2.5 per cent retention in 45 minutes; calcium, 10.1 mg. per 100 cc.; phosphorus, 2.7 mg. per 100 cc.; amylase, 31 units per 100 cc. Microscopic examination of the stool revealed no excessive fat, undigested meat fibers or increased starch. Quantitative studies on a low fat diet revealed a fecal fat excretion of 25.1 gm. in 24 hours (normal values under 5 gm.). The stool guaiac test was negative. A glucose tolerance test using 100 gm. glucose orally showed the following results: fasting, 236 mg. per 100 cc.; ½ hour, 420 mg.; 1 hour, 425 mg.; 2 hours, 450 mg.; 3 hours, 178 mg. The Schilling test was normal, the patient excreting in the urine 32.5 per cent of the ingested dose of radioactive cobalt B_{12}. The vitamin A tolerance showed the following values: fasting 42 micrograms per 100 cc.; 4 hours, 38 micrograms per 100 cc.; 6 hours, 47 micrograms per 100 cc.; 8 hours, 45 micrograms per 100 cc. (22). The carotene tolerance was performed and was flat. Intestinal intubation studies revealed no pancreatic function after secretin with a maximum bicarbonate concentration of 28 mEq. per liter, a maximum value of 0.38 cc. per kg. and a duodenal amylase of 0.3 micrograms per kg. (23).

X-ray studies of the chest were normal. X-ray examination of the skull and long bones showed considerable demineralization. Gastrointestinal series showed a functioning gastrojejunostomy with no disease in the region; there was normal progression of the barium through the small intestine.

The patient's diabetes was well controlled on 20 to 30 units of NPH insulin daily. When insulin was gradually replaced by 3.0 gm. of tolbutamide, polyuria, polydipsia, glycosuria and hyperglycemia appeared. The tolbutamide was discontinued and the diabetes was again well controlled with insulin. On a regular

diet with limited fat intake, without pancreatic extract, there was no diarrhea and the weight was maintained. In July 1957, more than six years after the pancreatoduodenectomy, she was feeling moderately well. However, on questioning she stated that she had begun to experience mild epigastric pain occurring one half hour after eating, which radiated to the back, was worse in the supine position, and was relieved by sitting up. The spleen was palpated two centimeters below the left costal margin.

COMMENT

The impression based on a survey of the literature is that pancreatoduodenectomy compared to palliative biliary-intestinal anastomosis results in prolongation of life. However, only good risk patients in whom survival would be expected to be longer are being selected for pancreatoduodenectomy (10). The indication for employment of pancreatoduodenectomy for carcinoma of the pancreas varies among surgeons. There are those who are against the use of pancreatoduodenectomy because of the few "cures" achieved in carcinoma of the head of the pancreas, high mortality rates of the complicated prolonged operation, and usually long and complicated postoperative course. The consensus of opinion appears to be that this procedure is indicated where the carcinoma is small and easily resectable (1, 8, 24, 25). In the opinion of some, pancreatoduodenectomy may be used as a palliative procedure in well selected cases with regional metastases to nodes but with no distant metastases (2, 5, 9).

It is of interest that of the 14 patients operated for primary carcinoma of the pancreas whose survival proved to be greater than five years, some presented extension of the disease into the surrounding structures. Study of the resected specimens showed duodenal invasion in five cases including our own case (2, 3, 4, 6) local lymph node involvement in three cases (3, 4, 6) and invasion of the common duct in one case (6). The duration of abdominal pain need not necessarily contraindicate pancreatoduodenectomy since in two of the patients with more than five year survival there are reports of abdominal pain for one year (3, 4).

There is general agreement against the use of the procedure in patients with portal vein involvement, and with advanced disease (1, 7, 24, 26). The mortality of the procedure is considered by some to be no higher than palliative biliary-intestinal anastomosis, varying from 14 to 33 per cent (1, 6, 9, 26). As the indications for pancreatoduodenectomy become more clearly defined, the operative mortality is expected to decline (1, 9). Five year survival with primary carcinoma of the head of the pancreas, excluding the islet cell carcinomas and cystadenocarcinomas, is assumed to be "cure". Exception is taken to this statement (5). One of the cases reviewed died of metastases probably from the original tumor (6). The patient presented in this report, who has survived over six years following radical pancreatectomy, has been complaining recently of epigastric pain, suggestive of recurrence of carcinoma.

Despite the extensive mechanical and physiological alteration of the gastrointestinal tract as the result of surgery, and especially ligation of the pancreatic

duct without anastomosis to the intestine in the case presented, only mild symptoms of malabsorption were observed, which could easily be controlled with diet. Nevertheless, on investigation flat vitamin A tolerance test, flat carotene tolerance test, with a low serum carotene level and increased fat excretion in the stools were seen, indicating poor absorption of fat. Malabsorption of protein has been observed in some patients after this procedure (1, 15, 16). Following pancreatoduodenectomy and ligation of the pancreatic duct, varying degrees of malabsorption has been described (1, 6, 15, 16). In patients who do not develop symptoms of malabsorption, one of the following changes may occur: spontaneous fistula between the pancreas and the intestinal tract resulting in return of pancreatic secretions to the intestinal tract (1, 15, 16), sufficient digestion of fat and protein by digestive enzymes in other parts of the gastrointestinal tract (1), and finally presence of functioning pancreatic tissue in the intestinal tract (5). There is general agreement that anastomosis of the pancreas to the intestinal tract at the time of pancreatoduodenectomy should be performed (1, 2, 5, 8, 9, 15, 16, 27).

In nine to 27 per cent of patients with carcinoma of the pancreas glycosuria is present, (17, 28) in 12 to 20 per cent hyperglycemia is noted (17, 25) whereas 78 to 85 per cent show abnormally high glucose tolerance curves (8, 19, 28, 29). There has been considerable controversy as to whether diabetes mellitus is a predisposing factor for the development of carcinoma of the pancreas. The controversy arose because of the difficulty in distinguishing abnormal carbohydrate metabolism associated with carcinoma of the pancreas from independent "primary" diabetes mellitus. In the patient presented, glycosuria and hyperglycemia were noted at a time when the diagnosis of carcinoma of the pancreas was made. One sister had diabetes suggesting that the patient was at least predisposed to diabetes mellitus. Patients in whom glycosuria was discovered prior to the diagnosis, had no increased incidence of carcinoma of the pancreas; the incidence of hyalinization of the isles of Langerhans and of renal arteriosclerosis was lower in these patients than in those in the pre-existing "primary" diabetes group (17). In contrast, the proportion of carcinoma of the pancreas to other malignancies is considerably higher among diabetic patients (17, 18).

Concerning therapy it has been suggested that patients with pancreatoduodenectomy be placed on a high protein diet, with reduced fat content (120 to 140 grams of protein and 50 to 70 grams of fat). This type of diet increases protein absorption and limits the development of symptoms resulting from excessive fat excretion. In patients with considerable impairment of intestinal absorption, pancreatin in large doses (5 grams or more three times a day) is advised. Pancreatin has been shown to increase the intestinal absorption of protein and fat even in patients presenting no symptoms due to malabsorption (15).

SUMMARY

Five year survivals following pancreatoduodenectomy for carcinoma of the head of the pancreas are reviewed. An additional case that has lived more than

six years after the operation is presented, the fourteenth case in the literature. The indications for pancreatoduodenectomy in carcinoma of the head of the pancreas, metabolic alterations and survival rates are discussed.

ADDENDUM

Since this paper has been prepared for publication, September 1957, the patient was readmitted to the hospital in October and in November 1957 because of weight loss, epigastric pain and abdominal swelling. There was ascites and hepatomegaly. She developed an abscess in the right upper quadrant scar which was incised and drained of a large quantity of pus. A fistulous tract developed at this site, which continued to drain biliary and fecal material for three months. X-ray examination of the abdomen after instillation of lipiodol into the fistulous tract, showed a collection of lipiodol in the infrahepatic region, which assumed the shape of a gall bladder. Examination of the cell block of the ascitic fluid on two occasions was not diagnostic of malignancy. Microscopic examination of needle biopsy specimen of the liver showed no evidence of tumor. The patient became progressively icteric and cachectic. An exploratory laparotomy was performed and a small, hard, immobile retrogastric mass was palpated. This was thought to be metastatic carcinoma. The patient died four days after the operation, March 4, 1958.

At postmortem examination, there was a 5 cm. mass inferior to the liver which grossly appeared necrotic. Microscopic examination showed this mass to be composed of adenocarcinoma and necrotic tissue. The proximal stump of jejunum traversed the mass. The common duct and pancreatic duct ended in the mass. The common duct was dilated considerably and there was a stone which almost completely occluded the lumen in its distal portion near the mass. Stones were impacted in the hepatic ducts. The gall bladder was intact and was somewhat thickened and fibrotic. In the liver, there were several scattered 2 to 3 cm. nodules which on microscopic examination revealed adenocarcinoma. In addition, there were multiple small abscesses in the liver, probably due to cholangitis secondary to the biliary obstruction. Additional sites of metastatic adenocarcinoma were to the lumbar para-aortic nodes, nodes near the hilum of the liver, and to both lungs subpleurally. The pancreatic duct was dilated and thickened. The residual 8 cm. pancreas grossly appeared somewhat atrophic. On microscopic examination, no acinar tissue was seen, the acinar tissue being replaced by fibrous tissue. The isles of Langerhans were normal in appearance and were situated unusually close to each other. The spleen was slightly enlarged. No fistulous tract was demonstrated.

Acknowledgments

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NEUROLOGICAL MANIFESTATIONS OF ACUTE PORPHYRIA

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The purpose of this report is to review the neurological manifestations of acute porphyria as seen in a general hospital over a twenty-year period. The discharge diagnosis of all admissions to the Mount Sinai Hospital since 1939 were reviewed. The diagnosis of acute porphyria had been coded for eighteen different patients; however, this diagnosis was adequately confirmed in only ten patients. The analysis of these ten proven cases of prophyria, together with a review of the literature—with emphasis on the neurological complications—provides the substance of this report.

DEFINITIONS

The porphyrins are pigments with a basic chemical structure of four pyrrole rings linked by methene bridges. The porphyrias are diseases in which there are increased quantities of uroporphyrins in the urine. This is in contradistinction to the porphyrinurias in which—as a manifestation of other disease states—there are increased amounts of porphyrins other than uroporphyrins in the urine. Some of the diseases of interest to the neurologist which can produce porphyrinuria include acute poliomyelitis, pellagra, lead and arsenic poisoning, liver disease, pernicious anemia, and various blood dyscrasias (1). The porphyrias have been classified by Schmid et al (2), as shown in Table I. Neurological disease does not occur with porphyria erythropoietica or pure porphyria cutanea tarda. The neurological signs of mixed porphyria are the same as those of acute intermittent porphyria. The remainder of this report will deal, therefore, with acute porphyria. All ten of the proven cases of porphyria in this series are of the acute variety. Their clinical features are summarized in Table II.

INCIDENCE

Acute porphyria occurs usually between the ages of 20 and 50. It is two to three times as common in women as in men. There is strong evidence (3–5), that it is inherited as a Mendelian dominant. Geographical factors may be involved (3, 6).

The youngest patient in the present series was 19 and the oldest 51. Six patients were females. In three patients there was evidence of familial tendency of the disease: the cousin of one had had porphyria diagnosed elsewhere; the father of a second died of an illness characterized by abdominal pain and a Landry's paralysis; the urine of the sister of a third was found to contain porphobilinogen.

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TABLE I

Classification of the porphyrias

I. Porphyria erythropoietica—congenital photosensitive porphyria, usually with splenomegaly and hemolytic anemia.
II. Porphyria hepatica—hepatic disease or functional impairment frequent
  (A) Intermittent acute type—abdominal and/or nervous manifestations.
  (B) "Cutanea tarda" type—late appearance of photosensitivity without other manifestations.
  (C) "Mixed" type—photosensitivity with intermittent abdominal and/or nervous manifestions.

CLINICAL PICTURE

Non-neurological Manifestations

Gastrointestinal symptoms (abdominal pain, constipation, and vomiting) are the most frequent group of symptoms. Such complaints were present in 95% of the 69 cases Markovitz collected from the American literature (7). Abdominal pain was prominent in 55% of the 80 cases analysed at the Mayo Clinic by Martin and Heck (8), and significant in 85% of the 233 cases studied in Sweden by Waldenstrom (3). All ten of the present cases had abdominal pain at some time in the course of their disease.

The abdominal pain can be so severe that patients with acute porphyria are frequently admitted to surgical wards. Forty-six per cent of Markovitz's patients were explored before the diagnosis of porphyria was established (7). Four of our ten patients were similarly explored prior to diagnosis. Only one was subjected to surgery in this hospital. This patient was a 24 year old female who was operated on twice (once by a general surgeon, and once by a gynecologist) during the first four days of her hospitalization, before the diagnosis of porphyria was considered. Multiple abdominal scars are listed as a frequent physical finding of the disease.

The passage of dark or red urine, or urine which becomes dark on standing (as the colorless porphobilinogen is changed to the pigmented porphyrins) is another frequent finding in the disease. Fifty per cent of the Mayo Clinic series (8) and 70% of Markovitz's (7) series gave a history of passing such urine. Four of our ten patients were noted to pass similar urine.

Hypertension is another common finding in the acute phases of the disease. Forty-nine per cent of Markovitz's (7) cases and 40% of Waldenstrom's (3) had significant blood pressure elevations. It has been reported that this hypertension may be associated with retinal artery spasm (9) (which thus might explain the blindness occasionally noted in the disease); and postulated that the ischaemia due to vasoconstriction may be a cause of some of the neuropathological changes noted in the disease (10). Five of the ten patients in the present series had significant blood pressure elevations in the acute disease process.

Other recorded non-neurological signs and symptoms include tachycardia, fever, pigmentation, jaundice, hirsutism, arthritis, and menstrual irregularities. Transient splenomegaly (11) and purpura were noted in our series.

Neurogenic mechanisms have been implicated in the pathogenesis of some of

TABLE II

Summary of the clinical features of ten proven cases of porphyria

No.	MSH Chart No.	Age, Race and Sex	Pertinent History	Positive Physical Findings	Abnormal Lab. Data	Therapy	Other
1	11876	20 yr. old white male	Gastrectomy for ? ulcer one month pta; post-op stiffness and numbness of legs; convulsions; red urine; weakness of legs; hoarseness; dysphagia	B.P. = 180/120; flaceid quadriparesis; absent DTR's; glove hyperesthesia; impaired position and vibration sense	Urinary porphobilinogen; urinary uroporphyrin III content = 24.6 mg/24 hr.; inereased uroporphyrin I	B12	Neuro exam completely normal in clinic three years later
2	24859	37 yr. old white female	Abdominal pain; constipation; convulsions; generalised weakness	B.P. = 150/94; left flank tenderness; right ankle jerk absent; mild organic mental state; ? hepatomegaly	Urinary porphobilinogen	Chlorpromazine	Readmitted several times with pain
3	5436	41 yr. old Negro male	Five year history of intermittent abdominal pain and red urine; confusion with hallucinations; paresthesias and weakness of legs; atrophy of shoulders	Appendectomy scar; hepatomegaly; shoulder atrophy; paroxysmal elevations of blood pressure; fluctuant organic mental state	BSP retention of 15 to 35%; urinary porphobilinogen; urinary uroporphyrins III and I increased	Taurocholate; thiouracil	Father died of Landry's paralysis; had periodic abdominal pain
4	3155	19 yr. old white male	Abdominal pain; vertigo; one convulsion; tremors	B.P. = 142/100; weakness and atrophy both arms and legs; absent DTR's; mild organic mental state; dysphagia; hoarseness; nystagmus	Urinary porphobilinogen; muscle biopsy: focal necrosis	ACTH; priscoline, glutathione, tryptophane, B12; BAL; versenate	Sister with urinary porphobilinogen; much improved in follow up clinic
5	55718	36 yr. old white female	Abdominal pain; previous negative exploration; heavy barbiturate therapy; "cataleptic episode",	B.P. = 144/100; Fluctuant organic mental state; dark skin; muscle weakness	Urinary porphobilinogen	ACTH	No follow up

6	51316	24 yr. old white female	Abdominal pain; vomiting; previous history of "auto hemotrophic" purpura	T = 102; B.P. = 180/90; purpura; red urine	Urinary porphobilinogen	ACTH; meticorten; thorazine	Two negative explorations; readmitted with pain in left lower extremity, and absent left knee and ankle jerks
7	637742	28 yr. old white female	Previous barbiturate and sulfa therapy; chest and abdominal pain; insomnia; progressive quadriparesis; transferred from another hospital in coma	Absent DTR's; quadriparesis; comatose; went into shock on admission	Increased urinary uroporphyrins III and I	ACTH; cortisone	Ceased on second hospital day from pulmonary embolus; cousin with porphyria diagnosed elsewhere
8	58406	36 yr. old white female	Periodic abdominal pain; episodes of blurring of vision	Completely negative; somewhat agitated	Urinary porphobilinogen	None	Apparently well after two years
9*	47766	51 yr. old Negro female	Vague abdominal pain five years; acute abdominal pain; vomiting; dark urine	Completely negative except for transient splenomegaly	Urinary porphobilinogen; BSP retention = 9.5%; transient positive Combs test; elevated ESR	None	No follow up
10	96955	39 yr. old white male	Lower abdominal pain; low grade fever; treated with barbiturates; organic mental syndrome with hallucinations; progressive weakness of extremities; dark urine	Bilateral facial palsies; quadriparesis with moderate muscle atrophy; tremors; inconstant glove-stocking hypalgesia	Urinary prophobilinogen; urinary uroporphyrins III = 97 mg./24 hrs.; coproporphyrin = 7 mg/24 hrs.; muscle biopsy: neurogenic atrophy	Thorazine; BAL; versenate; folic acid	Improvement of quadriparesis,

* This case has previously been reported (11).

the above symptoms. It has thus been postulated that the abdominal pain and other gastro-intestinal symptoms are due to involvement of the parasympathetic nervous system (12); and that the hypertension and tachycardia may reflect IXth and Xth cranial nerve lesions and interference with the sinoaortic "buffer" systems (13).

Neurological Manifestations

It is probable that every portion of the nervous system can be involved by the disease. The clinical symptoms, however, can conveniently be divided into three groupings: (a) those of peripheral nerve dysfunction—with or without an associated myelo-radiculopathy; (b) those of cerebral dysfunction; and (c) those of brain stem dysfunction. Signs and symptoms related to one, two or all three groupings may be found at one time or at different times in the individual patient. It is also possible to have porphyria without any neurological finding.

The peripheral neuropathy includes muscle weakness and atrophy (which is marked proximally as distally), transient or persistent diminution or loss of deep tendon reflexes (the ankle jerks may remain while the knee jerks are absent (14)), and severe paresthesias and dysesthesias of the limbs (which can occur with or without objective sensory findings). This peripheral nerve involvement may be isolated or multiple. The cerebral signs include organic mental states—varying from mild confusion to delirium and coma; convulsions—which can be focal or generalized; aphasia; hemianopsias; and total blindness. Personality changes suggesting those of hysteria or schizophrenia are recorded. The bulbar difficulties include dysphagia, diplopia, anisocoria, facial and laryngeal palsies. A frequent cause of death is medullary involvement as part of a rapidly progressing Landry's paralysis. Although the occurrence of the latter in porphyria is denied by Waldenstrom (3, 9), there have been several well-documented cases in America (7, 15–17) and Switzerland (18). The only fatality in our ten cases was a 28-year old female transferred from another hospital in coma and hypotensive. She ceased on the second hospital day despite vasopressors and other supportive measures. Her history was that of a rapidly progressing paralysis. However, the cause of death—as determined at autopsy—was a large pulmonary embolus.

Seventy-two per cent of Markovitz's cases showed evidences of neuropathy; 80% of his patients had mental changes (7). Forty-two per cent of Waldenstrom's patients had paresis of one or more muscle groups (3), and 39% of the Martin and Heck series had clear evidence of central nervous system involvement (8).

Neurological disease was clearly present in seven of our ten patients. Six had weakness or atrophy of muscle groups. This varied from mild atrophy of both shoulder muscles to almost complete quadriplegia. Six patients had disturbances of consciousness of varying degrees. Five had absence of one or more deep tendon reflexes. Three had grand mal convulsions, while two had loss of sensation suggesting peripheral nerve dysfunction. Two patients had bulbar signs such as dysphagia and hoarseness. One was noted to have nystagmus, and one complained of episodic blurred vision. No other visual findings were noted.

PATHOLOGY

The post-mortem findings in porphyria are not striking. There may be segmental dilatations of the small bowel, and slight focal necrosis in the liver. Examination of the nervous system may reveal patchy demyelination in the entire central nervous system, some roots and especially autonomic and peripheral nerves (10, 19–21). Chromatolysis of cells in the anterior spinal cord and posterior ganglia, as well as vacuolation of some medullary cells, has been described. The muscles show focal atrophy (16). Vanotti has described a disease like acute porphryia, except that there is marked muscle atrophy with loss of myoglobin from the muscle fibers (22). The term myoporphyria has been applied to this condition. A high incidence of muscular involvement has also been noted clinically (5).

It is probable that none of the pathological changes described for the disease are specific. It has been both claimed (23) and denied (20, 24) that the central nervous system contains increased quantities of porphyrin.

Muscle biopsies were performed in two of our cases. Both showed focal "neurogenic" atrophy. Patchy demyelination was found in the roots and peripheral nerves of the one patient who succumbed.

LABORATORY FINDINGS

Leucocytosis is not an infrequent finding and was present in several of our cases. If the small bowel is x-rayed, segmental dilations of the gut may be noted (12). There is occasional evidence of liver dysfunction (8, 25). Two of our ten patients had abnormal bromsulphalein retention.

Electroencephalographic (26–29) and electromyographic (7, 30–32), abnormalities have been described, and reports of cerebro-spinal fluid pleocytosis (33) and other abnormalities (32) have appeared.

Chemical analysis of the urine reveals that it contains large quantities of uroporphyrin III or I (34, 1) and increased amounts of coproporphyrin III. These porphyrins are combined with zinc, and the increased zinc excretion in the urine has been reported to be a characteristic finding, which correlates well with the course of the disease (27). The stool also contains porphyrins, and is reported to fluoresce readily (6).

The most significant and most readily determined laboratory finding is porphobilinogen in the urine. This was found to be present in 68% of the Martin and Heek cases (8), 80% of Markovitz's (7), and in nine of the present series. The presence of porphobilinogen as determined by the Watson-Schwartz reaction (35) is highly specific for the disease (36), although a few false positives have been reported (37).

ETIOLOGY AND PATHOGENESIS

The cause of porphyria is unknown. Infection has been mentioned frequently as a precipitating factor, but little proof of this could be found in the literature. Certain drugs (arsenicals, sulfonamides, acetanilid, and the barbiturates) are

known to increase the severity of the disease, or to precipitate exacerbations in victims of the disease. There is little evidence, however, that these drugs can produce the disease by themselves. Analysis of the urine of many patients receiving barbiturates has revealed almost none with porphobilinogen or pathological porphyrins (15, 38). None of our patients had preceding infections, but three had received heavy barbiturate therapy prior to the establishment of the diagnosis.

It has been possible to produce an "experimental porphyria" in certain laboratory animals by giving Sedormid (39) and other derivatives of allylacetic acid (40). This syndrome is characterized by transient paresis of the hind limbs, dilatation of the stomach (which can lead to death by rupturing), irregular small bowel spasm, and the presence of porphobilinogen and increased porphyrins in the urine and liver. The catalase content of the liver is diminished in these experimental porphyric animals (41). Study of the liver in a patient with porphyria, however, has revealed normal catalase activity (42). This experimental porphyria differs further from human porphyria in that no pathological changes are detected in the nervous system (43), in the former condition.

There are several investigations (44–46) showing abnormalities in the metabolism of porphyrin precursors in patients with the disease, but no evidence is given pertaining to the pathogenesis of the neurological and other symptomatology. The concept of vasospastic ischemia of the nervous system due to an unknown toxin (10) has received recent criticism (19, 20). Intra-venous porphyrin administration to normal humans has no effect (47), and the production of smooth muscle spasm by porphyrin has been claimed (48) and denied (49). There are some reports of convulsions (23) and irritability (50) in laboratory animals following intra-venous porphyrin administration, although Goldberg et al (49) noted no effects. One report of polyneuritis in a patient receiving intramuscular hematoporphyrin has appeared (51).

PROGNOSIS AND TREATMENT

It is said that 50% of all patients with attacks of porphyria will die with an attack. The mortality rate increases with the greater degree of central nervous system involvement (7). Only one of our ten patients died, and as noted above, the method of exitus here was pulmonary embolization. Several of the patients in this series have been followed in the clinic. It is remarkable to note that some patients who were confined to bed with marked muscle wasting and quadriparesis during their hospital stay had almost normal neurological examinations at follow-up clinic years later.

The therapy for the disease is unsatisfactory. Barbiturates and other drugs which may potentiate the disease process are best avoided. The following have been reported to be of aid in relieving the severe abdominal pain: intra-venous calcium, intra-venous procaine, tetra-ethyl ammonium chloride, glutathione, priscoline, vitamins, steroids, ACTH, electro-convulsive therapy, section of the splanchnic nerves and other agents (52, 53). Recently chlorpromazine has been reported (54, 55) to be of aid in the disease. However increased neurological

deficit following usage of the drug has also been described (27). None of the above agents affect the urinary excretion of porphyrins or porphobilinogen, and none of them, (with the possible exception of chlorpromazine (56)) protect against Sedormid induced porphyria in animals. The most recent therapeutic claims have involved the use of chelating agents, first introduced by Schrumpf (57), and now by Peters (27, 53) in an attempt to correct the disturbances of zinc metabolism in the disease.

Many of the above forms of therapy—including the chelating agents—have been used in our ten patients. Although our series is certainly small, there is no definite evidence that the improvement noted in any patient was greater following the above measures than would have occurred spontaneously in the natural course of the disease. The most effective therapy—in our limited experience—would appear to be early and active physical rehabilitation.

DISCUSSION

Ten additional cases of acute porphyria have been added to the rapidly expanding literature of the disease. The variety of neurological and other manifestations possible is again emphasized. Although there are many contradictions in the literature concerning the etiology and treatment of acute porphyria, this variety of clinical manifestations has led previous authors to one common conclusion: A high "index of suspicion" is necessary for diagnosis. Thus the moral of articles about porphyria appearing in such varied journals as those for psychiatrists (58) to those for surgeons (59) (and recently others (60, 26)) is to point out the mimicking aspects of acute porphyria, and to emphasize that this diagnosis must always be considered in difficult diagnostic neurological and other problems.

It is probable that this point has been well taken by now, and there may be a tendency for clinicians to over diagnose porphyria. That this is so may be suggested by the survey of the records of this hospital, where porphyria was diagnosed eight times without adequate proof (i.e., the presence of porphobilinogen or abnormal porphyrins in the urine). Thus the concept of "porphyria without porphyrinuria (9, 14)" is not considered valid. However, repeated study of the urine should be performed in patients with negative urines in whom the clinical suspicion of porphyria is present.

That the diagnosis of porphyria is being considered frequently (in this hospital) is suggested by the fact that during the three month period from January through March, 1958, twenty-one 24 hour urine specimens were submitted to the chemistry department for analysis for porphyrins; and at least twenty-six casual specimens were examined by the hematology department for porphobilinogen.

Most of the cases mis-diagnosed as porphyria were obscure peripheral neuropathies, or patients with mental and emotional changes. As an illustrative case, a 34 year old female was admitted to the surgical service with atypical severe pain in the middle portion of the right side of the abdomen. She was treated with large amounts of Demerol and atropine, and after the second of such injections she developed an acute confusional psychosis. She was transferred to the psychiatric service where her urine, when exposed to sunlight, was

noted to be "darker" than her fresh urine. The diagnosis of porphyria was thought established. At a subsequent admission she was found to have bilateral ovarian cysts with areas of necrosis in the right one, and repeatedly negative urines for porphobilinogen and porphyrins. It is quite possible that the previous episode of pain was due to her ovarian pathology, and the mental changes due to the drugs administered in an attempt to control this pain.

Thus, the moral of this report is, while porphyria is a diagnosis to be thought of frequently, it should not be made without adequate laboratory investigation.

SUMMARY

Ten cases of proven porphyria over a 20 year period at The Mount Sinai Hospital are reported. These cases are compared to many others in the literature, with emphasis on the neurologist's viewpoint. While the neurological and other manifestations of the disease can assume many forms, the diagnosis of porphyria can only be established by analysis of the urine for porphobilinogen or pathological porphyrins.

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A METHOD OF ANALYZING ELECTROCARDIAC ENTITIES IN SPACE

IV. The $\overline{QRS}$-$\overline{T}$ Angle as Determined from the Twelve-Lead Electrocardiogram

LOUIS BRINBERG, L.R.C.P., ED.

If the ventricular gradient were equal to zero, the time-integrated force of regression, $\overline{T}$, would be equal and opposite to that of accession, $\overline{QRS}$. The $\overline{QRS}$-$\overline{T}$ angle would be 180°, and the T wave discordant to the QRS in all leads. It has been found empirically that discordancy in certain leads is indicative of myocardial damage. As such discordancy intimates divergence of $\overline{T}$ from $\overline{QRS}$, the $\overline{QRS}$-$\overline{T}$ angle in space may be taken as an index of myocardial damage. A pilot study of 49 normal subjects was therefore performed in an attempt to establish the physiological range of this angle.

METHOD

As the gradients, electric axes, and $\overline{QRS}$-$\overline{VG}$ angles of these subjects had previously been determined from the twelve-lead electrocardiogram (1), it was decided to obtain $\overline{T}$ by vectorial subtraction, i.e., by applying the values to the equation, $\overline{VG} = \overline{QRS} + \overline{T}$. The $\overline{QRS}$-$\overline{T}$ angle was accordingly determined in the following manner.

$\overline{QRS}$ and $\overline{VG}$ are positioned on the surface of the sphere. They subtend a plane, the *plane of mean ventricular activity*, Pl_v (2). Wilson's parallelogram of forces, and therefore $\overline{T}$, lie on this plane (2). The plane is established by positioning the movable meridian (2) on $\overline{QRS}$ and $\overline{VG}$. It then traces the great circle on which the plane bisects the sphere, as in fig. 1a. If the 0° mark is placed on $\overline{QRS}$, the $\overline{QRS}$-$\overline{VG}$ angle is read on the graduated meridian. As the magnitudes of $\overline{QRS}$ and $\overline{VG}$ have previously been determined, we may draw these vectors in their true lengths and separated by the $\overline{QRS}$-$\overline{VG}$ angle, as in fig. 1b. The paper then represents the plane on which the vectors lie. Since $\overline{T} = \overline{VG} - \overline{QRS}$, the subtraction is performed vectorially by drawing a vector from the terminus of $\overline{QRS}$ to the terminus of $\overline{VG}$, as in fig. 1b. The magnitude of $\overline{T}$ and the $\overline{QRS}$-$\overline{T}$ angle are thus obtained.

As $\overline{QRS}$, $\overline{VG}$ and $\overline{T}$ lie on the great circle, $\overline{T}$ may be marked on this circle, separated from $\overline{QRS}$ by an arc distance equal to the value of the $\overline{QRS}$-$\overline{T}$ angle, as in fig. 1c. The $\overline{QRS}$-$\overline{T}$ angle may then be represented on the sphere by an arrow whose tail is at the $\overline{QRS}$ position and whose head is at the $\overline{T}$ position, as in fig. 1d.

RESULTS

The results are shown in figs. 2 and 3. The mean $\overline{QRS}$-$\overline{T}$ angle is 55°, the range is 13° to 91°, and the standard deviation is 19°. The mean bearing of $\overline{T}$ from $\overline{QRS}$ is N21°; W61°.

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Fig 1a

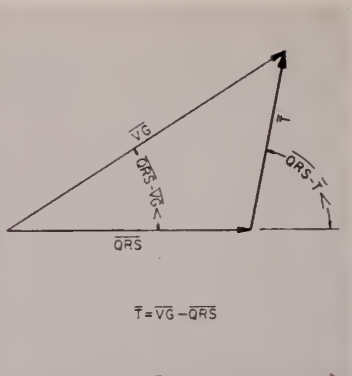

Fig 1b

Fig 1c

Fig 1d

FIG. 1a. The spherical coordinates of $\overline{QRS}$ and $\overline{VG}$ are determined, and these vectors represented by spots on the surface of the sphere. If the plane they subtend were passed through the sphere, it would cut off a great circle. This circle is visualized by positioning the moveable meridian over $\overline{QRS}$ and $\overline{VG}$. If the 0° mark on the meridian is placed on $\overline{QRS}$, the $\overline{QRS}$-$\overline{VG}$ angle is read at $\overline{VG}$ in degrees. In this case it equals 33°. Since $\overline{QRS}$, $\overline{VG}$, and $\overline{T}$ lie on the same plane, Pl_v, the *plane of mean ventricular activity*, the spot representing $\overline{T}$ must lie on the great circle.

FIG. 1b. The magnitude of $\overline{T}$ and the $\overline{QRS}$-$\overline{T}$ angle are determined by vectorial subtraction of $\overline{QRS}$ from $\overline{VG}$. As the magnitude of these two vectors and the angle they subtend have previously been determined, they may be drawn in their true lengths and separated by this angle. $\overline{T}$ is then drawn from the terminus of $\overline{QRS}$ to that of $\overline{VG}$, and the angle between its axis and that of $\overline{QRS}$ is the $\overline{QRS}$-$\overline{T}$ angle, which in this case 79°.

FIG. 1c. Since $\overline{VG}$ is the resultant of $\overline{QRS}$ and $\overline{T}$, it must lie between them. $\overline{T}$ is marked on the sphere at an arc distance from $\overline{QRS}$ equal to the $\overline{QRS}$-$\overline{T}$ angle.

FIG. 1d. The $\overline{QRS}$-$\overline{T}$ angle may then be represented by an arrow whose tail is at the $\overline{QRS}$ position and whose head is at the $\overline{T}$.

DISCUSSION

It might seem that determination of $\overline{T}$ by subtraction of $\overline{QRS}$ from $\overline{VG}$ is a roundabout method of obtaining the $\overline{QRS}$-$\overline{T}$ angle and that it would be simpler to measure the area of the T wave directly. This, however, presents certain difficulties. Of the three forces, $\overline{VG}$, $\overline{QRS}$ and $\overline{T}$, the first can be measured with the

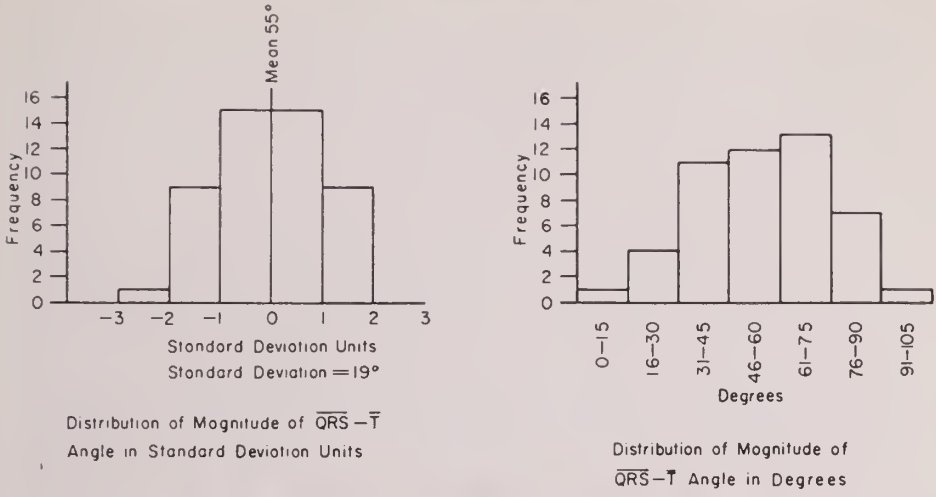

FIG. 2

FIG. 3. QRS-T angles of 49 normal subjects. The triangle, star and solid circle are at the mean $\overline{QRS}$, $\overline{VG}$, and $\overline{T}$ positions respectively. The mean $\overline{QRS}$-$\overline{T}$ angle is 55°, and the mean bearing of $\overline{T}$ from $\overline{QRS}$ is N21°; W61°. The posterior hemisphere is shaded.

most accuracy, and the last with the least, and the source of error lies on the baseline. The isoelectric level is difficult to ascertain in the case of the T wave for two reasons: the T of P, T_p, is hidden within the QRST complex, and there is in almost all cases an overlap of T and QRS, i.e., regression begins before accession is completed. These factors also affect the area of QRS, but to a lesser degree, as the QRS wave is generally of much shorter duration than the T. They do not, however, appreciably distort the values obtained in the case of the gradient, provided T_p is equal and opposite to P (there is evidence that this is so (3)), and provided there is no current of injury. By measuring the area of PQRST in one sweep of the planimeter, or by counting squares in such a fashion as to give a similar result (1), T_p is neutralized by P, and the area of overlap, which

represents the resultant time-integral of QRS and T for the period, is included as such. This is amplified elsewhere (4).

In determining $\overline{T}$ by vectorial subtraction, therefore, we are utilizing the two more reliable vectors, $\overline{QRS}$ and $\overline{VG}$, to obtain the third, $\overline{T}$, whose value by direct measurement is least accurate. If any current of injury exists, this indirect approach is no longer reliable as the gradient is then indeterminable (4). It is assumed that none was present in these normal subjects.

The method described above is a true vectorial subtraction in space. The same results may be achieved by subtraction of projections. In this case the frontal and horizontal projections of $\overline{QRS}$ are respectively subtracted from those of $\overline{VG}$, and the projections of $\overline{T}$ thus obtained. The spherical coordinates of $\overline{T}$ are then determined by revolution, and the $\overline{QRS}$-$\overline{T}$ angle measured on the sphere.

Scalar subtraction may also be performed. Thus if PQRST equals 30 m.c.v.s. and QRS equals 12 m.c.v.s. in lead I, then T is 18 m.c.v.s. in this lead. The problem here is to evaluate the transitional axis on the horizontal plane. As it is that axis on which PQRST minus QRS equals zero, it is not readily determined by inspection. Scalar subtraction is therefore impractical.

An alternate approach is to rotate the plane of the vectors, Pl_v, orthographically into a position parallel to the horizontal plane. The vector formation then appears in its true size. As several simpler methods have been presented in this series, this procedure shall not be described.

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COMPARATIVE STUDY OF VASODILATORS BY OBJECTIVE METHOD

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The purpose of this study is the collection, examination, and evaluation of data on the peripheral vasodilating effect of three commonly used drugs; nitroglyn®, peritrate®, and metamine®. Each drug was given on a separate day to a healthy normal adult. The effect on peripheral circulation was recorded objectively by the method described below.

The drugs used are at present widely employed as vasodilators. They are essentially organic nitrates. The following table gives some of their important characteristics.

METHOD

These substances were given as tablets, swallowed with a small quantity of water. The effects on the peripheral circulation were then recorded by means of an instrument called a capacigraph.

The capacigraph, which is essentially an alternating current bridge, was described by the author in 1937 in an article (1) which was summarized as follows: "The alternating current bridge offers a method of studying the peripheral circulation, and of recording changes produced by physiologic and pharmacologic agents." In 1956 (2) this instrument, then named a capacigraph, was used to demonstrate the prolonged action of nitroglyn®. The author concluded: "The method employed depends on an objective curve and may be used to investigate peripheral vascular changes."

For the reader not familiar with the instrument, its operation may be explained as follows. The capacigraph is a sort of electrical balance which can be adjusted to the object under examination just as an ordinary scale can be adjusted by adding or subtracting weights. The pointer of the scale moves when the balance is disturbed. In much the same way, the capacigraph is adjusted to the electrical state of the finger so that there is an electrical balance and then any electrical change in the finger will alter this balance. The pulse wave, which causes a slight flow of blood into the finger, disturbs the electrical balance and consequently registers as a deflection in the pointer. This deflection is recorded as a graph.

Detailed procedure was as follows: The subject sat in a comfortable chair and was allowed from fifteen to thirty minutes, depending on the outside temperature, to adjust to room temperature. This was done as an office procedure. One or more control capacigrams of the right index finger were taken, and the drug to be tested was then swallowed. Capacigrams of the right index finger were taken at intervals of ten minutes for the first hour, twenty minutes for the second hour, and thirty minutes for succeeding hours for a total period of about six and one half hours. A one hour break for lunch was allowed between the third and fourth hours. During the observation period the subject was permitted to read, converse,

TABLE I

Characteristics of Commonly Used Vasodilators

Pharmaceutical Name	Nitroglyn®	Peritrate®	Metamine® Sustained
Chemical Name	Glyceryl trinitrate	Pentaerythritol tetranitrate	Triethanolamine trinitrate biphosphate
Chemical Formula	$C_3H_5(ONO_2)_3$	$C_5H_5(ONO_2)_4$	$N(CH_2CH_2ONO_2)_32H_3PO_4$
Molecular Weight	227	316	480
Dosage Given	.013 G.	.020 G.	.020 G.
Percent of NO_2	60.4	58.2	28.75
Total NO_2	7.85 mg.	11.64 mg.	5.75 mg.

and move about, according to his inclination. Tobacco, excitement, or unusual exertion were avoided. This procedure was followed on separate days using each of the three drugs under examination. The recorded curves, or capacigrams, were then labelled and filed for subsequent examination.

RESULTS

Capacigrams were made in this fashion from twenty two normal, healthy individuals varying in age from eighteen to forty-two years. All twenty-two were tested with nitroglyn®; ten were also tested with peritrate® and metamine®. The curves obtained were examined and carefully corrected measurements made of the height of the katacrotic pulse wave. This wave was chosen because earlier work with nitroglycerin (2) demonstrated that the katacrotic pulse wave reveals the most constant and significant change in peripheral vasodilatation. Figure 1 will illustrate this point.

It can readily be seen on examination of Figure 1 that the finger capacigram before and after administration of vasodilators shows definite changes. The main pulse wave tends to rise more sharply and may become higher. These changes in the main wave have been observed repeatedly, but have been found unsatisfactory as a basis for measurement because they are not constant and are subject to a number of accidental factors such as emotion, fatigue, room temperature, ingestion of food, posture, etc. The significant changes illustrated in Figure 1 are shown by the secondary or katacrotic wave. This wave, which is ordinarily rather small, is affected by the vasodilators in such a way as to become much more prominent. The constancy and reliability of this change in the secondary or katacrotic wave make it suitable for objective measurement of the effect of vasodilating drugs. For these reasons, our attention has been concentrated on the katacrotic wave as an index of the effect of the vasodilating drugs.

After all measurements had been completed, they were tabulated and averaged for each drug, and three composite curves were drawn to show at a glance the comparative effect of the three drugs. These composite curves are shown in Figure 2.

The three curves in Figure 2 represent the intensity and duration of the vasodilating effect of the given drugs during the period of observation. Several characteristics of these curves are worthy of comment.

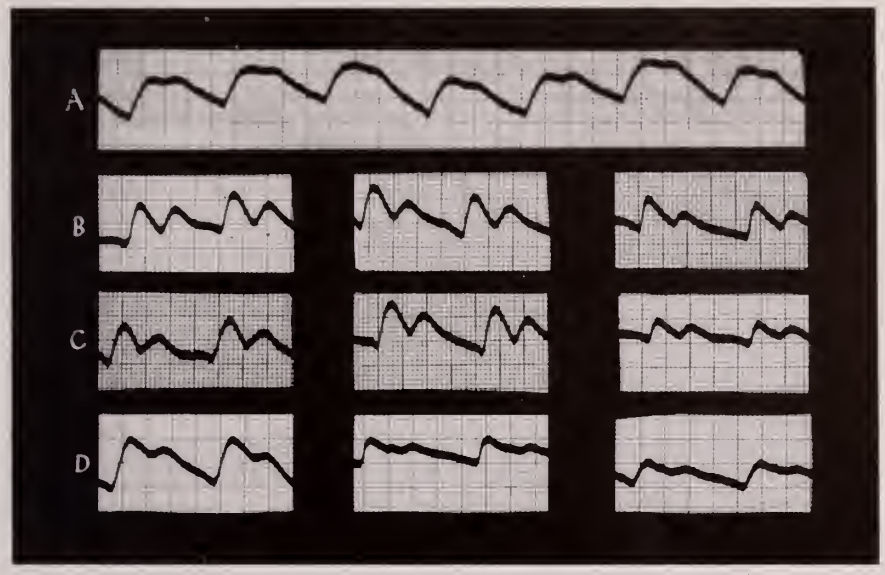

FIG. 1. Effect of Vasodilators on Circulation in Right Index Finger.
Capacigrams of Right Index Finger. A. Before administration of vasodilators. B. 1, 2, and 3 hours after NITROGLYN® Gr. 1/5. C. 1, 2, and 3 hours after PERITRATE® Mg. 20. D. 1, 2, and 3 hours after METAMINE® SUSTAINED Mg. 20.

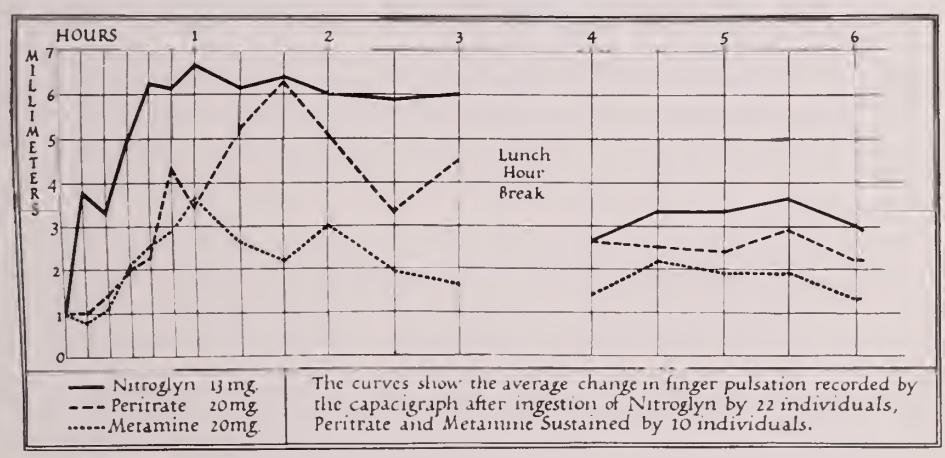

FIG. 2.

During the first three hours after ingestion of the drugs, there is decided elevation of the curve of nitroglyn®, less elevation of the curve of peritrate®, and least elevation of the curve of metamine® sustained. The nitroglyn curve reaches its maximum height from forty to sixty minutes after the ingestion of 13 milligrams of the drug (7.85 mg. of NO_2), and maintains this height until the lunch break three hours after ingestion. The peritrate® curve reaches its maximum height about one hundred minutes after ingestion of 20 milligrams of the drug (11.64 mg. of NO_2), but is considerably lower than the nitroglyn® curve during the first

three hours. This is in spite of the fact that the dosage of peritrate tested was approximately fifty per cent greater than the dosage of nitroglyn®. The metamine® curve rises more slowly, reaches its maximum height in about one hour, and falls steadily during the third hour. This curve is considerably lower than the other two. The dosage of metamine® used is 20 milligrams, but this represents only 5.75 milligrams of NO_2.

Following the one hour break for lunch, all three curves are sharply lowered, probably because of rerouting of additional blood to the digestive tract. The nitroglyn® curve is consistently higher than the peritrate® curve, and the metamine® curve remains in third place. At the termination of the period of observation, six hours, there is still some slight evidence of vasodilatation.

DISCUSSION

From a clinical point of view, the effect of these drugs on the coronary arteries is a matter of great importance. Many clinicians believe that vasodilating drugs, especially those of the nitrate group, dilate the coronary arteries and therefore improve the blood supply to the heart muscle. This opinion, though widely held, is based on clinical experience and is not, at present, supported by any reliable objective evidence. Unfortunately, there is no accurate method of examining the coronary circulation in the intact human heart. The induction of anaesthesia together with the mental and emotional strain of operation, and also operative techniques themselves, produce such profound changes in the general circulation that observations under operative conditions have little validity for the intact individual. The constant motion of the heart, its relative inaccessibility, and the labile nature of the heart rate and blood pressure all conspire to prevent exact or reliable observation of the coronary circulation. Up to the present time no method, to my knowledge, has been employed or even suggested to overcome these difficulties.

We are justified, however, as a result of almost a century of clinical experience, in affirming that vasodilators of the nitrite or nitrate group often relieve symptoms of cardiac distress. There is general agreement that this action is due to peripheral vascular dilatation, possibly combined with coronary artery dilatation. The results of such medication are often so spectacular that drugs of this nature warrant intensive study. For this reason, we have investigated these drugs from the standpoint of a property which is common to them all and which seems essential to their clinical use: namely, peripheral vasodilatation.

The question naturally arises: what is the comparative vasodilating effect of these three drugs when given in dosages of equal amounts of each drug or of equal amounts of NO_2? The answer to this question may be a valuable aid in adjusting the dosage, but the purpose of the present study is to investigate the effects of these agents in approximately the amounts generally prescribed at the present time.

Within these limitations the following conclusions seem reasonable:

Nitroglyn® in dosage of 13 milligrams (1/5 gr.) has a more rapid and more intense peripheral vasodilating action than either peritrate® or metamine® sus-

tained in doses of 20 milligrams. After three hours, following the ingestion of food, the peripheral vasodilating action of these three drugs is decreased, although it is still observable after six and one-half hours.

SUMMARY

Twenty two individuals, aged 18 to 42, ingested nitroglyn®, and ten individuals ingested peritrate® and metamine® sustained on separate days. The peripheral vasodilating effect was observed by an objective method: capacigraph recordings of finger pulsation. Measurements of these recordings were tabulated, averaged, and plotted as three composite curves to show the comparative vasodilating action of the drugs.

CONCLUSIONS

Nitroglyn®, in a dosage of 13 milligrams, has a more rapid and more intense vasodilating effect than either peritrate® or metamine® sustained in 20 milligram dosage.

After four hours and following a lunch period, the vasodilating effect of the three drugs drops sharply. After six hours, some vasodilating effect is still evident.

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CLINICAL CONFERENCE ON SARCOIDOSIS

THE MOUNT SINAI HOSPITAL

February 24, 1958

Chairman, Dr. Frederick H. King

Chairman King:

The evening's program is devoted, as you know, to the subject of sarcoidosis. This subject was chosen for several reasons. First, because we see this disease with increasing frequency, either because we are on the look out for it now, more than previously or because of a shift in the hospital population. It is a disease in which progress seems to come slowly. While the major problems of cause and pathogenesis remain in an unsolved state, there has been some progress in such phases as epidemiology, diagnosis, both by biopsy and intracutaneous tests, and in treatment with steroids.

For all these reasons, we thought it would be in order to take an inventory of what we know about this disease and what remains to be worked out. To this end we have invited the group in this hospital whose major concern is the investigation of the problem of the diagnosis and management of patients with sarcoidosis. This group was organized and is headed by Dr. Louis E. Siltzbach, who will remain in the Chair after he has introduced the subject with a discussion of the "Etiologic and Immunologic Considerations in Sarcoidosis."

Dr. Louis E. Siltzbach:

We learn a little more about sarcoidosis every year and it is about some of the newer knowledge as well as about already established data that we will be speaking tonight.

It is customary to define the condition one is considering but that is a little difficult when it comes to sarcoidosis. The truth is our definitions of sarcoidosis have something of the quality of the blind men's description of the elephant. We try to guess at the nature of the whole animal by adding together dim notions of some of its parts.

Actually, that is the best we can do at this point. After all, sarcoidosis still is a condition or perhaps a group of conditions of undetermined etiology with a mysterious pathogenesis and a characteristic but non-specific histologic picture, of unknown incubation period and manner of spread, and certain peculiar im-

munologic and metabolic features which are really not clearly understood. Above all, no one has yet been able to transmit sarcoidosis to an experimental animal and this presents quite a barrier to its investigation.

All this sounds bleak but, as you know, there is a brighter side. We now make the diagnosis of sarcoidosis more readily by means of scalene fat pad biopsy and biopsies at other sites. The Nickerson-Kveim intracutaneous test has proved itself a valuable confirmatory aid. We can distinguish better between sarcoidosis on the one hand, and, on the other, beryllium poisoning, histoplasmosis and other granulomatous conditions which mimic it. This is so because the diagnostic tools in all these conditions as well have become more effective.

We know more about the geographic and racial distribution of sarcoidosis in our country, thanks to the work of Dr. Michael and Dr. Cummings.

And with the advent of corticosteroid therapy we have, it seems to me, for the first time, drugs which although in no sense curative, have helped tide our patients over some very trying and hazardous episodes. With the help of hormonal therapy we have returned not a few disabled patients to a useful, more or less normal daily life. I add hastily that, as in any chronic and recurrent condition, relapse is common when the drugs are stopped.

Almost half of our sarcoidosis patients have experienced a relapse after discontinuation of steroid therapy but we find that with the resumption and prolongation of treatment a fair end-result can eventually be achieved for most patients. We shall refer again to some aspects of these problems during the case presentations and the discussions which are to follow.

Now I shall try to give a short summary of the conflicting views regarding the etiology of sarcoidosis.

For more than fifty years the big questions have been:

Is sarcoidosis one disease with one etiologic agent not yet known? Or,

Is sarcoidosis a syndrome—a composite of many distinct and unrelated granulomatous diseases? If so, shall we adopt the practice of labelling our cases tuberculous sarcoidosis, beryllium sarcoidosis, histoplasma sarcoidosis and so forth? And how are we to regard the large group of patients for whom no etiologic agent is detectable—the group which concerns us tonight—those with idiopathic sarcoidosis?

It seems that one's views on these questions depend in some degree upon what country he is from. In the United States and the Scandinavian countries most investigators favor the concept of a single disease entity with its own not yet fathomed cause or pathogenesis. In Great Britain and in some continental countries, on the other hand, the more popular view is that idiopathic sarcoidosis is primarily a form of tuberculosis in an unusual phase, a phase marked by a lack of tubercle bacilli and caseation in the patient's tissues and very often by tuberculin insensitivity as well. Indeed, sarcoidosis has sometimes been equated with tuberculin-negative tuberculosis.

This calls to mind another well-known instance in which a disease was first held to be a form of tuberculin-negative tuberculosis but which later was shown to be an unrelated independent condition. I refer to histoplasmosis.

About ten years ago in the Mississippi Basin asymptomatic pulmonary calcification was being encountered on survey chest films of young adults and children. These patients did not react to strong doses of tuberculin and it was first supposed that the asymptomatic pulmonary calcifications were the result of a tuberculosis infection in these young persons which had run through infection, caseation and healing by calcification relatively silently and in an unusually short time. It was speculated that the healing by calcification had been so complete that the individual lost the ability to react to intracutaneous tuberculin. In short, a tuberculin-negative tuberculosis. Well, this explanation of the lack of tuberculin sensitivity did not sit well with most investigators, and tuberculin-negative asymptomatic pulmonary calcification in that region was for a time considered an idiopathic condition. Not much later, however, the close relationship to histoplasma capsulatum infection was established. Idiopathic tuberculin-negative pulmonary calcification was recognized as a sequella of a benign histoplasmosis and the incidence of true idiopathic cases dropped in that area to the vanishing point.

This is, of course, reasoning by analogy and the analogy may be inapplicable to the problem of idiopathic sarcoidosis. Some investigators have objected on grounds of logic to defining idiopathic sarcoidosis as a disease of unknown etiology. The parallel with histoplasmosis is made here only to show that it is *logically* possible that a single agent could underlie idiopathic sarcoidosis and its discovery might conceivably reduce to insignificance the number of true idiopathic cases of sarcoidosis.

In weighing the pros and cons of the tuberculous etiology of sarcoidosis—and it must be stated that the tubercle bacillus above all merits the most serious etiologic consideration—it may be helpful to examine some of the theoretical tenets involved.

It has been postulated that patients with sarcoidosis possess an enhanced capacity for destroying tubercle bacilli in their tissues. This accounts for the difficulty of finding them within the sarcoid follicles. As a further development of this thought, it has been reasoned that in destroying tubercle bacilli so rapidly and effectively, great quantities of tuberculoprotein, lipids and other bacillary fractions must be released into the bloodstream of patients with sarcoidosis. These fractions, it is assumed, evoke an immunological response in the form of tuberculin-neutralizing substances. This would account for the fact that two-thirds of the patients with sarcoidosis are insensitive to tuberculin. The resultant hyperimmune state in sarcoidosis has been termed "positive anergy." Now, I realize, this is an oversimplification of the theory but I believe it expresses the gist of it. Incidentally, not all workers belonging to the school of the tuberculous etiology of sarcoidosis subscribe to the hypothesis of "positive anergy."

The hypothesis of "positive anergy" has recently lost favor because convincing support for it has not been forthcoming. Indeed, recent data have come to hand which contradicts most of its elements. For example, a study by Magnussen shows that tuberculin-neutralizing substances are not present any more frequently nor in any greater amounts in the serums of patients with sarcoidosis.

Furthermore, if one may draw a parallel between BCG organisms and human

tubercle bacilli, the enhanced capacity of sarcoidosis patients for destroying acid fast bacilli cannot be substantiated. BCG organisms appear to live just as long in the inoculated sites of sarcoidosis patients as in normal susceptible control subjects.

Returning to the tuberculin test in patients with sarcoidosis; we know that their negative cutaneous tests need not imply the absence of a previous tuberculous infection. We have studied patients on several occasions, as have others, whose positive tuberculin reaction turned negative with the onset of sarcoidosis. Moreover, cases have been observed in which the tuberculin sensitivity returned after the sarcoidosis regressed and without any evidence of a new tuberculous infection or re-animation of an old one.

Of greater importance, it seems to me, is the fact that a positive tuberculin response can be obtained in patients with sarcoidosis when tuberculin is suspended in paraffin, in the so-called depot tuberculin, instead of saline. With depot-tuberculin the frequency of positive tuberculin reactions among sarcoidosis patients approaches that of the general population of the area.

These findings with depot-tuberculin suggest that in sarcoidosis there may be a defect in fixing saline tuberculin long enough at the injection site to initiate a reaction, and that the paraffin menstruum overcomes that difficulty. There may be also some abnormality in the production and transport of white blood cells of proper quantity and quality—which cells are thought to conduct to the skin the antibodies responsible for the delayed tuberculin type reaction.

To bring the subject of skin tests in sarcoidosis to a close, I would like to add two points. The first is that dermal insensitivity in sarcoidosis extends beyond tuberculin to a large group of unrelated cutaneous antigens of the delayed tuberculin type—trichophytin, oidiomycin and histoplasmin among others. Recently, attempts to induce dermal sensitivity in sarcoidosis patients with chemicals which are normally potent sensitizers reaffirmed the fact of the relative cutaneous refractoriness among patients with sarcoidosis when compared to normal individuals.

The apparent exception in respect to dermal sensitivity in sarcoidosis is the Nickerson-Kveim reaction which shows an impressive specificity with infrequent false positive reactions in non-sarcoid subjects. Here, however, we are dealing with a most unusual response requiring about four weeks to mature in contrast to the maturing period of 48 to 96 hours of the cutaneous antigens we have been discussing.

The second point is that patients with Hodgkin's disease have a dermal insensitivity much like the one we find in sarcoidosis. In Hodgkin's disease the insensitivity ranges from tuberculin right through the same cutaneous antigens of the delayed-type reactions previously enumerated. And as in sarcoidosis the complement fixation and agglutination mechanisms are not interfered with.

This parallel between sarcoidosis and Hodgkin's disease has led some to speculate on whether the difficulty with dermal sensitivity mechanisms are to be ascribed to an altered reticulo-endothelial system which is widely affected in both disorders.

Now I shall list some of the arguments favoring the tuberculous etiology of

sarcoidosis and the refutations offered by those opposed to that concept. It need not be emphasized that, although this debate on etiology gets quite lively at times, neither camp maintains that it has the final answers.

Proponents of the tuberculous etiology point out that tubercle bacilli are eventually demonstrated in a substantial proportion of patients with sarcoidosis. In fact, some autopsy series of sarcoidosis patients report between 10 per cent and 25 per cent of active tuberculosis.

The absence of tubercle bacilli in non-caseating epithelioid-cell tubercles of classical tuberculosis is well-known and even the most careful histologic studies sometimes fail to distinguish between the follicle of sarcoidosis and the tubercle.

Bacterial residues such as diaminopimelic acid and mycolic acid, two components of tubercle bacilli, have been identified in sarcoid tissues suggesting that these tissues contained live tubercle bacilli in the past. This is a most important lead and requires intensive investigation.

There is a marked similarity between certain clinical and roentgenographic aspects of the two conditions particularly in respect to indolent tuberculin-negative forms of pulmonary tuberculosis. As in sarcoidosis, lack of response to antituberculosis drugs is said to be common among patients with this unusual form of tuberculosis.

Erythema nodosum, as you will hear, occurs at the onset of sarcoidosis and tuberculosis. The higher incidence of both sarcoidosis and tuberculosis among Negroes is also to be noted.

In countering these arguments the opposing school offers the following:

Finding tubercle bacilli in the secretions and tissues of patients with sarcoidosis is not etiologically conclusive. Tubercle bacilli are isolated even more frequently from patients with silicosis, and leprosy when tuberculosis supervenes. In short, the tuberculosis may be viewed as a complication of sarcoidosis.

When tuberculosis and sarcoidosis are both present, the caseous foci and the sarcoid follicles as a rule lie side by side without evidence of transition from one type of lesion to the other. The sarcoid follicle contains no tubercle bacilli whereas the neighboring caseous focus may be teeming with bacilli.

Other important differences between the two conditions include the pattern of organ involvement. Symmetrical enlargement of the bronchopulmonary nodes is the commonest roentgen manifestation of sarcoidosis. As you will hear later, it is relatively uncommon in tuberculosis. Tuberculosis does not often affect the uveal tracts, salivary or lacrimal glands, cardiac or skeletal muscle or the phalangeal bones, as does sarcoidosis. In contrast, pleural involvement is common in tuberculosis but rare in sarcoidosis.

Now, when tuberculosis is associated with sarcoidosis, the caseous lesions usually develop in those organs normally found susceptible to the tubercle bacillus; the lungs, lymph nodes, liver, adrenals and meninges, among others. Sarcoid follicles in the salivary glands, the eyes and muscles do not undergo caseation as one might expect if sarcoidosis were the non-caseating phase of tuberculosis.

Regarding bacterial residues in sarcoid tissues, some question has been raised

as to their origin and identity. But conceding that these are the remains of once live tubercle bacilli, by themselves these residues may not constitute conclusive evidence for a connection between the two conditions. Transient hematogenous seeding of many organs during the establishment of the tuberculous primary complex is a common enough event to account for residues of tubercle bacilli in some sarcoid tissues. Analysis of tissues from normal positive tuberculin human controls may help elucidate this aspect of the problem.

Other considerations which lead away from the tuberculosis concept of sarcoidosis are the apparent non-contagiousness of sarcoidosis, its rural rather than urban distribution, and its failure to respond to potent anti-tuberculosis drugs.

But one of the most telling points brought against the tuberculosis concept is the high specificity of the Nickerson-Kveim intracutaneous test in patients with sarcoidosis. A review of the world literature shows that all but one group of investigators* have found this test useful in helping distinguish sarcoidosis from other, similar, conditions. Unfortunately, standardized testing material has not as yet become generally available, and the microscopic reading of the test requires considerable experience.

Finally, attempts to implicate other bacteria, fungi and viruses have failed. Teilum's theory of allergic hyperglobulinosis and Refvem's speculations on the relationship of phospholipids to sarcoidosis still command interest. The question of auto-antibodies has not been investigated in sarcoidosis. Such environmental factors as soil, vegetation and diet are also under close scrutiny.

Confronted with all this conflicting evidence, one can only keep an open mind and hope that some fresh eye will suddenly apprehend something all of us have been overlooking; and with this new insight we may be able to explain the odd explosive assault on the organism of some individuals which we call sarcoidosis and which expresses itself by an extensive seeding of the tissues with epithelioid-cell granulomas in a most unusual organ constellation.

Thank you.

We now come to the case presentations and first we have two examples of bilateral hilar lymphadenopathy in sarcoidosis. These will be presented by Dr. Gerald Weissman.

Dr. Gerald Weissman:

The first patient is a 35 year old Puerto Rico-born male who was admitted because of chest pain three weeks previously. A chest X-ray was obtained which showed bilateral hilar lymphadenopathy and he was referred to the hospital by his local physician. He was first seen six years before because of bilateral bronchopneumonia and essential hypertension. He remained well after discharge.

On examination, his blood pressure was normal and the pertinent findings were prolonged breath sounds over the entire chest and scattered inspiratory rales

* Further work by the same investigators reported recently supports the specificity of the Nickerson-Kveim reaction in sarcoidosis. False positive tests were no longer obtained among patients with tuberculosis in a new series of 40 patients tested.

at the right base and in the right axilla. There was no significant peripheral lymphadenopathy.

Laboratory findings showed a serum-globulin level of four grams per cent. A second strength PPD skin test was positive. The chest X-ray showed bilateral hilar and paratracheal lymphadenopathy suggesting mediastinal lymphoma (Fig. 1). A scalene fat-pad biopsy was performed and the histological picture was that of a non-caseous epithelioid cell granulomatous reaction with slight central necrosis and multinucleated giant cells. No acid-fast bacilli were seen with special staining techniques. This report was considered compatible with what is found in sarcoidosis.

Nickerson-Kveim skin tests were performed and these were microscopically positive at several sites.

In summary then, we have a 35 year old man with minor respiratory symptoms

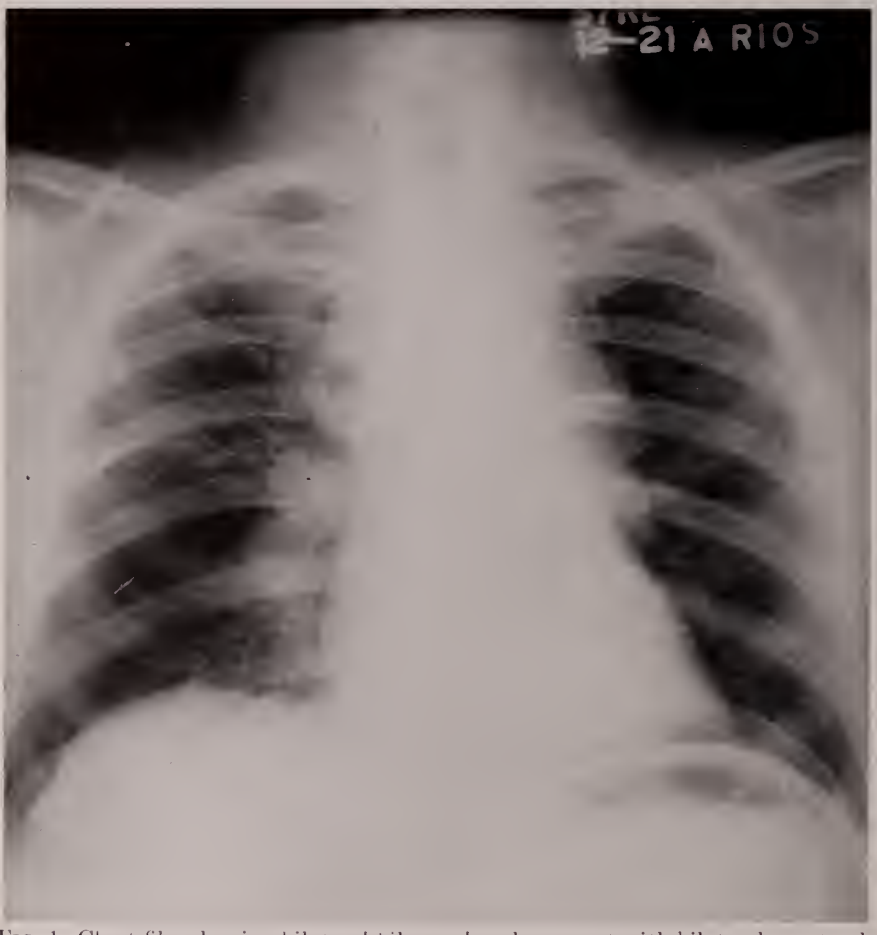


FIG. 1. Chest film showing bilateral hilar node enlargement with bilateral paratracheal nodes as well. Hodgkin's disease first suspected but Nickerson-Kveim test and pre-scalene lymph node biopsy revealed characteristic picture of sarcoidosis.

prior to admission, who on X-ray was found to have bilateral hilar and paratracheal lymphadenopathy. A positive scalene fat-pad biopsy and positive Nickerson-Kveim skin tests established the diagnosis of sarcoidosis.

The second patient is a 53 year old Puerto Rico-born female who was admitted in April 1952 because of severe polyarthritis of four weeks' duration. This involved her knees and ankles. Two weeks prior to admission she had the onset of a low-grade fever and occasional chills. This was followed by the development of painful cutaneous lesions below the knees bilaterally.

The family history was pertinent; her son and daughter both had rheumatic fever.

On physical examination the patient's temperature was found to be elevated to 102 degrees. Her pulse was 100. She had an acutely tender, swollen and warm left knee and ankle. Subcutaneous nodules were noted over the knees, ankles, olecranon processes and palms, as seen in erythema nodosum. There was episcleritis of both eyes. Examination of the heart revealed no murmurs and the chest was clear to percussion and auscultation. Laboratory studies showed the serum globulin to be three grams per cent. An anti-streptolysin titer and an L.E. preparation were both negative. The tuberculin test was weakly positive and only to the second strength PPD.

A biopsy of one of the subcutaneous nodules showed a histological picture compatible with erythema nodosum. An electrocardiogram showed changes

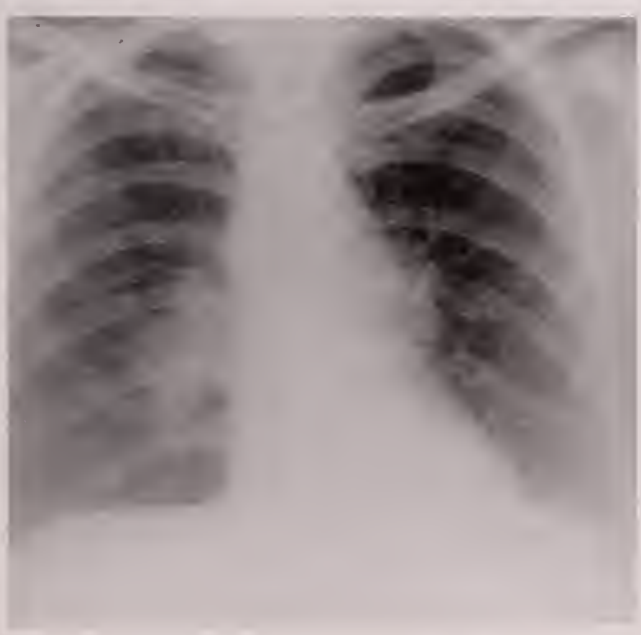


FIG. 2, A. Bilateral hilar node enlargement in patient suspected of having acute rheumatic fever although erythema nodosum was present. Nickerson-Kveim test positive. Mesentric node removed during gall-bladder surgery five months after this film was made showed changes compatible with the diagnosis of sarcoidosis.

compatible with myocarditis. The presumptive diagnosis at that time was acute rheumatic fever. However the electrocardiogram in five days became normal and a chest X-ray showed bilateral hilar lymphadenopathy the nodes being slightly more prominent on the right side. Because of this, a Nickerson-Kveim intracutaneous test was performed and this was microscopically positive.

Following two weeks of bedrest her symptoms of joint pain and fever subsided and she was eventually discharged relatively asymptomatic. Five months later, following an episode of acute cholecystitis a cholecystectomy was performed. At laparotomy in addition to the acutely enlarged gall-bladder, mesenteric nodes were noted. One of these was removed and the histological picture was compatible with sarcoidosis. A chest X-ray one year later showed regression of the nodal enlargement.

In summary, this 53 year old woman presented initially with a clinical picture of migratory polyarthritis, fever and myocarditis by electrocardiogram and the original diagnosis was acute rheumatic fever. A few days later there developed erythema nodosum and hilar lymphadenopathy was found; the so-called erythema nodosum syndrome. However, with a positive Nickerson-Kveim test and later the positive histological picture by lymph node biopsy, the diagnosis of sarcoidosis was established, thereby explaining her clinical picture.

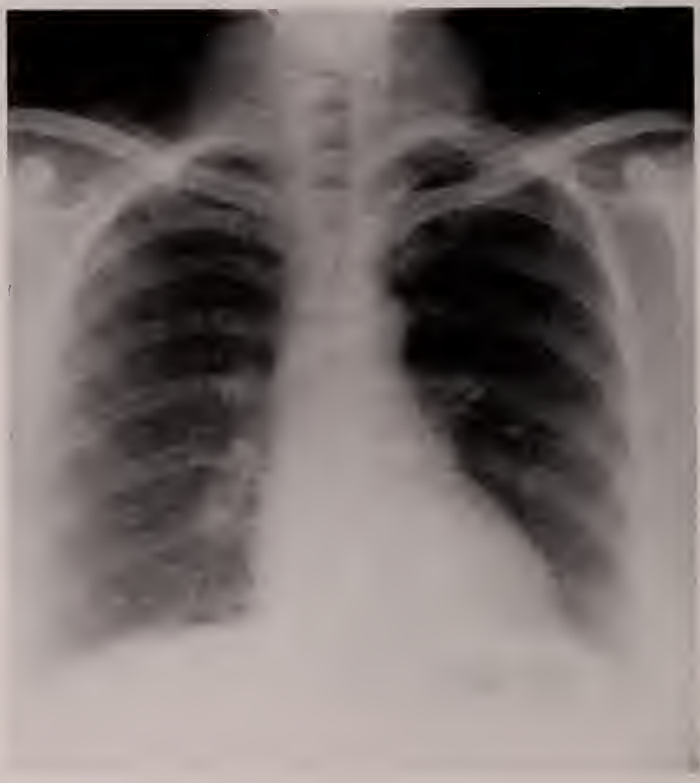


Fig. 2, B. The hilar areas are within normal limits one year later. The patient made a full recovery.

Chairman Siltzbach:

Thank you, Dr. Weissman.

We have asked Dr. Mortimer E. Bader to discuss these two cases and to make some general remarks on the problem of bilateral hilar adenopathy and erythema nodosum in sarcoidosis.

Dr. Mortimer E. Bader:

Bilateral hilar lymph node enlargement is seen as the first roentgenographic evidence of sarcoidosis in 30 to 60 per cent of the cases, most often without detectable associated evidence of sarcoidosis such as abnormalities in the eyes, skin or bones. When serial chest x-rays are available dating back to the onset of disease, the incidence of hilar node enlargement approaches 90 per cent. It should be noted however that bilateral hilar lymphadenopathy may be due to a wide variety of causes including lymphomatous diseases, metastatic carcinoma, or may be simulated by engorgement of the pulmonary blood vessels in heart failure. The advent of improved biopsy techniques and the Nickerson-Kveim test have, however, demonstrated that, in the adult, isolated symmetrical bilateral hilar lymphadenopathy is most frequently due to sarcoidosis.

The first case presented by Dr. Weissman illustrates several features which are typical of this manifestation of sarcoidosis. Establishment of the diagnosis was possible only after the Nickerson-Kveim test was positive and the scalene fat-pad biopsy confirmed it.

It is obvious that bilateral hilar node enlargement occurring in conjunction with uveitis, parotid enlargement or skin changes should immediately suggest the proper diagnosis. Also if superficial lymphadenopathy exists which is readily accessible for biopsy, there is no real problem. However, when the bilateral hilar lymphadenopathy apparently exists alone, then the two measures resorted to in the first case make diagnosis possible.

Doctors Louis E. Siltzbach and Mark Imberman afforded me the opportunity of reviewing their experiences in the sarcoidosis clinic of The Mount Sinai Hospital. Their data relating to hilar lymphadenopathy and erythema nodosum in sarcoidosis will be reported more fully elsewhere. For the present, suffice it to say, their findings indicate that the Nickerson-Kveim test is positive in about 90 per cent of instances of bilateral hilar node enlargement due to sarcoidosis. Scalene fat-pad biopsies are positive in about 60 per cent of the cases in this and in larger series. These two observations plus the findings in our series of tuberculin insensitivity to usual doses in more than 85 per cent of such cases help establish the diagnosis.

From the differential diagnostic standpoint, tuberculosis rarely appears in this fashon since it usually produces a positive tuberculin skin test and unilateral hilar node enlargement, although occasional exceptions may occur. Lymphomatous diseases may be excluded by clinical findings in the blood, by lymphadenopathy elsewhere permitting biopsy differentiation and by the absence of a positive Nickerson-Kveim test.

Metastatic carcinoma may also produce bilateral hilar lymph node enlarge-

ment as a presenting radiographic finding, but this is uncommon. Careful search for the primary site of the tumor as well as the ominous clinical course will exclude the diagnosis of sarcoidosis. Furthermore, there is about a 90 per cent chance, as stated previously, that a positive Nickerson-Kveim intracutaneous test will be found if sarcoidosis of the hilar nodes is indeed present.

The second case was presented to illustrate a problem in diagnosis and to emphasize the relationship of erythema nodosum to sarcoidosis. The case, as you heard, was that of a female with a clinical picture of erythema nodosum, with joint symptoms which were originally considered to represent acute rheumatic fever. However, because of enlarged hilar lymph nodes, a Nickerson-Kveim test was done and was found positive. The diagnosis of sarcoidosis was confirmed when a mesenteric lymph node was excised at the time of cholecystectomy and revealed typical non-caseating tubercles in the node.

It is appropriate at this point to consider the syndrome of erythema nodosum *per se*. Briefly, it is characterized by a triad of symptoms; joint swelling and redness, skin lesions consisting of reddish tender elevated warm areas up to several centimeters in size located on the anterior tibial surface of the leg; and finally by an episcleritis in some cases. Fever as high as 102 degrees Fahrenheit is seen, but less constantly and more rarely there may be electrocardiographic changes. It should be emphasized that the clinical picture of erythema nodosum is the same regardless of etiology, although the incubation period may differ depending upon the cause.

The skin nodules and joint symptoms are short-lived, lasting from two to six weeks, but they may recur. Half of the cases of erythema nodosum occur in children and bear no relationship to sarcoidosis. In children, males are affected almost as frequently as females and the usual etiology is sensitivity to streptococcal infection or to some drug.

The picture in adults in quite different. Here erythema nodosum may appear with or without bilateral hilar lymphadenopathy or with unilateral hilar lymphadenopathy. In those cases *without* any node enlargement, a negative Nickerson-Kveim test is found, and the usual etiology is again, in adults, sensitivity to a drug or streptococcal infection. Another but less common cause of erythema nodosum in this geographic area, is ulcerative colitis. More rarely we encounter it in leprosy, and lymphogranuloma venereum.

If erythema nodosum occurs with *unilateral* hilar node involvement, tuberculosis or coccidioidomycosis should be suspected. Sarcoidosis can usually be excluded by a negative Nickerson-Kveim skin test and by the fact that the tuberculin or coccidioidin skin test will be positive depending on which of these infections is present.

Finally, erythema nodosum associated with *bilateral* hilar node enlargement must be considered. In all twenty of our cases the Nickerson-Kveim test has been positive, and about 85 per cent of these have had insensitivity to tuberculin. The incidence of erythema nodosum combined with enlarged hilar nodes as a mode of onset of sarcoidosis is about ten per cent of cases seen in the Sarcoidosis Clinic. It rarely occurred in the male, the ratio being 19 female to one male. Indeed, if one considers only the female population, then erythema nodosum

and bilateral hilar node enlargement was the first sign of sarcoidosis in almost 20 per cent of the cases in this sex. An even higher incidence has been reported by others. For example, Loefgren of Stockholm found an incidence in all cases, male and female, as high as 113 out of 212 cases or greater than fifty per cent.

As a rule, bilateral hilar node enlargement precedes or accompanies the appearance of erythema nodosum. This was true in every case but one of our series.

In the past erythema nodosum was often considered to be frequently related to tuberculosis or rheumatic fever. This high incidence is now seriously questioned. For example, in 121 cases of erythema nodosum from this hospital, only four had tuberculosis, usually with unilateral node enlargement or a pleural effusion plus a positive tuberculin test. Similarly, of 155 cases of erythema nodosum reported at Peter Bent Brigham Hospital only four had tuberculosis.

Insofar as rheumatic fever is concerned, the purported association with erythema nodosum in the past is not surprising in view of the fever and migratory polyarthritis which belong to the erythema nodosum syndrome. We could find only one instance in the Mount Sinai records in which there was a probable relationship between the initial attack of acute rheumatic fever and erythema nodosum. In six hundred cases of acute rheumatic fever studied at a large convalescent home devoted to the care of patients with this disease, only two began with erythema nodosum. In the adult the rare possibility of acute rheumatic fever being the etiological factor producing this syndrome may be excluded by following the antistreptolysin titer, by the Nickerson-Kveim test and by the presence of bilateral hilar lymphadenopathy. It may be concluded therefore that tuberculin-negative bilateral hilar lymphadenopathy with erythema nodosum in this area is practically always a manifestation of sarcoidosis.

Treatment in these cases of bilateral hilar sarcoidosis with or without erythema nodosum is no special problem since none is required. In general, patients with the hilar node manifestations have a very favorable prognosis. In 80 to 90 per cent there is clearing of the chest film within two years with no further sequelae. The remainder have either an unchanged film or less commonly go on to fibrotic changes in the lung field or have extra-thoracic sarcoid lesions. The benign course helps to differentiate this condition in some cases from metastatic or other malignant involvement of the hilar nodes. Here followed illustrative cases of hilar and mediastinal node enlargement caused by conditions other than sarcoidosis.

Summarizing: The feeling of the sarcoidosis group at this hospital may be summed up as follows:

1) Bilateral bronchopulmonary node enlargement is a common-place finding in sarcoidosis, and an unusual occurrence in other conditions.

2) Erythema nodosum when combined with bilateral hilar node enlargement is, regarded in our hospital, almost exclusively as an expression of early sarcoidosis. Almost all such patients are or become tuberculin insensitive. Females far outnumber males and the prognosis in the bilateral hilar node syndrome in sarcoidosis is usually excellent.

3) Erythema nodosum with a normal chest film usually spells streptococcal

infection, sensitivity to drugs or ulcerative colitis. In rare instances here but more common in other areas, it may be associated with a variety of infectious diseases. Erythema nodosum with *unilateral* enlargement of hilar nodes may occur in tuberculosis or coccidioidomycosis.

4) Rheumatic fever is easily confused with the joint swelling that accompanies erythema nodosum. However, rheumatic fever rarely starts with erythema nodosum.

5) The bilateral hilar node syndrome accompanied by erythema nodosum in tuberculin-negative individuals in this area is practically always due to sarcoidosis.

Chairman Siltzbach:

Thank you, Dr. Bader. You have presented the views of our sarcoidosis group on this subject most clearly.

The next presentation is on the "Uveo-Parotid Syndrome," and the case will be presented by Dr. Louis Southren.

Dr. A. Louis Southren:

The patient, a 20 year old Puerto-Rican born carpenter was admitted to the Sarcoidosis Clinic of Mount Sinai Hospital on May 16, 1950 with lung infiltrations and enlarged mediastinal lymph nodes found two weeks previously in a survey chest film. However, his illness began six months prior to admission when he had an attack of parotid swelling which lasted two months and was associated with low grade fever. There were no ocular complaints at the time. He was admitted to another Hospital for eighteen days where a diagnosis of mumps was made. No chest film was taken and sarcoidosis wasn't suspected. Physical examination on admission to the Sarcoidosis Clinic revealed bilaterally palpable parotid glands of rubbery consistency. There were also enlarged posterior cervical nodes. A liver palpable two fingers below the right costal margin was found. The spleen was not palpable.

The Nickerson-Kveim test was positive and biopsy of one of the lymph nodes on April 26, 1950 showed a picture compatible with sarcoidosis. Tuberculin tests were negative. Chest X-ray in 1950 showed bilateral hilar and right paratracheal lymph node enlargement with fine nodular stippling throughout both lung fields.

The patient had a mild uveitis in both eyes with numerous keratic precipitates. The serum calcium was elevated to 13.3 milligrams per cent with an elevated globulin of 5.9 grams per cent.

During the next six months the patient's condition improved spontaneously, but then fairly suddenly both parotids became markedly enlarged and were now associated with enlargement of the inguinal and sub-mental nodes which were not enlarged previously. He was admitted to Mount Sinai Hospital in December 1950 where an eleven-week course of oral cortisone was started. The patient received 100 mg. of cortisone per day or a total of 10.2 grams in all. In one week the parotid glands decreased in size and he was discharged to be followed in the

Sarcoidosis Clinic. After two weeks the lymph nodes in both inguinal and submental regions began to shrink. This improvement continued until the 25th day of treatment when the patient, being unable to appear for the drug, missed one week of therapy. During the lapse, the parotid swelling promptly recurred and the glands regained their former size. The lymph nodes, however did not flare up and after two more weeks of therapy, the parotids again responded. Thereafter both nodes and parotid glands continued to decline until after eight weeks of treatment neither could be felt. On the 70th and 75th day respectively, an inguinal and sub-mental node were excised for histologic examination. The node revealed extensive replacement of the lymphoid tissue with hyalinized connective tissue. There were a few residual granulomas seen after careful search.

The pulmonary lesions which were regressing before cortisone were barely visible after one month of therapy. The mediastinal lymph nodes also dwindled. The uveitis remained quiescent.

Following the initial response to cortisone, the patient experienced recurrent parotid swelling every few years which generally cleared spontaneously after a short interval. He was able to work without difficulty. However, in March 1957 the patient returned to the Sarcoidosis Clinic because of a nine-months history of substantial parotid swelling. No dyspnea or visual difficulties were noted. The parotids were large and firm and hepatosplenomegaly was noted. There were no enlarged peripheral lymph nodes and the eyes were asymptomatic.

The clinical findings were normal except for a slightly elevated serum globulin level. Repeat chest X-ray showed only residual streaking bilaterally. A needle aspiration biopsy was performed on the right parotid gland and this showed characteristic granulomas of sarcoidosis. Prednisone therapy was begun with good response.

In summary, we had a patient who was first thought to have mumps but was suspected of having sarcoidosis after a chest survey film showed enlarged hilar lymph nodes plus miliary nodulation in both lung fields. The diagnosis of sarcoidosis was established with the aid of a Nickerson-Kveim test and lymph node biopsy. He had an excellent response to steroid therapy but was unusual in the respect that while most areas of sarcoid involvement did not show recurrence, the parotid glands pursued a smoldering and exacerbating course.

Chairman Siltzbach:

Thank you, Dr. Southren.

I think Dr. Grossman who will discuss this case will also show you the needle biopsy of the parotid gland made here.

Dr. Grossman of the Sarcoidosis Clinic.

Dr. Howard Grossman:

The case just presented represents a classical example of uveo-parotid syndrome, sometimes known as Heerfordt's syndrome. It has become common practice for us to think of parotid and uveal involvement as being almost inseparable in sarcoidosis. Yet, as you will see in Table I uveitis without salivary gland

TABLE 1

Ocular, lacrimal and salivary gland involvement in sarcoidosis (40 patients among 200 patients with this disease)

Organ Involved	Number of Patients	Per Cent
Eyes	32	16.0
Lacrimal glands	7	3.5
Salivary glands	16	8.0
Combined forms—Heerfordt's and Mikulicz's syndrome		
Uveo-parotid (Heerfordt)	9	4.5
Salivary and/or lacrimal glands (Mikulicz)	8	4.0
Unassociated involvement*		
Eyes alone	23	11.5
Salivary or lacrimal alone	4	2.0

* All patients but one had lesions of sarcoidosis elsewhere as well.

disease is the more common occurrence and that the combined uveo-parotid syndrome ranks lower in incidence.

The table relates to our experiences with ocular, lacrimal and salivary gland involvement in sarcoidosis. We have had forty such patients among 200 patients with sarcoidisos or an incidence of 20 per cent of ocular or salivary gland involvement. Of the organs involved, the eye showed a 16 per cent incidence in combination with lacrimal or salivary gland enlargement. Uveitis alone represented 11.5 per cent.

Lacrimal gland involvement was present in 3.5 per cent of the cases, and salivary gland involvement in 8 per cent. The combined forms represent two types, the so-called Heerfordt's Syndrome, which is actually the uveo-parotid syndrome, present in 4.5 per cent of our cases and the salivary and/or lacrimal gland which is known as Mikulicz's syndrome present in four per cent of our cases. It is also to be noted that all patients but one had lesions of sarcoidosis elsewhere in the body as well.

Next to pulmonary involvement the commonest disabling form of sarcoidosis is uveitis. In any case of proven or suspected sarcoidosis the uveal tract must be examined with the slit-lamp to detect the possible presence of uveitis. Often the patient may have asymptomatic involvement either fresh or old. In the acute phase of uveitis the patient may complain of blurring of vision, excessive lacrimation or even pain in the orbit. Inspection under the slit-lamp is characterized by an acute inflammatory reaction. Ciliary congestion, turbid aqueous humor, keratic precipitates, sometimes of the so-called "mutton-fat variety," are often seen.

In the chronic form of sarcoid uveitis ciliary congestion is usually absent but the anterior and posterior chambers of the eyes are cloudy and cells are pres-

ent. Nodules may be seen in the iris which represent sarcoid granulomata and synechiae are common.

Patients with uveitis are perhaps more prone than others to granulomatous central nervous system involvement which can occasionally be quite serious. This takes the form of cranial nerve, peripheral nerve or even brain and meningeal lesions.

In the healing phase of uveitis fibrosis of the granulomas sometimes with hyalin or para-amyloid deposition, takes place and may lead to disorganization of the globe and total loss of sight. Figure 3 shows the microscopic appearance of an enucleated eye which had undergone phthisis bulbi secondary to extensive uveitis. The sarcoid follicles are still visible in the ciliary body. Of 32 patients we have seen with ocular involvement, seven became blind in one or both eyes. Only one of the blind patients recovered her vision totally on steroid therapy. That patient had loss of vision for nine months and was totally blind for five months before therapy. Initially that patient showed steamy cornea seen in both eyes. Steroid therapy was initated and four weeks later there was a marked improvement in the cornea with recovery of 90% of vision which she retained during the next eight years of observation.

Like the eyes, the parotids are generally involved early in the acute phase of sarcoidosis and may have many periods of exacerbation and remission. Recurrences of parotid swelling are occasionally seen under steroid therapy when the dosage is lowered too quickly. Yet once the parotid swelling has subsided, it

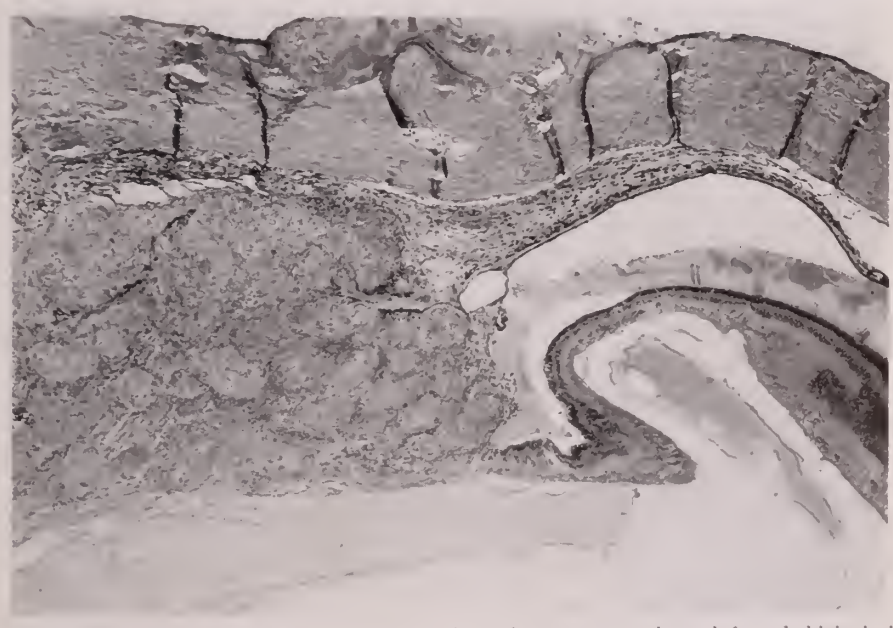


FIG. 3. Microscopic appearance of a portion of an eye enucleated for phthisis bulbi caused by chronic sarcoidosis of the uveal tract. The partly fibrotic sarcoid follicles completely replace the ciliary body seen in the lower left hand portion of the illustration.

usually does not recur. It is of interest that Dr. Southren's patient had a significant recurrence of parotid enlargement seven years later, an unusual phenomenon in sarcoidosis.

The facial palsy often seen in parotid enlargement is of a peripheral type and is of unknown etiology. It has been felt to be secondary to pressure of the enlarged gland on the nerve. However, we, as well as others, have seen paralysis without obvious parotid swelling. We have seen two cases in which at different times both facial nerves were alternately affected. One of these patients had peripheral nerve involvement in her lower extremity.

When lacrimal glands are involved with sarcoidosis the involved gland is not attached to the skin and is of a firm and nodular consistency. We have seen one patient recently with a huge mass in the left eye, first mistaken for a malignant orbital tumor. The patient later demonstrated bilateral parotid swelling and an enlarged right hilar lymph node. The microscopic section of the excised ocular mass showed typical sarcoid granulomas crowding out normal lacrimal glandular tissue. The tumor was in fact an enormously enlarged lacrimal gland. The patient also had a positive skin biopsy and a positive Nickerson-Kveim test. One month later lacrimal swelling of the other eye developed which responded dramatically to steroid therapy.

Lesions of the conjunctivae are considered less common. Small nodules or large follicles may occur in the palpebral conjunctivae, bulbar conjunctivae or cul de sac. The nodules are firm, painless, removable and yellow-brown or yellow-red in color. They can cause considerable bulbar congestion and photophobia.

We treat all patients with uveitis because of fear of secondary glaucoma from synechiae which may lead to phthisis bulbi.

In general we do not find that topical steroid therapy alone is efficacious. Although most cases of mild anterior chamber involvement are self-limiting, the dangers of secondary glaucoma, of phthisis bulbi are great enough to warrant therapy with systemic corticosteroids. Inactive uveitis is not treated with steroids nor is parotid enlargement in sarcoidosis treated unless extremely disfiguring, or there are other associated lesions necessitating treatment or the dryness of the mouth or pain is excessively discomforting to the patient.

Our approach to the treatment of lacrimal gland involvement is similar to that of parotid enlargement.

Chairman Siltzbach:

Thank you very much, Dr. Grossman.

I think we might add that our starting prednisone dosage, is usually between 20 and 30 milligrams of prednisone and we try to get the patient down to ten milligrams in four to six weeks, a dosage which we find adequate for most patients as maintenance therapy. Our courses generally last about six months but uncommonly are maintained indefinitely.

The next presentation concerns a patient in whom there was an unusual location of sarcoidosis in a major bronchus. This case will be presented by Dr. Melvin

Kahn and then I shall have something to say about bronchial and pulmonary sarcoidosis.

Dr. Melvin Kahn:

The patient, a 40 year old white male, was admitted to the Mount Sinai Hospital on March 2, 1951 complaining of fever, cough and night sweats. About one year prior to admission he noted a dry paroxysmal cough with intervals of wheezing respiration.

Two months before admission his cough became more severe with production of three ounces of yellow sputum daily. For one month previous to admission he had nightly fever to 102 degrees with night sweats, accompanied by a weight loss of 18 pounds. In spite of penicillin therapy symptoms progressed and hospitalization was advised.

On admission the patient appeared acutely ill. He was diaphoretic with moderate cyanosis of the lips and nail-beds. Sub-crepitant rales and rhonchi were heard over the right hemithorax with prolonged wheezing expiration. There was slight enlargement of the posterior cervical and inguinal lymph nodes. The spleen was palpated three finger breadths below the left costal margin.

The white count revealed a slight shift to the left with a hemoglobin of ten

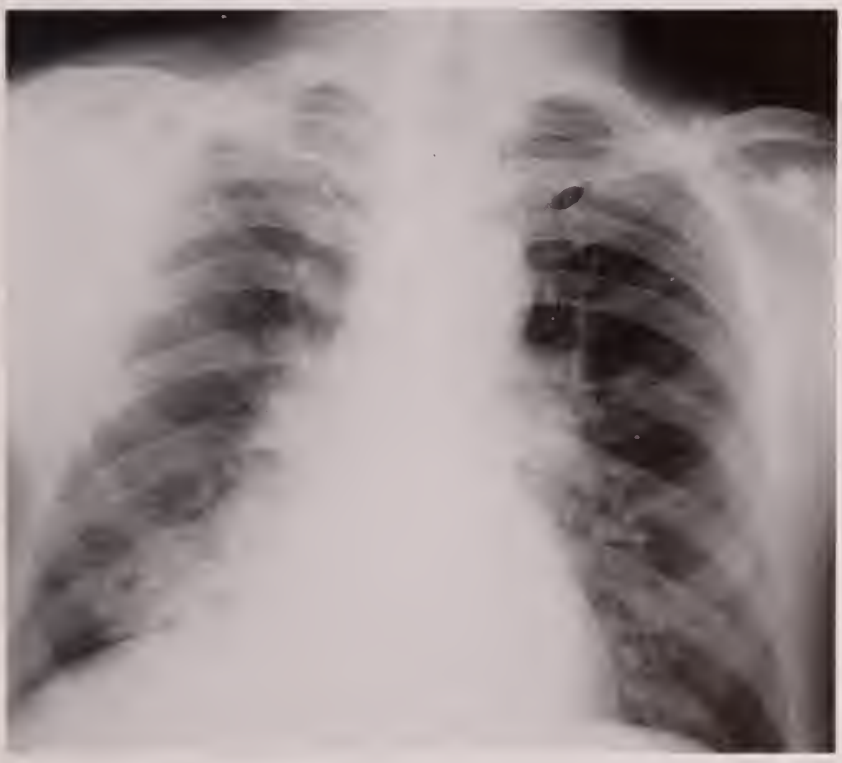


FIG. 4, A. Chest film showing shrinkage and consolidation of right middle lobe caused by suppuration behind a bronchial stricture composed of sarcoid tissue.

grams. The erythrocyte sedimentation rate was 40 millimeters (Westergren) with a serum albumin of 3.6 grams and a globulin of 3.5 grams per 100 cc.

Sputum culture yielded a normal flora. Examinations for acid-fast bacilli were negative.

As the chest X-ray on March 26, 1951 shows, there was shrinkage and consolidation of the right middle lobe. In addition there were faint linear streaks and nodular densities in both midzones, with a prominence of the left hilar shadow.

Bronchoscopy revealed a copious flow of thick nonodorous pus welling out of the right middle lobe orifice preventing adequate visualization of the right middle lobe lumen. No biopsy was performed. A bronchiogram showed cylindrical bronchiectasis of the right middle lobe as seen in the right lateral view. The bronchi of the other lobe segments were apparently normal. (Fig 4B).

FIG. 4, B. Bronchogram with lipiodol made in the right lateral view to demonstrate cylindrical and saccular bronchiectasis of the right middle lobe in the same patient. The mouth of the right middle lobe was narrowed by sarcoid tissue.

The clinical impression was that the patient had bronchiectasis with a suppurative bronchopneumonia of the right middle lobe probably secondary to broncholithiasis. Splenomegaly was unexplained but assumed to be due to a secondary amyloidosis.

In spite of a regimen of antibiotics for six weeks the patient continued with wheezing, weight loss and fever. Sputum volume was 100 cc. daily.

Bronchoscopy was repeated after four weeks and the mucosa of the right

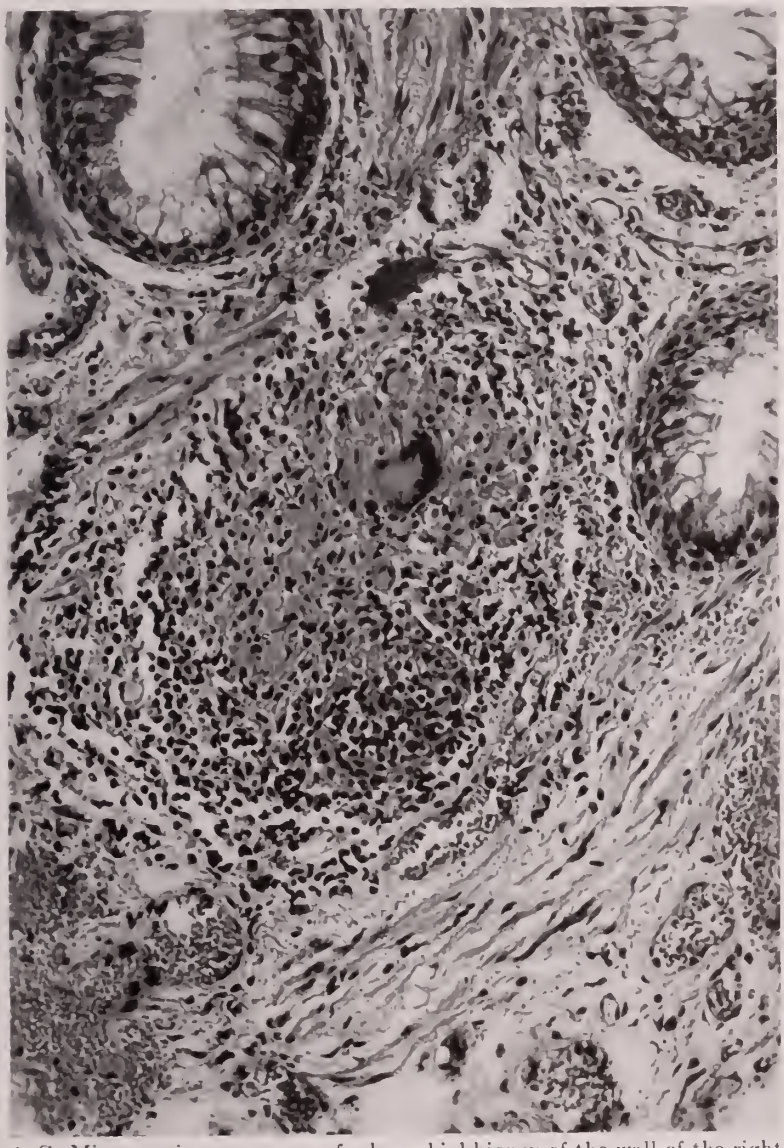


FIG. 4, C. Microscopic appearance of a bronchial biopsy of the wall of the right middle lobe in the same patient. The section shows a typical non-caseating tubercle with a giant cell located in the submucosa. Note bronchial glands above and to the right.

middle lobe bronchus was noted to be granular and thickened causing narrowing of the lumen. A biopsy was obtained from the abnormal appearing mucosa. The remainder of the bronchial tree was noted to be normal.

Microscopic sections showed that the submucosa was infiltrated with non-caseating epithelioid cell granulomas with giant cells surrounded by inflammatory cells. (Fig. 4C). Stains for acid-fast bacilli were negative. Bronchoscopic biopsy was repeated one week later with the same results.

Because of these findings further investigations were carried out. Tuberculin skin tests with OT up to 1:100 dilution were negative as were histoplasmin and coccidioidin tests. An axillary lymph node biopsy revealed the same non-caseating granulomata with giant cells surrounded by inflammatory cells. Acid fast stains were negative. The Nickerson-Kveim test was positive. A quiescent uveitis of the right eye rounded out the clinical picture.

A chest x-ray made one year prior to admission was obtained and revealed bilateral hilar lymph node enlargement with a fine nodular seeding and linear streaking in both lung fields. The right middle lobe process was not evident at that time.

It appeared therefore that the patient had a generalized sarcoidosis involving peripheral and mediastinal lymph nodes, spleen, right uveal tract and lungs with submucosal involvement of a major bronchus. Lobectomy was considered in view of the poor therapeutic response with antibiotics, but it was feared that endobronchial involvement with sarcoidosis might interfere with healing of the bronchial stump and lead to a broncho-pleural fistula.

The patient was therefore started on cortisone, 100 to 150 milligrams daily with antibiotic coverage, and a fall in fever with reduction in sputum volume and a gradual shrinkage of peripheral lymph nodes occurred. After three weeks of therapy the right middle lobe orifice was noted to be widely patent by repeat bronchoscopy. A chest x-ray after five weeks revealed marked clearing of the right middle lobe consolidation with residual streaking. The diffuse nodular and linear densities were no longer apparent, but the left hilar enlargement was still prominent.

The patient was discharged with maintenance hormonal therapy. He had residual streaking of the right middle lobe and some moist rales heard over this area.

Since discharge, the patient has been able to resume his usual occupation. He had occasional exacerbations of cough and sputum which were treated with antibiotics and increased steroids. Attempts to stop steroids have resulted in exacerbation of his symptoms and a small maintenance dose has been required. During the last year, he has required from 7½ to 10 milligrams of prednisone daily.

For five years following discharge, bronchoscopies revealed slight thickening of the spur of the right middle lobe bronchus with biopsies repeatedly showing sarcoid follicles. The last positive bronchoscopic biopsy was found in December 1956, more than five years after the first positive biopsy. In October 1957, the patient was readmitted to The Mount Sinai Hospital and for the first time

bronchoscopic biopsy was negative. Bronchograms at that time showed considerable diminution of the bronchiectatic process. The spleen was still palpable and in spite of a persistent anemia which has not yet been clarified, the clinical status has remained essentially unchanged within the past 6½ years. The Nickerson-Kveim test has remained positive to date, i.e.—seven years.

Chairman Siltzbach:

Thank you, Dr. Kahn:

The case presentation you have just heard is an example of sarcoidosis in which the first inkling of the diagnosis was obtained by bronchoscopic biopsy. We have one other patient out of a total of nine with sarcoidosis of small or large bronchi in which the first diagnosis of sarcoidosis was unexpectedly made at bronchoscopy.

This second patient was a 35 year-old Negro woman who had been treated elsewhere for asthma, bullous emphysema, bronchitis and bronchiectasis for six years. She had had many attacks of pneumonia from which she recovered with difficulty. When we first saw her she was having hemoptysis and stridor. She was bronchoscoped to locate the source of the bleeding.

Her chest film (Fig. 5) shows marked emphysema, numerous bullae and trabeculations in both lungs but no enlarged hilar nodes. Bronchoscopy showed only thickened and reddened mucosa in the right upper and middle lobe bronchi. But biopsy from both sites showed epithelioid-cell follicles in the submucosa. Her Nickerson-Kveim test was positive. We have followed her for five years now through two more severe attacks of pneumonia and a full-term delivery which she bore with remarkable equanimity in spite of her marked stridor. She has had one episode of spontaneous pneumothorax when a bulla ruptured.

We have had in our series of 200 patients with sarcoidosis two who had predominantly unilateral lung lesions, and in both instances sarcoid follicles were found in the submucosa of major bronchi on bronchoscopic biopsy although the gross appearance of the bronchial wall was not remarkable. One of these patients had asthmatic attacks. Her chest X-ray is shown in Fig. 6.

Three more patients whose bronchoscopic biopsies showed epithelioid-cell tubercles had either wheezing or cough which was mild and not incapacitating.

One may conclude that granulomatous involvement of the major bronchi in sarcoidosis constitutes more of an annoyance than a threat to the patient except when narrowing is sufficient to cause distal pulmonary suppuration. In no instance was there any evidence of erosion of lymph nodes through the bronchial wall with ulceration such as occurs in tuberculosis. In fact, pressure from enlarged hilar and mediastinal nodes with bronchial compression was uncommon. I have no doubt that involvement of major bronchi in sarcoidosis is more common than supposed. Routine bronchoscopic biopsy made to include the submucosa would help turn up a goodly proportion of such localization in sarcoidosis.

More threatening to the patient is the granulomatous involvement of smaller bronchial radicals which of course cannot be reached bronchoscopically. How often bronchi of lesser calibre are narrowed by granuloma or, as is more fre-

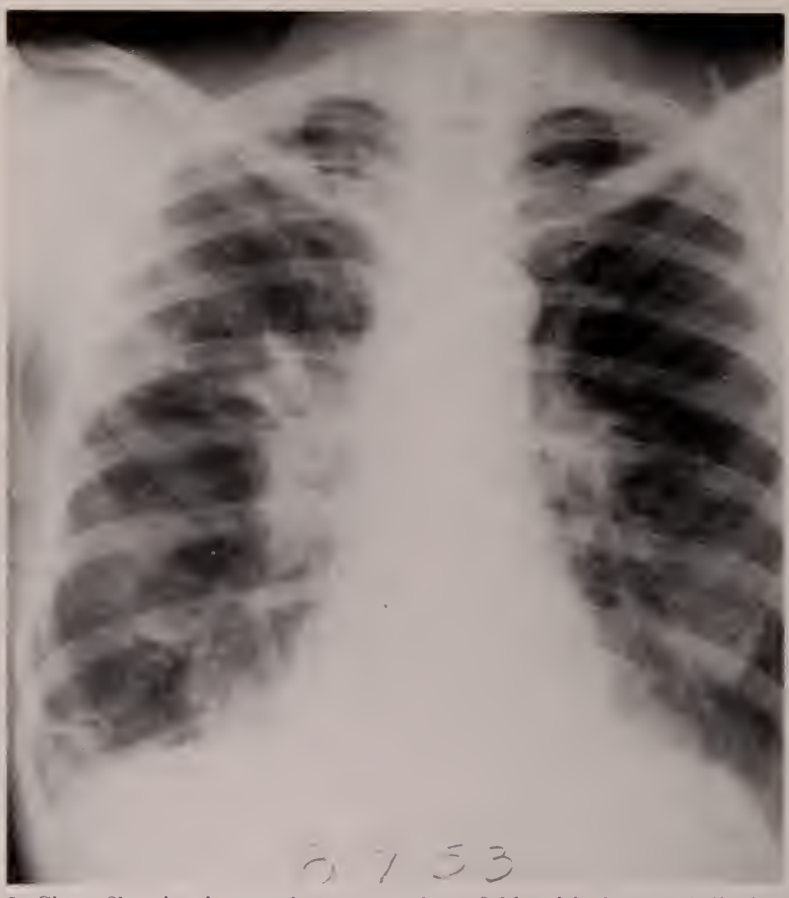


Fig. 5. Chest film showing emphysematous lung fields with depressed diaphrams and numerous areas of scarring particularly in the mid and lower half of the right lung field. Considered initially to have asthmatic bronchitis with repeated lung infections. The diagnosis of sarcoidosis was unexpectedly made from two bronchoscopic biopsies. Positive Nickerson-Kveim tests confirmed the diagnosis.

quently postulated, by the deformity resulting from peribronchial fibrosis in the healing stage of pulmonary sarcoidosis, cannot be stated. We suspect that the patient I described where some bullae had ruptured, might also have had granulomas narrowing some the smaller bronchi. We have found these granulomas in smaller bronchi in two of our cases: once at autopsy where both large and small bronchi as well as many other organs were seeded; and once, in a lung biopsy specimen from a patient with sarcoidosis whose history follows.

We were dealing with a young Negro male 23 years old who was admitted in an oxygen tent with a story of increasing dyspnea, tachypnea and fever of almost nine months duration. His tuberculin test was negative, his serum globulin was 5 Gm. and his serum calcium 12 mg./100 cc. His chest film showed both lung fields diffusely clouded with faintly outlined streaks and nodules and, in the upper portions, small grape-like lucencies. (Fig 7A).

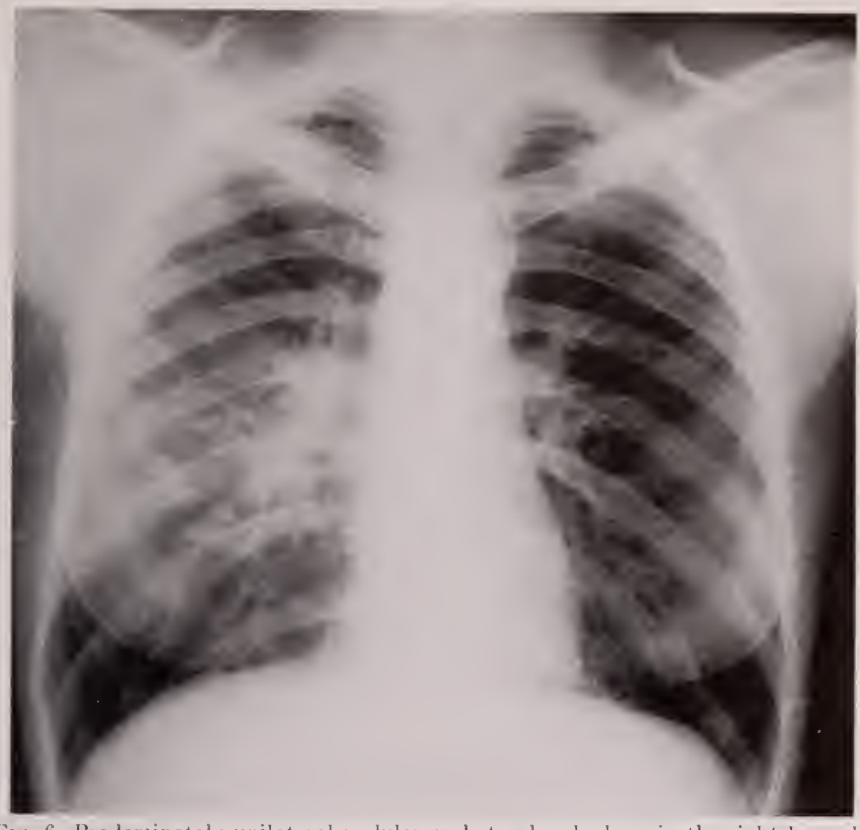


FIG. 6. Predominately unilateral nodular and streaky shadows in the right lower lung field in a patient who had a negative tuberculin test and a lymph node biopsy compatible with sarcoidosis. Nickerson-Kveim was positive for sarcoidosis as was bronchoscopic biopsy of the right bronchial tree. The patient suffered from asthma-like attacks.

Before steroid therapy, an open lung biopsy through a limited incision was performed. His lung function studies had shown that his main difficulty was with diffusion—the so-called "alveolar capillary block" syndrome. In addition to the expected finding of granulomatous thickening of the alveolar septa accounting for the diffusion difficulty, another change was present which was rather unexpected. Fig. 7B, shows the wall of small bronchus and jutting into it, like a ball-valve, is a sarcoid granuloma with a marked thinning of the intact mucosa stretched over it. It is easy to imagine this granuloma approximating the opposite wall when the bronchus contracts on expiration, and I believe that through the ball-valve action of such granulomas in this and other small bronchi we have the precondition for the formation of the small bullae seen on this patient's chest film. Whether these granulomas in the small bronchi are the main basis for the damaging bullous emphysema which eventually leads to pulmonary insufficiency and right heart failure in sarcoidosis or whether the distortion of small bronchi by scar tissue in the later stages is a more usual basis for the bullae, cannot be stated. But this case suggests the likelihood that small bronchi may be

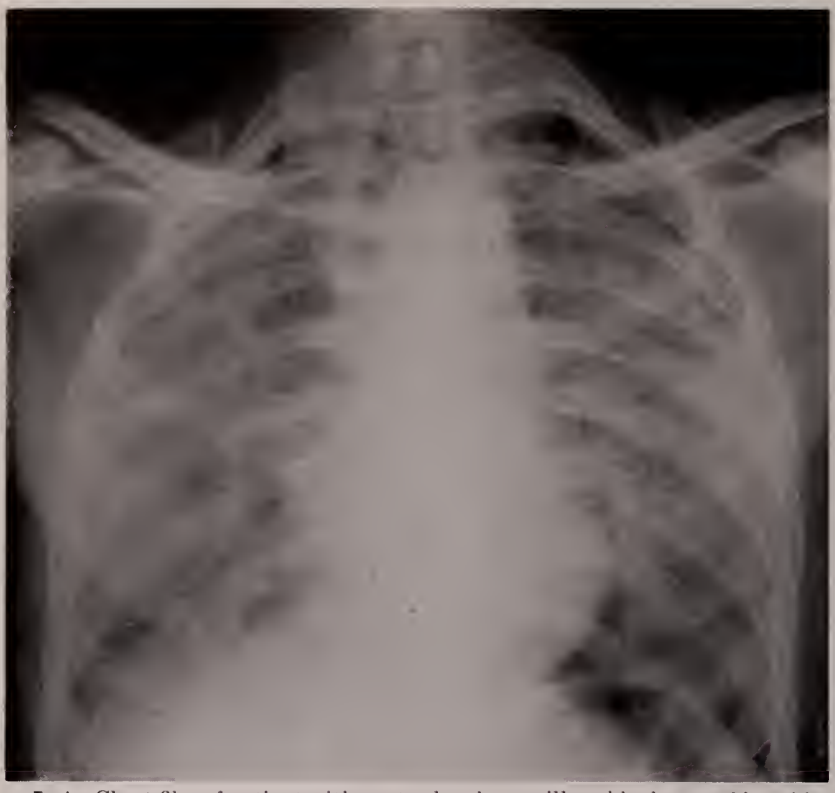


FIG. 7, A. Chest film of patient with acute alveolar capillary block caused by widespread pulmonary sarcoidosis. The chest film shows marked haziness of both lung fields with nodules and streaks throughout. The upper portion of both lung fields show grape-like lucencies. Lung biopsy showed sarcoidosis.

seeded *early* more often than we realize and that some of the *ventilatory* defects described in patients with isolated hilar node enlargement may rest on these unseen granulomatous obstructions of smaller bronchi and bronchioles.

Pulmonary Sarcoidosis

Now let us turn briefly to some of the *pulmonary* manifestations of sarcoidosis.

Of all the organs involved in sarcoidosis, patients with significant lung involvement show the greatest toll of disability. We have had eight deaths among our 200 patients in the last ten years, and seven of them had evidence of pulmonary insufficiency. Among our living patients a small minority are severely disabled by their pulmonary lesions, and a fair number still have some degree of discomfort, mostly cough or dyspnea on exertion.

In our clinic we classify pulmonary sarcoidosis radiologically into three chronological categories: early, transitional and late fibrotic. The early cases are of three types. There is the earliest stage consisting of isolated bronchopulmonary node enlargement with paratracheal and tracheobronchial nodes often added but with-

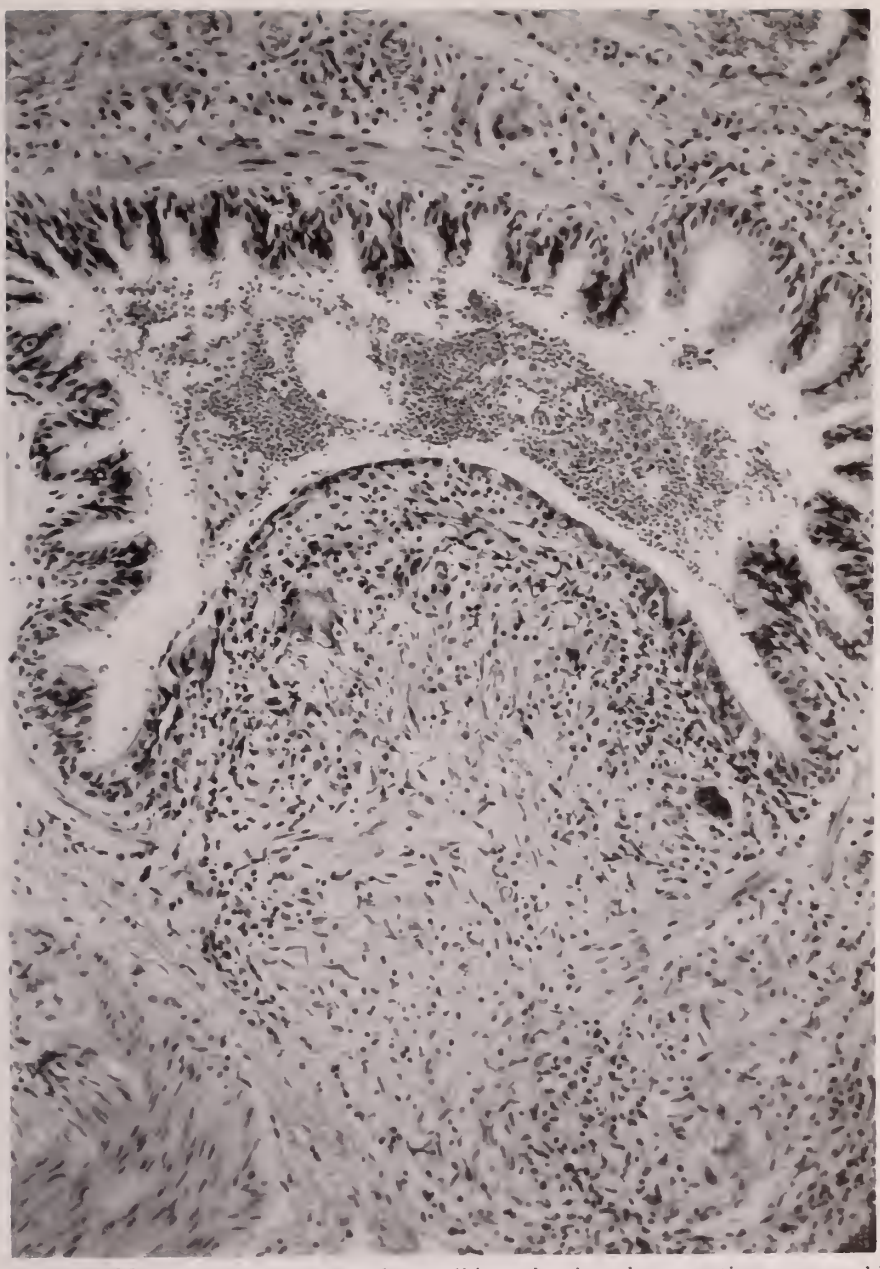


FIG. 7, B. Microscopic appearance of a small bronchus in pulmonary tissue removed by open lung biopsy in the same patient. Jutting into the bronchial lumen is a large epithelioid cell granuloma which stretches the overlying mucosa. The mucosa is flattened in contrast to the folds in the normal portions of the mucosa above. The appearance is very suggestive of a ball-valve which would open during inspiration and shut during expiration, preconditions for bulla formation which are seen in the upper portions of the preceding chest film.

out identifiable pulmonary lesions except perhaps for a little perihilar streaking. The nodal type has the best prognosis. Next best is the second early type, the generalized or localized miliary nodulation with recession or persistence of nodes. It is this type that has been widely studied by lung function measurements in contrast to the late fibrotic stage which has received less attention in this regard. The third early type of sarcoidosis is the least common and it seems to be the most dangerous—i.e. those with disseminated fluffy bronchopneumonic patches, usually with enlarged hilar nodes.

If the disease progresses for two or more years after the onset, the patient enters the second or transitional stage of pulmonary sarcoidosis with the gradual replacement of lung granulomas by scars with paramyloid or so-called hyaline.

The third and final or fibrotic stage usually is reached in about five years or more. This stage is marked by almost complete recession of the granulomas and their widespread replacement by dense scar tissue. Bullous emphysema is a common feature at this stage. While pulmonary symptoms may be present in any stage, patients with chronic progressive disease suffer most.

As you have heard, the roentgen picture of enlargement of the hilar and other mediastinal nodes in early sarcoidosis must be differentiated from enlargement caused by malignant lymphoma, tuberculosis, fungal disease, and metastatic neoplastic involvement of the nodes. The miliary pattern which follows nodal enlargement in sarcoidosis can easily be confused with the micro-nodular densities caused by miliary tuberculosis, pneumonoconiosis, lymphangitic carcinoma, among others. The uncommon fluffy bronchopneumonic shadows of early sarcoidosis can simulate the appearance of scattered non-specific bronchopneumonia, exudative tuberculosis, eosinophilic pneumonia or even metastatic lung deposits.

Because of the streaky shadows found in the second or transitional stage of pulmonary sarcoidosis, such conditions as chronic beryllium poisoning, lymphangitic carcinoma, and idiopathic interstitial fibrosis of the Hamman-Rich type are usually considered in differential diagnosis at this stage.

The third or late fibrotic stage of pulmonary sarcoidosis with its scarred lungs and its "frozen" hilar areas, with its bullous emphysema, mimics chronic fibroid tuberculosis, silicosis, and many other conditions in which obstructive emphysema and its sequellae are found.

This brings to a close our conference on sarcoidosis in which we have presented some typical and some not so typical instances of this disease encountered in our clinic devoted to its study, and on our hospital wards. We have tried to touch on some of the high points of this puzzling condition which is receiving increasing attention in many medical centers both here and abroad.

Clinico-Pathological Conference

Edited by

FENTON SCHAFFNER, M.D.

A 10 week old Negro female was admitted to The Mount Sinai Hospital with a history of "yellow eyes" since shortly after birth.

The patient was a full-term Negro infant weighing 2900 grams at birth. Her stay in the nursery was uneventful and she was discharged as a "normal newborn" on the fifth day of life. Family history was non-contributory. The mother stated that she had received three injections in the sixth month of pregnancy because of possible rheumatic fever. She stated further that the child had had yellow eyes when she was discharged after delivery and that the urine was dark and that the stools were light in color, varying from white to light yellow. When the child was nine weeks old, she suffered a severe upper respiratory infection and when she was ten weeks of age, she was admitted to the hospital because of fever and respiratory difficulty. The child was said to be feeding well and gaining weight when she was brought to the hospital.

The child was well nourished and well developed, weighing 4200 grams. There was obvious icterus of the sclerae and mucous membranes. Additional pertinent findings were confined to the abdomen. The liver was felt 2 to 3 cm. below the right costal margin. The tip of the spleen was palpable. There were no other abnormalities noted.

During her 25 day stay in the hospital, the child was afebrile. She seemed well and her weight gain was satisfactory. The accompanying chart illustrates the pertinent laboratory data (Table 1). The only medication given was a preparation of bile salts. Bilirubin concentration in the blood showed a downward trend and the child was discharged after 25 days to the care of the Pediatric Out-Patient Clinic.

Five days after discharge from the hospital, the child was brought to the Out-Patient Department for treatment of pyoderma. This condition was treated with erythromycin, with prompt clearing of the infected skin. Four weeks later she was thought to be doing well but after another month, when the child was five months old, she was readmitted because of fever, cough and dyspnea of two days duration. According to the mother, the child's abdomen had been increasing in size for about a month and it had also been noticed that the feet had become swollen during the two days prior to admission to the hospital. The day before admisssion, the child refused feedings and vomited a great deal. The mother stated that the stools had continued to be light yellow or white in color.

The child was acutely ill, intensely jaundiced and in moderate respiratory distress. Temperature was 98° F., pulse 150, respirations 50, blood pressure 120

From the Department of Pathology, The Mount Sinai Hospital, New York, N. Y

TABLE I

Laboratory Data

Date	Hgb.	Sed. rate	WBC	Urine bile	Urine urobilinogen	Stool stercobilin	A/G ratio	Serum bilirubin		Serum cholesterol		Serum alk. phos.	Ceph. floc.
								Total	Direct	Total	Est.		
	G.%	*mm/hr*						*mg.%*	*mg.%*	*mg.%*	*mg.%*	*KAU*	
7/2/57	11.4		13000	1+	1:10	+	4.9/2.5	19.0	11.4	214	160	60	1+
7/6				1+	1:20	+		15.8	8.9				
7/8				neg.	neg.	+		14.7	8.9				
7/10	10.6		16100	tr	1:5	+	3.9/2.3	10.2	7.5	198	152	53.4	
7/12		12		neg.	1:20	+							neg.
7/15					1:10			11.6	6.8				
7/17								8.1	6.4				
7/23					1:40	+		9.7	5.6				
8/27								10.3	5.5				3+
10/1	7.8		10600	4+	1:20	+	2.1/6.1	25.8	15.0	157	112	25	2+
10/2	7.3		23200										
10/4		75											
10/6								21.8	12.0				
10/10				4+	1:60								

Additional laboratory data

Serology negative	Heterophile 1:7	Repeated blood culture negative
Blood type O Rh+	Sickle preparation negative	Nose and throat culture: Staph. Aureus "A"
Maternal type O Rh+	BSP on mother negative	Urine analyses negative except for trace of sugar on one occasion.
Coombs negative	Tuberculin tests negative	

	1st admission	2nd admission	
Mucoproteins (mg.%)	45.0	11.8	CO_2, Na, K, Ca, P and Cl all normal.
Acid precipitable globulin (mg.%)	2.5	5.0	Vitamin A—14 gamma %
$ZnSO_4$ turbidity (units)	1.7	31.0	Carotene—2 gamma %
SGO-Transaminase (units)	193		Vitamin C—normal
Thymol turbidity (units)	6.8		Prothrombin time (patient/control) 46/12 seconds.

(systolic). The baby weighed 6740 grams, head circumference was 40 cm., chest 38 cm., and abdomen 49 cm. The skin was dry with a generalized eczematoid eruption. There were no petechiae or ecchymoses. The anterior fontanelle was depressed and the sclerae were icteric. There was a purulent nasal discharge. The neck was supple and the chest normal to percussion and auscultation. Examination of the heart revealed sinus tachycardia and a grade II apical soft

systolic murmur. The abdomen was protuberant with shifting dullness and a fluid wave. The liver edge was palpable 4 cm. below the right costal margin; it was firm, smooth and sharp. The spleen was felt 2 cm. below the left costal margin. There was marked edema over the sacral and tibial areas.

On the day after admission, the temperature rose to 102° F. and varied between 100° and 102° F. thereafter. The infant was treated with penicillin and tetracycline. Paracentesis with removal of 500 ml. of clear amber fluid was done the day after admission to relieve the respiratory distress. Cytological examination failed to reveal any pathological cells. No cytomegalic inclusion bodies were seen. Bone marrow aspiration also failed to reveal any tumor cells. Serum electrolytes were normal. Because of a markedly prolonged prothrombin time, the child was started on vitamin K intramuscularly, but without improvement. Roentgen examination of the long bones showed evidence of both rickets and scurvy, despite the daily administration of 0.6 cc. of a multivitamin preparation and an apparently adequate diet. Deficiency in prothrombin, labile and stable factors and fibrinogen of the blood were found. Additional laboratory findings included a serum glutamic oxalacetic transaminase activity of 193 units, markedly diminished serum vitamin A and carotene levels, and a normal plasma concentration of vitamin C. Plasma protein studies showed elevated gamma globulin and depressed alpha and beta globulin concentrations. Skull and chest x-rays were normal. The child expired on the 13th day in the hospital.

DR. HORACE L. HODES: To sum up the clinical data, we were dealing with an infant who was jaundiced from birth, or at least from the fifth day of life, the mother herself having observed the jaundice at this time. As we shall see in more detail later, there were fluctuating serum bilirubin levels. The child, by the time it was four months of age, had some evidence of cirrhosis with ascites which caused respiratory distress. Bleeding tendency did not appear until there was obvious cirrhosis of the liver and the prothrombin levels were low. The bleeding was not due to thrombocytopenia.

Some important negative findings should be mentioned. First, sugar and other reducing substances were absent from the urine. There were no ketones in the urine. The gamma globulin levels found in this infant were higher than one would expect. At the age of about three months, the gamma globulin level in the infant drops to a very low point. The amount given to the child through the placenta by the mother is gone and the child at only that point begins to make gamma globulin. Here we have a level which was distinctly elevated even for older children. This might be interpreted as being due to infection, very possibly associated with infection of the liver. The glutamic oxalacetic-transaminase level was 193 units on one occasion. Again, the normal values for the infant are different from adults and a level up to 120 is normal. This child's was higher than 120 but it was not, in the one determination that was done, exceedingly high. Certainly it is not high enough to enable us to make a diagnosis of hepatitis from this finding alone.

The mucoprotein values are of special interest, and I have asked Dr. Greenspan to speak at this point.

DR. EZRA GREENSPAN: At ten weeks, our first determination showed a normal serum mucoprotein level and a normal alpha$_2$-beta globulin level for an infant of that age. The gamma globulin at ten weeks was 0.5 units, which is about the normal for an infant of that age. However, as the liver disease progressed, this patient showed a remarkable shift in the globulin distribution, including marked reduction of mucoprotein to the range which we now consider as signifying severe hepatic insufficiency, and death (usually in hepatic coma). This child had 12 mg. per cent mucoprotein, a very poor prognostic sign. Associated with such a low mucoprotein, the zinc sulfate turbidity, which was 1.5 units, had risen to 35, which is really a phenomenally high gamma globulin.

My personal experience with children is limited, but ordinarily we find this type of pattern associated with postnecrotic cirrhosis or with progressive fatal hepatitis. In biliary atresia we would expect the opposite pattern, quite different from the one seen in this child's case.

DR. HANS POPPER: How much gamma globulin in grams is 35 units?

DR. GREENSPAN: Thirty-five units is 3.5 grams, roughly.

DR. HODES: Now we come to the differential diagnosis and I think we can divide the possible causes of this child's disease into groups, some of which we can exclude quite readily.

One of the things that would come up in another climate might be deficiency of proteins and vitamins, which would lead to liver disease. In the West Indies and in Africa, for instance, this might be a possibility. I think that deficiency diseases can be excluded because of the feeding history, because of the child's state of nutrition, and also because in dietary deficiency states cirrhosis occurs only quite late in childhood or in adolescence. One of the diseases we may exclude immediately is congenital galactosemia, which is characterized by jaundice, fever and enlargement of the liver. In this disease galactose is excreted in the urine which causes reduction of the copper compounds used in Benedict's reagent. Absence of reducing substances in the urine excludes galactosemia in this case. Incidentally, galactosemia is one of the conditions in which cirrhosis occurs quite early.

Glycogen storage disease has been reported with cirrhosis. Again, this occurs later in life than occurred here. In this case there was no ketonuria, no acidosis, and no hypoglycemia, all of which exclude glycogen storage disease.

Certain infections of the liver might cause many of the findings in our case. Syphilis of the newborn may cause severe jaundice, enlargement of the liver and later cirrhosis. Syphilis may be excluded, however, because serologic tests for syphilis were negative and none of the accompanying signs of severe congenital syphilis such as changes in the bone marrow were present.

It is possible that abscess of the liver, with diffuse involvement, might cause a picture that resembles acute hepatitis. In this connection we do know that the child did have extensive pyoderma at one point. If this were due to a staphylococcus, these might gain entrance to the liver and lie dormant for a long time. However, we have no evidence that there was septicemia. If the child had been transfused, the question of transfusion malaria could come up. We have seen two instances of transfusion induced malaria with rapid development of cirrhosis.

Wilson's disease could cause cirrhosis but, as far as I know, only in later life.

A more common infantile disease, erythroblastosis due to incompatibility between the blood of the child and the mother (Rh disease), can infrequently cause cirrhosis. On the whole, cirrhosis following erythroblastosis is quite rare and I do not think it was present here. No incompatibility between the mother's and the child's blood was detected.

There are some other unusual conditions such as familial nonhemolytic jaundice which should be mentioned. I think this disease can be excluded because in this condition the indirect bilirubin rises much higher than the direct bilirubin. Here, a good deal of the bilirubin rise was due to direct bilirubin. The same consideration excludes congenital familial hemolytic jaundice.

Several other conditions are excluded a little less easily. On a statistical basis, the most common one is congenital obstruction of the bile ducts. This anomaly accounts for about sixty per cent of the cases of persistent jaundice in infancy. Also, congenital atresia of the bile ducts may be followed by cirrhosis. On the whole, the symptoms of cirrhosis develop considerably later than they did in this case, but occasionally they are seen in the first four or five months of life. In addition to this, the level of bilirubin in our case fluctuated more than is usual in atresia of the bile ducts. In this condition, bilirubin usually rises steadily to a plateau.

Now, some might wonder why we did not exclude congenital atresia of the bile ducts by surgical methods or by needle biopsy of the liver. This child was not biopsied because she exhibited deficiency of plasma prothrombin at the time this action was considered. There was a second reason for omitting surgical exploration to determine whether or not congenital atresia of the bile ducts was present. This is that the chance of surgical repair in such cases is very small. The Boston survey of 106 cases showed only six children with biliary atresia who had conditions that were cured by surgery. In addition, if there is some other condition, such as neonatal hepatitis or cytomegalic inclusion disease, the operation may actually cause the death of the child, who might recover spontaneously.

While talking about obstruction of the bile ducts as a cause of jaundice, there are several other conditions which I should mention. One is cystic fibrosis of the pancreas or fibrocystic disease. In some cases of this syndrome, there has been obstruction of the bile ducts for reasons not quite understood. It is believed by some that the obstruction is due to precipitation of mucoproteins in the bile ducts, resulting from abnormal mucus formation by the bile duct cells. However, there was no evidence that the child had fibrocystic disease.

There is another, to me mysterious, condition known as inspissated bile syndrome in which for unknown reasons the bile becomes inspissated and causes blockage of the biliary ducts.

Another possible cause of the obstruction is an external one, such as choledochus cyst, for example. We know that no such cause existed here because one can feel the mass of the choledochus cyst, and this was not felt on examination of this child. Other tumors can obstruct the bile ducts but I do not think any tumor of the liver was present, again because it was not felt.

On occasion we have seen a child with a neuroblastoma with metastasis to the

liver who actually developed symptoms which resembled diffuse hepatitis followed by cirrhosis. The bone marrow examination partially excludes this possibility. The x-rays of the child did not show any evidence of neuroblastoma.

Now we come to cytomegalic inclusion disease or what probably ought to be called generalized salivary gland virus disease. Salivary gland virus, as you know, is found in a number of different species, in guinea pigs, for instance, and in man. These are viruses which are species specific and have not been transferred from one animal to another. In other words, the guinea pig virus does not cause disease in the hamster and so on. The human virus has been isolated in human tissue culture at least twice. Once it was from an infected salivary gland and once from adenoid tissue.

I think this virus certainly may be the cause of the disease which we have described in the case under discussion. In one to five per cent of autopsies on infants and children, evidence of infection with this virus is found in the salivary glands. Large infected cells, with large nuclear inclusion bodies, are found in some of the cells. In other cells there are cytoplasmic inclusions. The nuclear inclusions are more numerous. In this small percentage of the children, the virus is confined to the salivary glands. In an even smaller percentage, something under one per cent, of autopsies carried out in St. Louis, evidence of infection with the salivary gland virus was found in other organs including liver, spleen, pancreas, kidneys, and in some cases in the brain. When the generalized form of the disease occurs in infants, it produced a recognizable clinical picture. The child has jaundice, large liver and spleen, and will frequently suffer hemorrhages in the skin, mucosa and internal organs. These hemorrhages are due to thrombocytopenia. No thrombocytopenia was found in our case.

In some of the cases, there is calcification in the brain, which can be seen on x-ray. In some cases the linings of the ventricles have been diffusely calcified. No cerebral calcification was present in this case. If it had been present, I think we should have been convinced that generalized salivary gland virus disease was the correct diagnosis. There are other less fulminating cases of salivary gland virus disease, and our patient might fall into this category. Also, the cytomegalic cases in which there has been liver damage have, in one or two instances, gone on to cirrhosis early in life. The diagnosis has been made in life a number of times from the clinical picture. In addition a few times the diagnosis has been established by examination of the urinary sediment in which cells with intranuclear occlusions have been seen. In the child whom we are presenting today, the urinary sediment was examined, but cells containing inclusions were not found.

I think the most likely diagnosis in the present case is neonatal hepatitis. This may be an instance in which the virus of serum hepatitis has been transferred across the placenta from the mother to the infant.

There is one case on record of a woman proven to have serum jaundice by having her blood injected into human volunteers, who developed with typical jaundice. Two years later she delivered a baby who was jaundiced at or in a very few days after birth. From the serum of that child, human volunteers were inoculated, again with the production of hepatitis. Perhaps some of the neonatal cases

might not be serum hepatitis but might be due to infectious hepatitis virus. There are a number of multiple familial cases of neonatal hepatitis. For example, a woman delivered three children in a row, all of whom had hepatitis and died. This came from Scott's clinic in Washington. In this city, Crainin reported two cases in siblings.

Neonatal hepatitis differs in several ways from hepatitis of older children and of adults. The neonates exhibit a great deal of diarrhea as compared with older children. Secondly, the cephalin flocculation and thymol turbidity tests are usually negative. This has been thought to be due to differences in the plasma proteins of these children. Normal infants in the first few days of life show a positive cephalin flocculation which disappears.

Cirrhosis of the liver occurs quite commonly in the neonatal hepatitis, relatively much more frequently than it does in adults and certainly more often than it does among older children with infectious hepatitis or serum hepatitis.

I think that neonatal hepatitis is the most likely diagnosis in our case, and that it was followed by cirrhosis. We cannot exclude atresia with complete assurance but it is unlikely. I believe that generalized salivary gland diseases with hepatitis and cirrhosis is also a possibility but, even if this is the case, our patient does not represent one of the typical fulminating cases of this disease.

To sum it up, I think this is a case of neonatal hepatitis transmitted across the placenta and followed by cirrhosis of the liver.

DR. POPPER: At autopsy, despite the skin pigmentation, icterus was quite clearly apparent. As the abdominal cavity was opened, about 300 cc. of a clear yellow ascitic fluid poured out. A significantly enlarged liver protruded under the thoracic cage. We also saw the characteristics of rickets with protrusion at the costal edge and marked enlargement of the cartilage at the costochondral junction (Fig. 1).

In various bones, particularly the ribs and thoracic vertebrae, marked widening and lengthening of the cartilage were seen while calcification was not apparent. The cartilage in places was invaded by marrow. This is the characteristic feature of calcium deficiency as an expression of rickets. Vitamin D deficiency interferes with the death of the cartilage and its subsequent calcification.

We therefore found overgrowth of cartilage and, instead of calcification of cartilage, matrix for bone formation. The calcification which does take place is laying down of an osteoid poor in calcium. All this results in a very irregular appearance of the osteochondral junction. These changes were not as apparent in the long bones in which the osteochondral junction was yellow and somewhat widened. We failed to find any abnormality of the bone marrow structure.

As we turned to the abdominal cavity, we were impressed by distention of the colon as well as of the small intestine. Marked dilatation and collateral formation were seen over the cecum and ascending colon connecting the mesenteric vessels to the vessels of the anterior abdominal wall.

The heart was somewhat larger than would be found in a child of this age but there were no abnormalities except for severe jaundice. Histologically, the heart

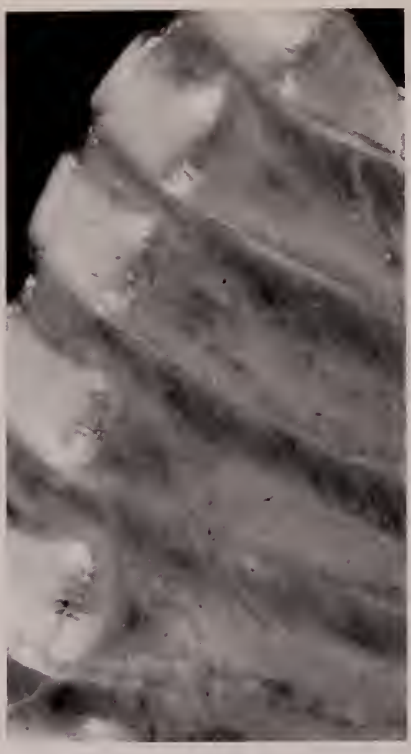


FIG. 1. Chest wall showing rachitic rosary.

appeared entirely normal except for some thickening of the endocardium, not to a degree of fibroelastosis but definitely thicker than normal. Liver disease and malnutrition have been associated with endocardial fibrosis but from what I have seen of this material, it is entirely different in that it extends deep into the myocardium.

In the lungs only a moderate amount of edema and some increase in the alveolar markings were seen. There was no consolidation present and the lung was entirely aerated. The pleura was markedly hyperemic. Whatever the pulmonary changes may have been a month or two weeks before death in the sense of pneumonitis, in the specimen we saw there were no significant changes except for the edema and hyperemia.

The urinary bladder was markedly dilated, protruding and filled with a large amount of urine. The kidneys appeared normal grossly. The only significant finding was a greater blood content on the cortico-medullary junction which is a shock phenomenon, and we assumed that the deeply jaundiced child died in shock. Microscopically, the most impressive findings were the large amount of bile pigment in the distal convoluted tubules, which we call icteric nephrosis because the renal function is not impaired. I would prefer to call it icterus of the kidney than to designate it as a renal disease.

The pancreas, of interest in view of the suspected diagnosis of a salivary gland

disease, was entirely normal. The salivary glands were removed and subjected to histologic study. No significant changes could be found in them.

The spleen weighed almost ten times the normal weight for the age, some 130 grams. It appeared rather homogeneous (which the microscopic examination confirmed). We saw rather small follicles and the red pulp was congested with blood. We immediately raised the question if reticuloendothelial hyperplasia was present. We had a high serum gamma globulin level and we have assumed on previous occasions that the excess gamma globulin is formed in postnecrotic cirrhosis. However, here, reticuloendothelial hyperplasia was not part of the picture. There was accumulation of hemopoietic foci as frequently appears in the spleen in such conditions.

The liver weighed 220 grams and was not significantly enlarged. Some hyperemia was noted between the diaphragm and the liver, a reflection of a disturbance of hepatic blood flow with collateral formation. The liver was deeply green and, on the cut surface, the architecture was greatly disturbed. Fibrous bands extended throughout and the liver was deeply jaundiced. Microscopic examination of enlarged lymph node at the hilum of the liver showed some mild lymph node hyperplasia. There was no reticuloendothelial hyperplasia but pigment was seen in the lymph nodes. The gallbladder and the biliary tract were perfectly normal.

On this basis we excluded any biliary atresia which would have been amenable to surgical management.

We were somewhat surprised when we looked at the histologic picture. The architecture was intact with bands of connective tissue running throughout the liver. This certainly was not a full-fledged cirrhosis but the architecture was far more disturbed microscopically than grossly. We could still recognize the portal tracts but primarily the central zones were very much distorted. A large amount of connective tissue extended throughout the parenchyma from the central zones accounting for the fibrosis. In the centrolobular zone, we saw complete collapse, disappearance of the liver tissue with some remnants of narrow veins in the collapsed area (Fig. 2). In this areas there was tremendous formation of the irregularly arranged fibers, thicker than normal and connected with each other. We saw normal portal tracts (Fig. 3) and just outside of them were a large amount of newly formed membranes and pre-existing fibers. Ductular cells were rather prominent in the lobular periphery throughout the liver (Fig. 4). Toward the center we found cells which more closely resembled liver cells. I call the arrangement of the ductular cells a bile ductular structure because it looked like a bile duct but in reconstructions, which we do not have in this case, we really have plates rather than ducts, plates which are like those in the hepatic parenchyma. Furthermore, in the embryo, transformation of liver cells into ductular cells is apparent. Regenerating cells which were unable to form liver cells seemed to join degenerating cells which were still connected to ducts. We assumed, therefore, that we were dealing with regenerative or degenerative transformation of liver cells into the bile ductular structure. They were surrounded by a large amount of fiber formation with or without fibroblasts, usually without. Fibers formed the basement membrane around the ductules. In the intermediate portion of the

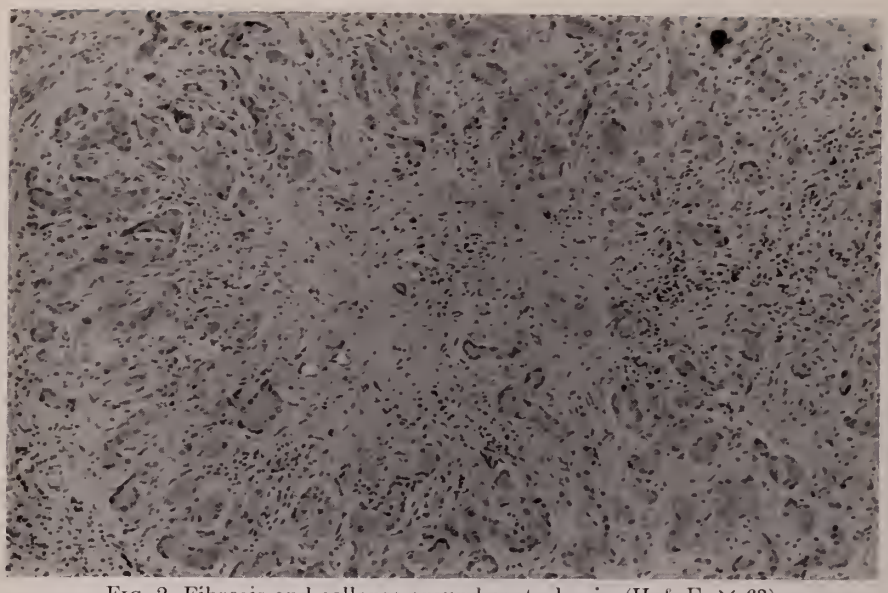


FIG. 2. Fibrosis and collapse around central vein (H & E, × 63).

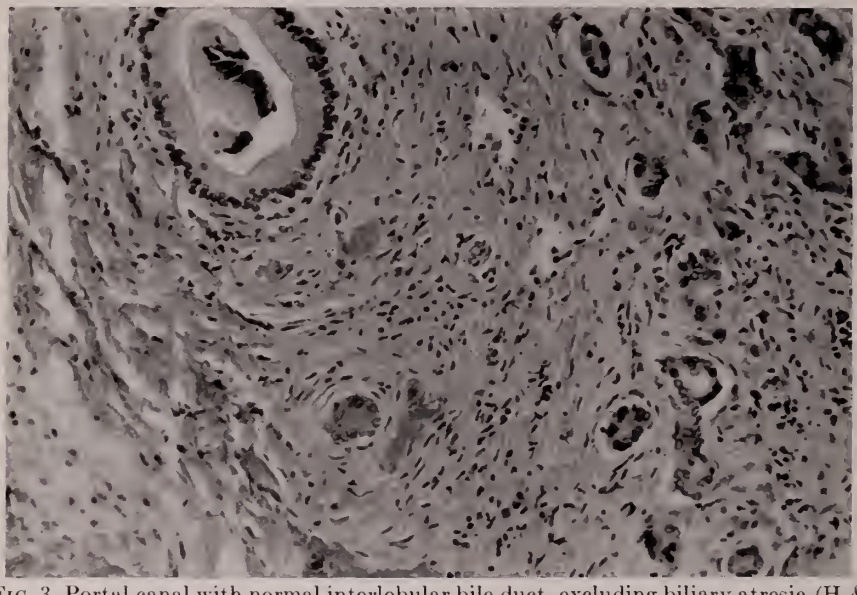


FIG. 3. Portal canal with normal interlobular bile duct, excluding biliary atresia (H & E, × 120).

lobule, liver cells were distinctly arranged in regenerative nodules which showed peripheral bile stasis and in which there was very little stroma. We found a large amount of stroma, usually around the regenerative nodule (Fig. 5). On the other hand, the nodules compressed the stroma to form a dense envelope. In the center of the lobule, the cells were larger and formed formidable giant cells (Fig. 6).

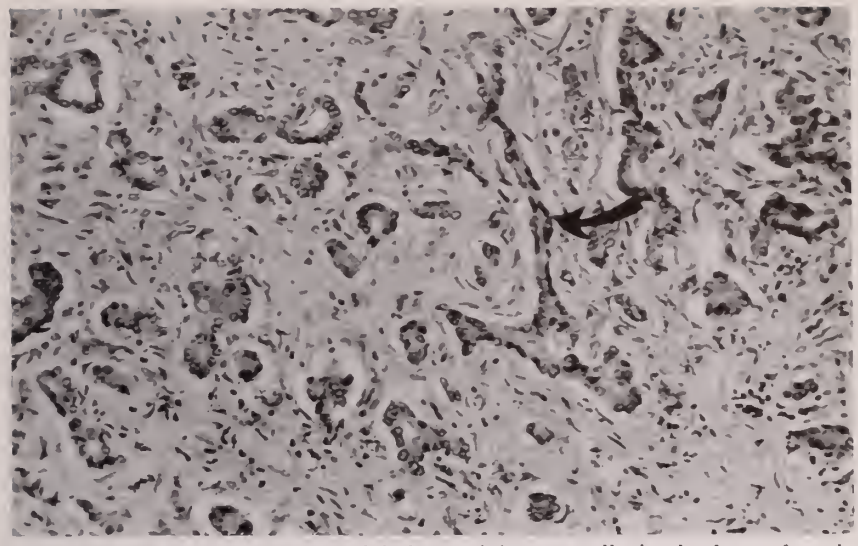


FIG. 4. Ductular structures in the lobular periphery usually in the form of cords (arrow) but occasionally in plates surrounded by thick connective tissue fibers (H & E, × 120).

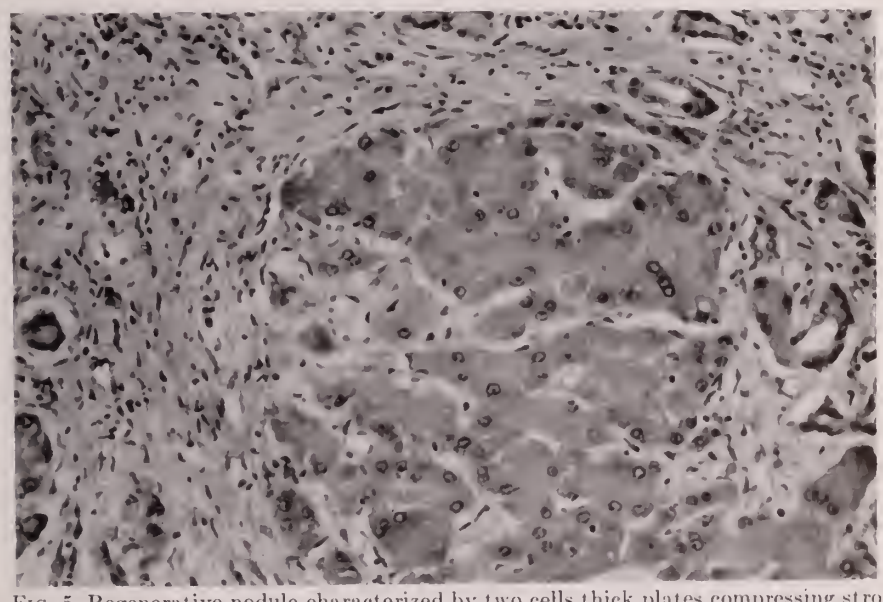


FIG. 5. Regenerative nodule characterized by two cells thick plates compressing stroma (H & E, × 240).

Bile accumulation was seen and it appeared that this bile had no outlet. We therefore had what is called giant cell hepatitis, in which large neonatal liver cells do not drain into bile ductules. The bile is not permitted to escape and accumulates, causing bile staining. Giant cell hepatitis is considered by many synonymous with viral hepatitis but it is only a reflection of the increased regeneratory

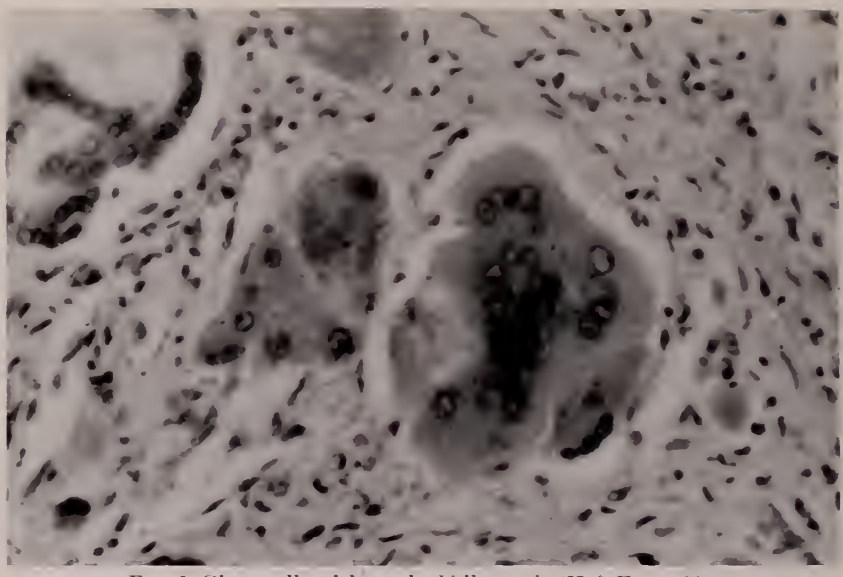


FIG. 6. Giant cells with marked bile stasis (H & E, × 400).

ability of the infantile liver. We can see giant cells just as well in syphilis, salivary gland disease, and hemolytic disease of the newborn from blood group incompatibility.

A severe inflammatory reaction was present with mononuclear and polymorphonuclear cells mixed with fibroblasts. This inflammatory component led to the fibroplasia with many reticulum fibers being formed as well as many thick or fibrous membranes. The inflammation, however, extended into the central vein and this endophlebitis is rather characteristic of viral hepatitis (Fig. 7). When we used another staining technique, namely, the periodic acid Schiff (PAS) reaction, which stains polysaccharides and protein polysaccharides, we saw quite a lot of such material. Some was in liver cells, especially the degenerating liver cells, and the strongest stain was given by cells with brown pigment. We were dealing with some kind of pigment accumulation just as we saw in the lymph node which also gave a PAS reaction. The PAS positive liver cells disintegrated and the fragments appeared in the Kupffer cells, in the giant cells, and in scavenger cells around the necrotic liver cells. The cells with the PAS positive reaction clearly represented the pigment carrying cells. The material in the scavenger cells was probably derived from the polysaccharides in the degenerating liver cells. Acid mucopolysaccharides were also found in degenerating liver cells and in the scavenger cells.

When we stained for nucleoprotein with pyronine, which is a means of estimating the protein formation in the cell, we found that the degenerating liver cells showed a small amount of pyroninophilic material reflecting a rather low protein forming ability. The ductular cells, as we would expect, had hardly any. However, many scavenger cells were distinctly pyroninophilic. What protein did these cells form? We suspect that it was gamma globulin which was so markedly ele-

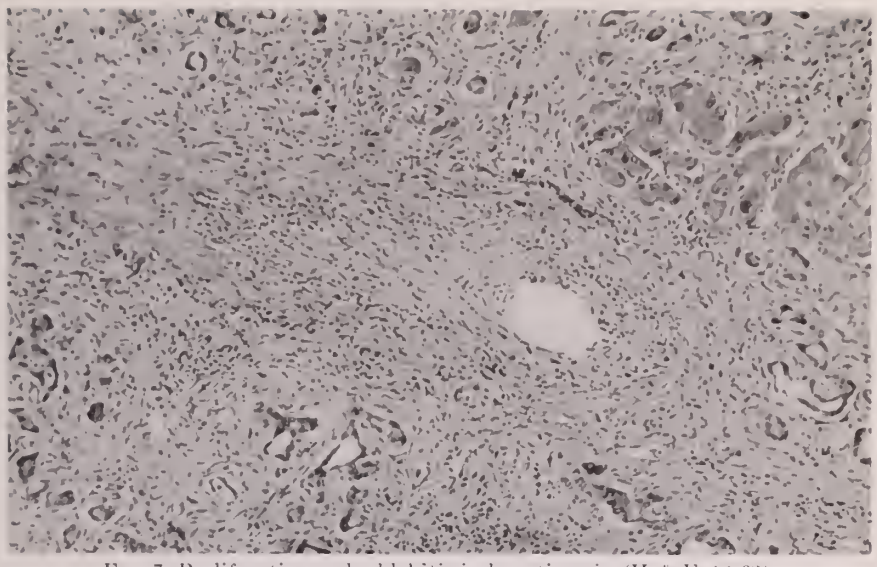


FIG. 7. Proliferative endophlebitis in hepatic vein (H & E, × 63).

vated. A very good correlation exists between the serum gamma globulin level and the pyronine reaction of these scavenger cells.

The fact that the greatest reaction was given by the cells which were pigmented suggests that the stimulus for gamma globulin production is polysaccharide from liver cells which disintegrated. The fragments were taken up by and irritated the scavenger cells. The result was excess gamma globulin formation. Whether this was an antigen-antibody type of reaction, I am unable to say, but strongly suspect so. The cells that gave the pyronine reaction quite often had plasma cell-like nuclei and we have called them plasmacytoid cells.

Trying to correlate the clinical and pathological findings, we assumed that the patient had giant cell hepatitis of viral origin because of the phlebitis, the severe ductular cell reaction, and the early destruction of the lobular architecture. There may have been maternal viral hepatitis from injections which the mother received but nothing could be demonstrated in the mother. Intrauterine infection was thought to be present because the jaundice supposedly started at birth.

The child developed normally and gained weight but absorbed fat soluble vitamins poorly which led to rickets. Within three months, progressive liver cell destruction occurred with leucocytosis, anemia and abnormal cephalin flocculation. The serum albumin, alkaline phosphatase and serum mucoproteins dropped. Vitamin A and prothrombin were low despite therapy. Liver cell destruction caused regeneration with formation of giant cells and then nodules.

The nodules in turn were a late development and produced the collaterals. In the presence of the liver cell damage, ascites developed. The liver cell destruction led to the severe ductular cell transformation which led to fibrosis. The liver cell breakdown products evoked the parenchymal reaction which also produced

fibrosis with fibroblasts and polysaccharides which we could stain. This led to the formation of high gamma globulin possibly by way of an antigen-antibody reaction.

Finally, postnecrotic cirrhosis developed, with formation of collaterals and regenerative nodules.

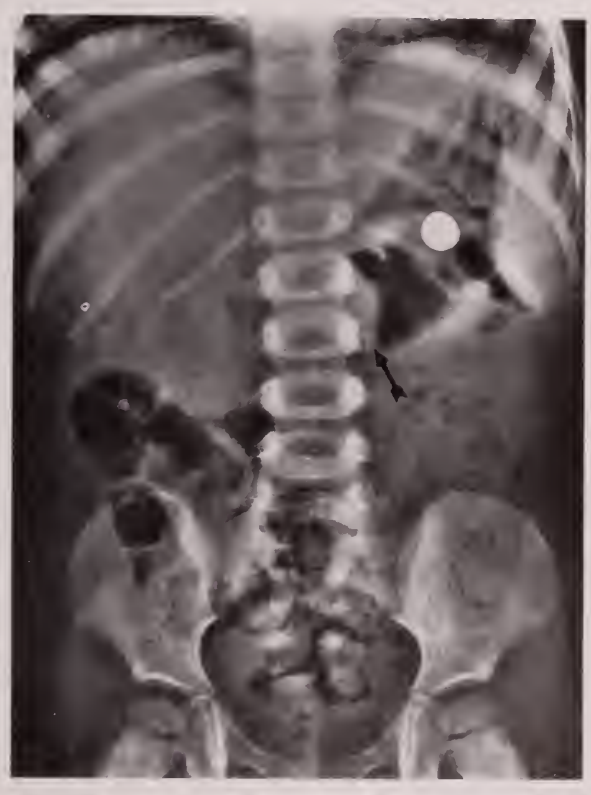
DR. HODES: One other vitamin was involved, namely, carotene and vitamin A. Carotene was so low because it was not absorbed and vitamin A also was not absorbed. Furthermore, the liver was unable to change the carotene that was present into vitamin A.

FINAL PATHOLOGIC DIAGNOSIS: (1) Neonatal giant cell hepatitis with early postnecrotic cirrhosis. (2) Rickets due to impaired vitamin D absorption.

Radiological Notes

CASE NO. 54

A $2\frac{1}{2}$ year old child was admitted with a history of 12 hours of abdominal pain. At the age of 6 months, this child had had an ileocolic intussusception reduced by barium enema examination. Clinical diagnosis was recurrent intussusception despite the absence of bloody diarrhea. Simple examination of the abdomen (Fig. 1) showed findings typical of an ileocolic intussception. This was confirmed on barium enema examination which also reduced the intussusception after maintaining a column of barium 36 inches high for a period of 9 minutes.



Case 54, Fig. 1. Simple film of the abdomen shows a soft tissue intraluminal mass occluding the lumen of the transverse colon (arrow) which is actually widened at this point. This is the characteristic appearance of the leading edge of an intussusceptum. To the right of the spine, below the liver, there is a spherical density which represents the distal part of the intussusception. Below this, loops of air-containing small bowel occupy the normal position of the ascending colon. (The small dense circular shadow in the left upper quadrant is an opaque button on the skin.)

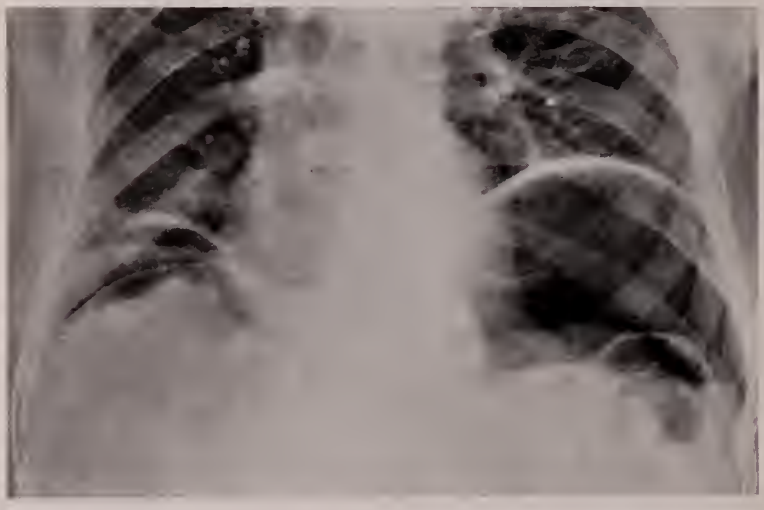
A simple film of the abdomen is shown in this case in order to emphasize that the diagnosis of intussusception can often be made without barium enema examination. If there is any doubt, air may be injected into the colon prior to taking a film of the abdomen in order to demonstrate the characteristic features of the leading edge of the intussusceptum. If attempts to reduce the intussusception by barium enema examination are not to be made, the findings on a simple film of the abdomen in combination with the clinical features are sufficient to permit operative intervention. Barium enema examination with additional radiation exposure to the child can thus be avoided.

Incidentally, in this particular child, despite the fact that there was no question that the intussusception had been reduced by the barium enema examintion, a recurrence occurred 21 hours later. At operation, no lesion which would explain recurrent intussusception was found.

Final Diagnosis: Ileocolic intussusception—diagnosis on simple film of the abdomen.

CASE NO. 55

A 76 year old male was admitted to the hospital with the history of a known duodenal ulcer for 14 years. Two days prior to admission, he developed severe epigastric pain, nausea, vomiting and a rigid abdomen. When the patient presented himself, his severe symptoms had subsided, but on fluoroscopy a large amount of free air was evident below both leaves of the diaphragm. He was therefore admitted and the presence of free air confirmed (Fig. 1). Three years previously, the patient had been admitted to the hospital and a perforated duodenal ulcer treated medically. At that time, free air was also demonstrated in the abdominal cavity. The patient again did well on a medical regime and 8 days after admission was referred for barium meal examination. It was noted,



Case 55, Fig. 1. Erect film shows a large quantity of free air below both leaves of the diaphragm.

Case 55, Fig. 2. Film from barium meal examination done 18 days after Fig. 1 showing persistent free air. There was no extravasation of barium.

however, on preliminary fluoroscopy, that there was a large quantity of free air in the peritoneal cavity. Despite the fact that the patient was taking fluid by mouth, no barium was administered. Ten days later, the patient was again referred for a barium meal. A large quantity of free air was still present. Nevertheless, barium was administered and a conventional gastro-intestinal examination performed (Fig. 2). None of the barium entered the peritoneal cavity and the patient had no complication as a result of the procedure. The patient was discharged and returned 6 months later for performance of a gastroenterostomy. Prior to this procedure, examination of the abdomen (Fig. 3) again revealed a large quantity of free air in the peritoneal cavity despite the fact that the patient gave no history suggesting a recent perforation. Barium meal examination was done a second time without incident. The presence of free air was confirmed at the time of operation but no perforation was discovered.

Case 55, Fig. 3. Erect film taken 7 months after Fig. 1 still shows a large quantity of free air below the domes of the diaphragm. Another barium meal examination was done at this time without incident.

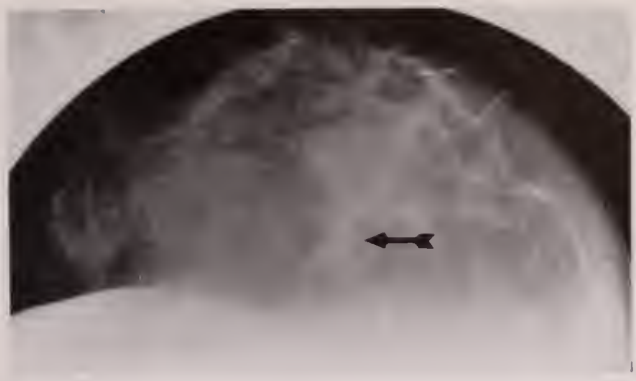
In this patient, it was demonstrated that a large quantity of free air remained in the peritoneal cavity over a period of about 7 months. The explanation for this is not clear but it may have been related to his previous chemical peritonitis three years earlier.

Final Diagnosis: Chronic duodenal ulcer with recurrent perforation; persistence of free air in the peritoneal cavity for 7 months.

CASE NO. 56

(Submitted by Herman C. Zuckerman, M.D.)

Radiography of the breast has been recently recommended on a survey basis for cancer detection. The case presented below is not unique in the experience of those radiologists who perform this type of examination but is a good example of the value of the method. This was a 49 year old woman who one year before the current observation was noted to have lumps in her left breast. She was followed and the masses appeared to recede in the intermenstrual intervals. Since, however, the masses persisted, she was re-examined and referred for roentgen examination. This showed (Fig. 1) three abnormal areas, two of which appeared to be homogeneous and globular and had the appearance of benign cysts. The third, however, situated more deeply in the breast behind these cysts showed irregular thickened strands of tissue with a central density con-containing minute pinpoint size calcifications. The appearance of this area is practically pathognomonic of a carcinoma; the calcifications are characteristic. At the time of operation, frozen section confirmed the roentgen findings. A radical mastectomy was performed; no nodes were involved.



Case 56, Fig. 1. Radiography of the left breast shows two sharply demarcated, globular, homogeneous shadows which have the appearance of cysts. However, deep in the breast (arrow) there is a small irregular dense area with radiating streaks, containing scattered pin-point calcific deposits. This appearance is characteristic of duct cell carcinoma.

Final Diagnosis: Infiltrating duct carcinoma of the breast. multiple cysts.

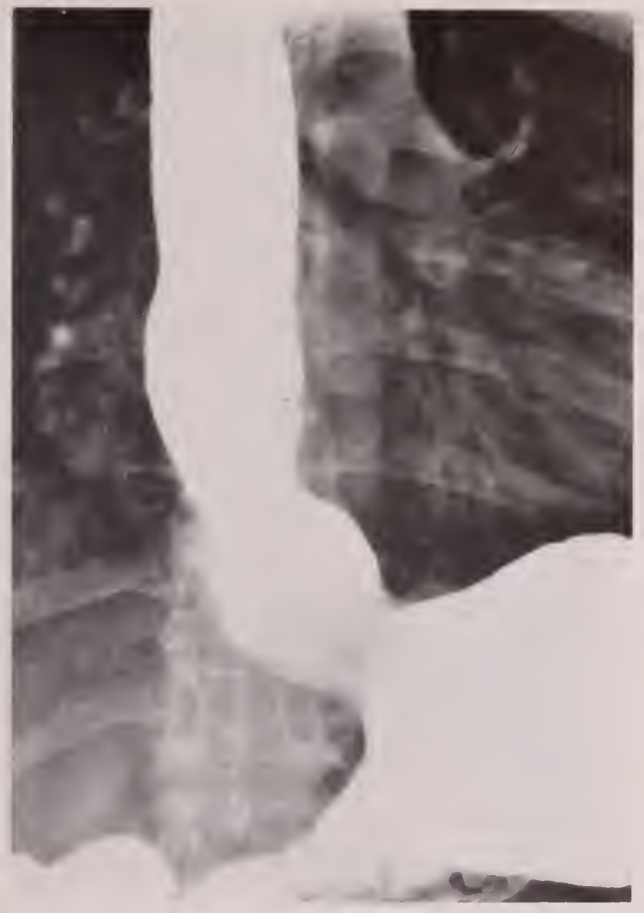
CASE NO. 57

A 70 year old man was admitted with the chief complaint of generalized crampy abdominal pain for 18 hours. Eight months previously, an anterior resection for an infiltrating carcinoma of the sigmoid had been performed. An unusual feature at that time was that the sigmoid had been drawn over to the right lower quadrant by fibrous adhesions and it was diffusely and densely adherent to the cecum, to the posterior parietal peritoneum and also to the anterior parietal peritoneum in the region of an appendectomy scar. Resection and an end-to-end anastomosis were performed after mobilizing the sigmoid. No involved lymph nodes were found. The tissue which was adherent to the anterior abdominal wall was also examined and showed only old fat necrosis without evidence of tumor. Post-operatively, the patient did quite well and gained about 10 pounds in weight.

On admission, the clinical and roentgen findings were that of a low small bowel mechanical intestinal obstruction. This was treated with a long tube and bowel movements soon returned. Barium enema examination showed no abnormality in the colon and a small bowel series was then performed. This showed a short, markedly constricted, rigid segment about one inch in length in the distal ileum, located about a foot from the ileocecal valve. There was minimal dilatation of the ileum proximal to this site. At the site of constriction, there was an additional fine tract of barium which suggested fistula formation. Moreover, the medial aspect of the terminal portion of the ileum adjacent to this narrowed segment showed multiple indentations suggesting an extrinsic neoplasm infiltrating the bowel wall.

Case 57, Fig. 1. In the distal ileum about a foot from the ileocecal valve, there is a segment about 1 inch in length (arrow) which is markedly narrowed, quite rigid, with destroyed mucosa. There is a second, thin tract of barium which appears to be in the inferior or medial aspect of the wall of the bowel at this site. In the terminal ileum, immediately lateral but adjacent to the narrowed segment, there are multiple indentations on the medial aspect of the bowel, indicative of neoplastic involvement. A soft tissue mass intervenes between the two involved portions of ileum. The appearance of a neoplasm involving two adjacent loops of ileum suggests that the original lesion was a serosal implant.

The findings described above were interpreted to be the result of a serosal implant which involved two adjacent loops of ileum and had produced marked narrowing with partial intestinal obstruction. At operation, an ileocolic resection was performed. The ileum formed a tight loop within which, on the serosal aspect, there was a mass which was extremely firm and which infiltrated the ileum on both sides. The mucosal surface of the ileum was ulcerated and invaded from the outside. A fistulous communication could be demonstrated by a probe passing between the two adjacent adherent portions. Histological examination was reported as metastatic adenocarcinoma. The mesenteric lymph nodes showed no evidence of tumor.

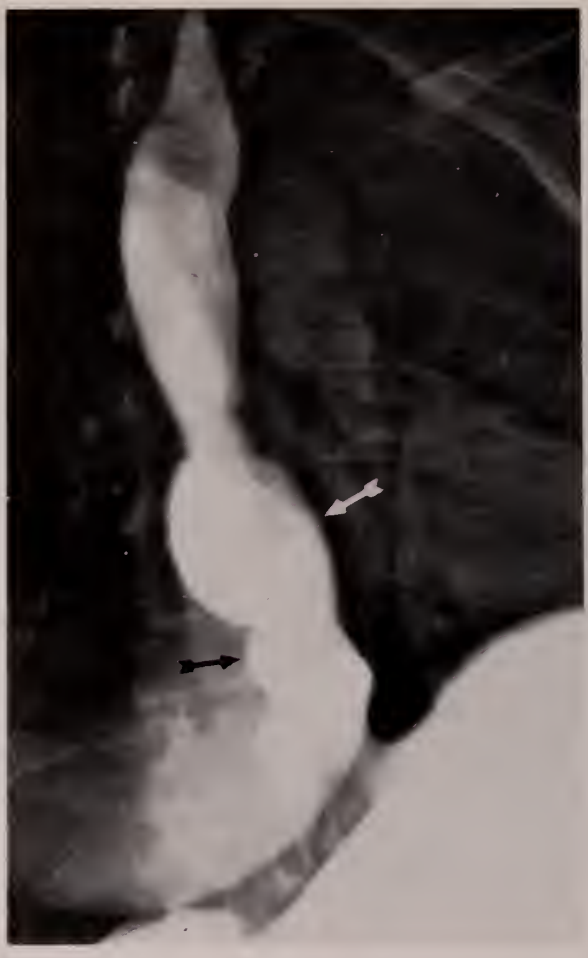


Case 58, Fig. 1. Film taken during continuous swallowing of fluid barium shows a small direct type of hiatus hernia with moderate widening of the hiatal ring. The borders of the esophagus for several inches above the hernia are finely spiculated or serrated. Free regurgitation was demonstrated during this examination.

Final Diagnosis: Metastatic carcinoma of the ileum—primary in the sigmoid.

CASE NO. 58

The first admission of this patient was at the end of 1956 with a history of progressive scleroderma of the skin for at least 2 years. She was admitted because of palpitations accompanied by shortness of breath and sticking precordial pain. During the four months before this admission, she had had five such episodes. Physical examination showed the skin on the face to be typical of scleroderma with similar changes in the hands, claw-like fingers and clubbing. The heart rate was 200. There was 1 plus sacral and pretibial edema. Blood pressure was 90/60. Electrocardiogram was difficult to interpret but suggested paroxysmal ventricular tachycardia although the possibility of auricular flutter



Case 58, Fig. 2. Re-examination on last admission shows a flat ulcer crater (black arrow) on the right posterior wall of the esophagus immediately above the hernial sac. There is no associated stricture. A somewhat globular segment about 2 inches in length (white arrow) extends proximal to the crater with an abrupt transition to tubular esophagus of normal calibre. In general, a transitional segment of intermediate distensibility intervening between normal tubular-shaped esophagus and a hernial sac particularly if ulceration or narrowing is present at either end or at both ends, indicates that so-called gastric-lined esophagus is present.

could not be entirely excluded. A variety of medication was used in an attempt to control the tachycardia, without success for 48 hours. The tachycardia finally subsided and the patient was maintained on digoxin. Because the patient survived, it was assumed that the tachycardia must have been supraventricular in origin.

The patient also complained of recurrent epigastric pain after eating, and barium meal examination (Fig. 1) demonstrated an unusually distensible esophagus

with an absence of peristaltic activity as well as a small direct type of hiatus hernia. The contour of the filled esophagus for a short distance proximal to the hernial sac appeared slightly serrated. This indicated the presence of peptic esophagitis in addition to scleroderma and a small hernia. When the patient was placed in the Trendelenburg position, there was completely free retrograde flow of barium from the stomach into the hernial sac and into the esophagus. The patient was re-admitted on two further occasions over the next five months because of recurrence of paroxysmal tachycardia. During her last admission, because of increased dysphagia, barium meal examination was repeated. The roentgen findings in the distal esophagus (Fig. 2) were different from those previously seen. In addition to the small hernial sac, there was a flat projecting ulcer niche on the posterior and right aspect of the esophagus immediately proximal to the hernia and, above this, there was a somewhat globular more distensible region with an abrupt transition into the tubular esophagus above this area. The diagnosis of marginal peptic ulceration was suggested but the significance of the distended segment proximal to the ulceration was not realized. This patient ceased during an episode of paroxysmal tachycardia which could not be controlled. At post mortem, it was evident that sclerodermatous changes involved the myocardium in a diffuse fashion. Of interest from the point of view of the present presentation is the fact that approximately the distal 3 inches of the esophagus were lined by so-called heterotopic gastric epithelium ("gastric-lined esophagus, esophagus lined by columnar epithelium, congenital short squamous esophagus, Barrett anomaly"). The punched-out ulceration was present at the junction of this segment with the small herniated portion of stomach. Intramural sclerodermatous changes in the wall of the esophagus were also present.

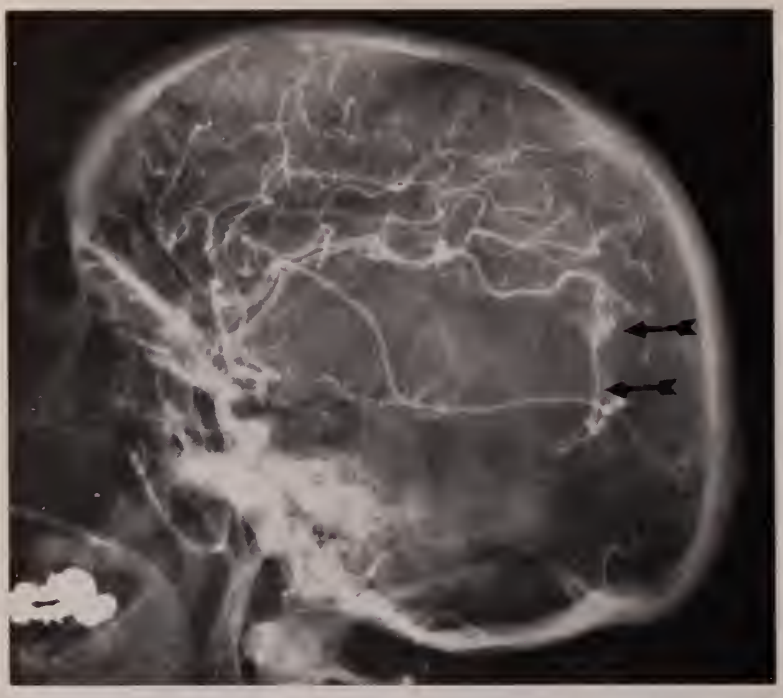
Final Diagnosis: Scleroderma involving a "gastric-lined" esophagus with peptic ulceration at its distal end.

CASE NO. 59

(Submitted by Charles Newman, M.D.)

This was the first admission of a 32 year old female who, the day before admission, suddenly complained of left temporal headache and rapidly became stuporous. After admission, the patient became somewhat more responsive and evidenced a right hemisensory and right hemimotor syndrome. Lumbar tap showed grossly bloody spinal fluid with a pressure of 300. Over the period of the next week, the patient showed some improvement but there were intermittent episodes of stupor and hypotension.

Roentgen examination of the skull showed slight displacement of the pineal towards the right side. Cerebral angiography in the lateral projection (Fig. 1) showed marked elevation of the vessels in the Sylvian fissure. The posterior temporal branch of the Sylvian group was stretched and elongated over the region of the temporal lobe. In the parieto-occipital area, in the arterial phase, a small half-centimeter nest of vessels was demonstrated with premature visualization of a vertical draining vein which extended downward towards the lateral



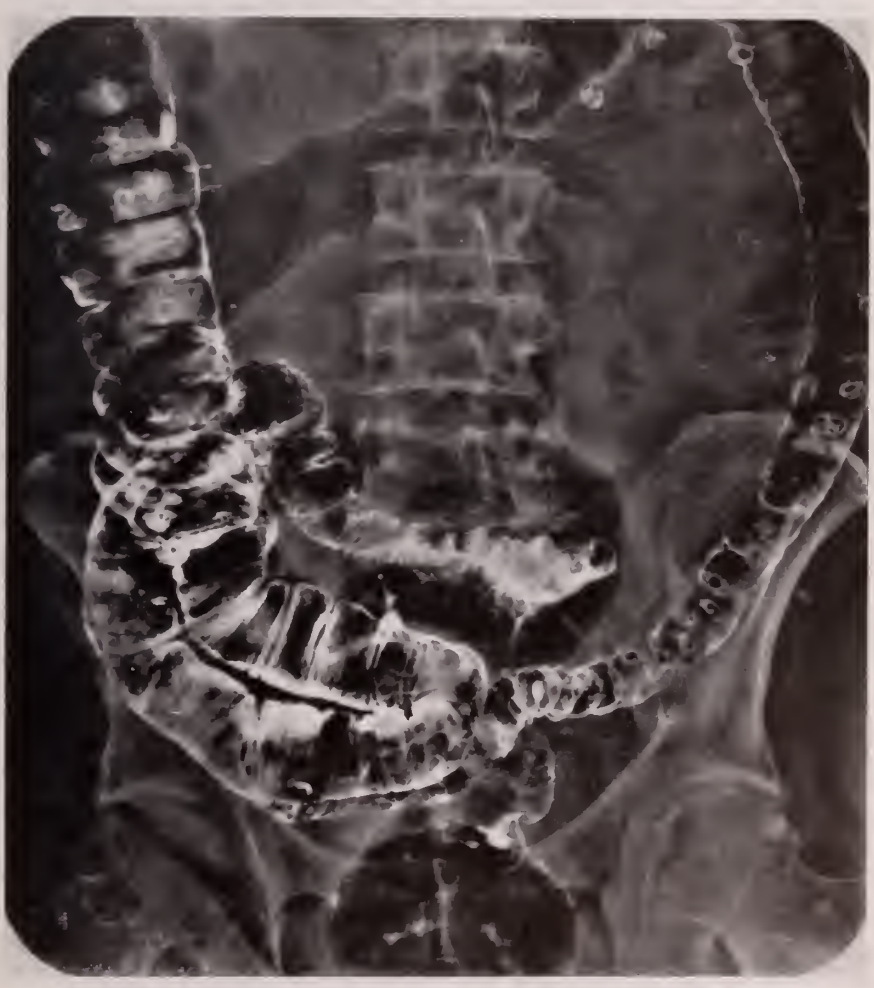
Case 59, Fig. 1. Lateral view taken during the course of percutaneus carotid angiography shows marked elevation of the vessels in the Sylvian fissure throughout its entire course. The posterior temporal artery leaves the fissure anteriorly and appears to be draped over the region of the temporal lobe. This vessel also appears to be elongated and stretched, and extends well posteriorly. In the parieto-occipital region (upper arrow), there is a small circular collection of minute vessels supplied by one of the Sylvian vessels. In addition, during this, the arterial phase, there is premature visualization of a draining vein (lower arrow) extending inferiorly towards the lateral sinus. The appearance of the nidus of vessels suggests the presence of an arteriovenous anomaly of the nature of an angioma. The space-occupying lesion in the temporal lobe is avascular and is consistent with a large intracerebral hematoma.

sinus. No tumor stain was seen in the area below the Sylvian fissure and this region gave the impression of relative avascularity. The angiogram was interpreted as showing a space-occupying lesion in the temporal lobe with a vascular abnormality in its periphery posteriorly. The possibility of a neoplasm presumably with bleeding or cystic changes could not be entirely excluded, but the impression was that the patient was suffering from a small vascular anomaly, an angioma, which had bled extensively into the substance of the temporal lobe.

Craniotomy was performed 8 weeks after admission to the hospital. The dura was found to be under moderate tension. The convolutions in the posterior temporal region were flattened and widened and the sulci were almost obliterated. The middle temporal convolution was discolored posteriorly. A transcortical incision was made through this area and a large encapsulated hematoma im-

mediately encountered. Yellow fluid was aspirated from the hematoma which was then carefully stripped from the brain substance through a clear line of demarcation. In the postero-medial portion of the cavity, a small vascular malformation was exposed which was then freed from the white matter and resected. Post-operatively the patient did quite well except for residual aphasic phenomena.

The type of vascular anomaly that this patient demonstrates must be differentiated from the more conventional type of arteriovenous anomaly or aneurysm which shows a conglomeration of anomalous arteriovenous communications with very large arteries supplying the lesion and large veins draining it. Resec-



Case 60, Fig. 1. Double contrast portion of the barium enema examination shows numerous diverticula in the sigmoid and scattered diverticula elsewhere in the colon. There is minimal lack of complete distensibility of the sigmoid with slight flattening of its superior aspect. There was no evidence of fistulization or of perforation or of an extrinsic inflammatory mass.

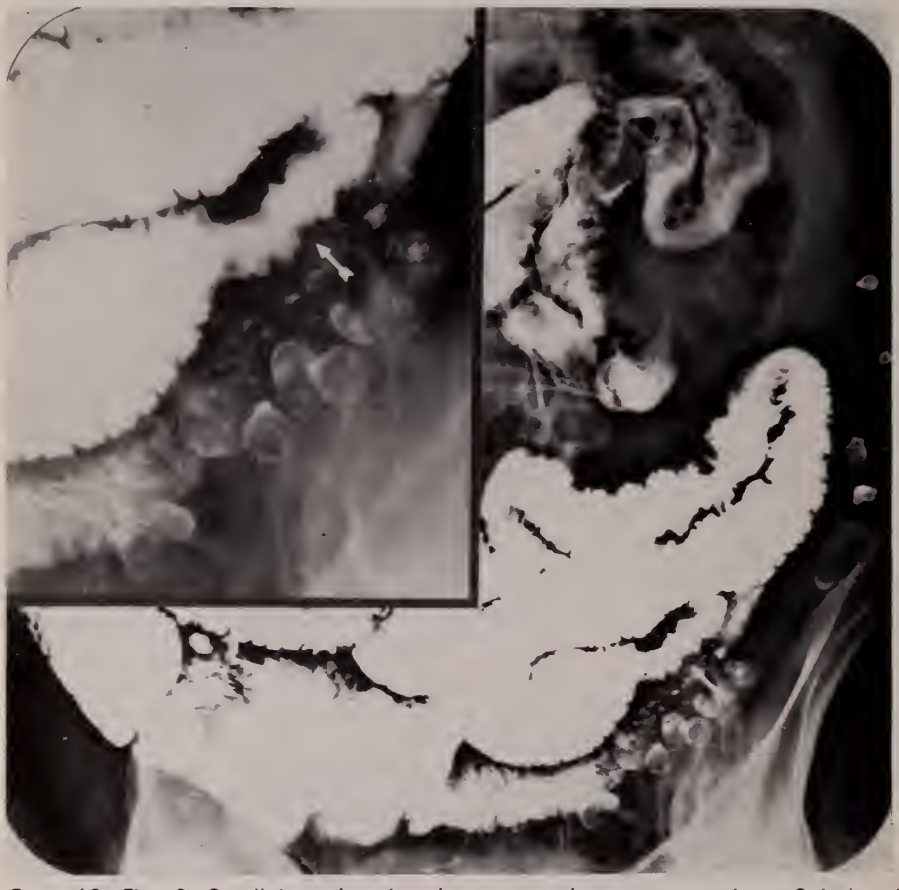
tion of this type of lesion is difficult and treatment often unsatisfactory. In the patient presented, however, the vascular anomaly is small, almost of capillary nature, and the supplying and draining vessels are not numerous or markedly enlarged. This type of lesion, therefore, can be completely resected. Clinical symptoms are not evident until intracerebral bleeding occurs.

Final Diagnosis: Small cerebral angioma with intracerebral hematoma.

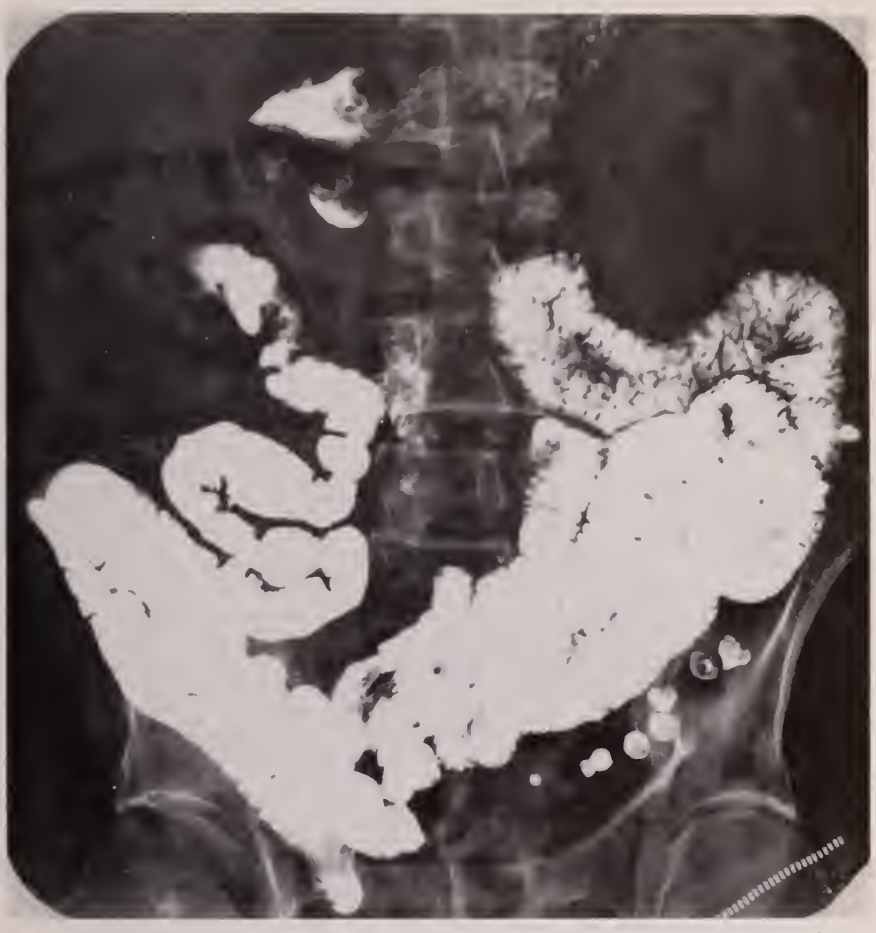
CASE NO. 60

(Submitted by Richard H. Marshak, M.D. and Joan Eliasoph, M.D.)

A 58 year old man was referred for barium enema examination with the chief complaint of recurring episodes of left lower quadrant pain occurring over a



Case 60, Fig. 2. Small bowel series demonstrated a segment about 2 inches in length in the distal jejunum immediately adjacent to the sigmoid (arrow) which showed limited distensibility, markedly irregular contours, effacement of the normal valvular pattern and coarsening of the mucosal surface. The segment parallels the sigmoid, appeared fixed in position and is separated from the sigmoid by a soft tissue layer about 1 cm. in thickness.



Case 60, Fig. 3. Repeat barium enema examination done two weeks after that illustrated in Fig. 2 showed no abnormality in any loop of small bowel adjacent to the sigmoid. (Incidentally, a right inguinal hernia is demonstrated containing a knuckle of small bowel).

period of several years, each lasting for a period of several weeks. During these episodes, there was moderate tenderness to palpation in the left lower quadrant but a mass was not palpable. The most recent episode had been accompanied by low grade fever lasting for several days.

Barium enema examination (Fig. 1) showed a large number of diverticula in the sigmoid and scattered diverticula elsewhere in the colon. There was minimal limited distensibility of the sigmoid and slight flattening along the superior aspect of the sigmoid loop. No evidence of fistulization or perforation or of an intramural inflammatory mass or of any remarkable extrinsic pressure was demonstrated.

The findings in the sigmoid on the barium enema were so minimal that the question arose as to whether sigmoid diverticulitis was the explanation of the

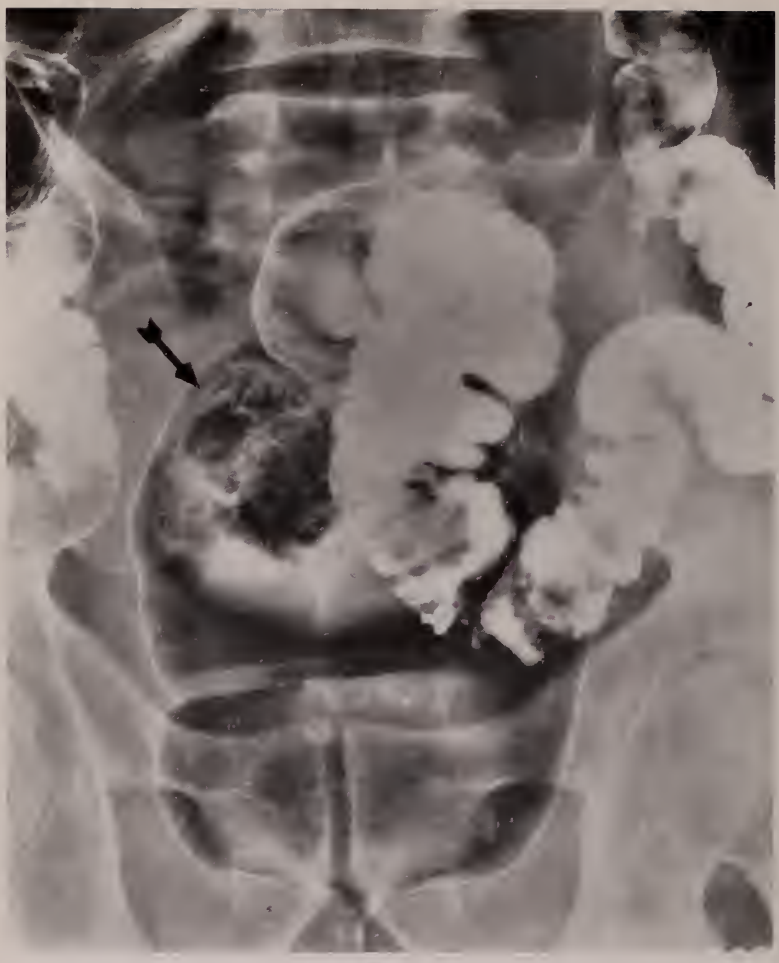


Fig. 1. Villous adenoma in the rectum (arrow). A discrete somewhat lobulated intraluminal mass, with a network of streaks of barium in a cobblestone pattern composing its surface, is characteristic. This lesion is about 1½ inches in its largest diameter. In addition, there are two smaller, typical polyps in the mid-sigmoid.

patient's recurring symptoms. For this reason, a small bowel series was performed. This demonstrated a short segment of distal jejunum about 2 inches in length immediately apposed to the sigmoid which showed limited distensibility, coarsely irregular contours, obliteration of the valvulae conniventes and a coarse mucosal pattern (Fig. 2). This segment of jejunum appeared to be fixed in position; the small bowel proximal to it was somewhat dilated. There was no remarkable obstruction to the flow of barium through this segment and the loops of small bowel distal to it did not appear abnormal.

The changes in the small bowel were difficult to interpret. They appeared not to be neoplastic in nature, but more likely due to inflammatory changes in and

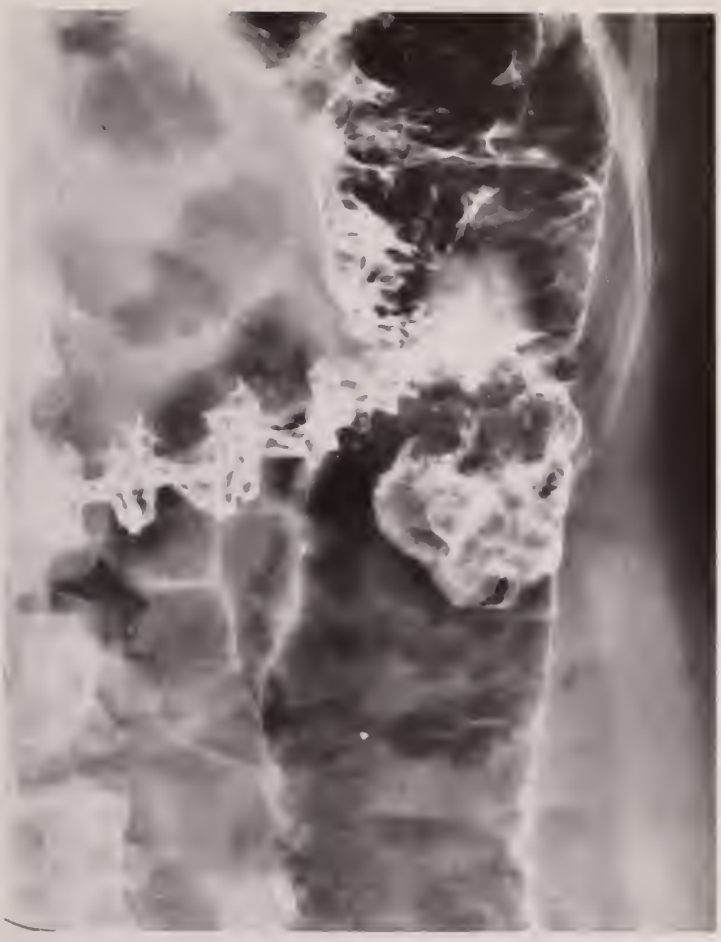


Fig. 2. Villous adenoma in the descending colon. The lobulation in its superior portion is coarser than is ordinarily seen. Microscopic examination showed malignant transformation.

around the involved segment as the result of a previous pericolitis associated with an acute sigmoid diverticulitis. Antibiotic therapy was administered for an additional period of two weeks and the small bowel series then repeated (Fig. 3). No abnormality was noted in any loop of jejunum including those immediately adjacent to the sigmoid. The rapid subsidence of the changes in the small bowel confirmed the previous impression.

This case is presented as an unusual example in which there was demonstrable intrinsic inflammatory involvement of a short segment of small bowel as a result of a sigmoid diverticulitis. It is remarkable that the small bowel changes appeared to require a considerably longer period of time for subsidence of the inflammatory changes than the site of original disease in the sigmoid.

Final Diagnosis: Sigmoid diverticulitis with adjacent enteritis.

ROENTGEN DIAGNOSIS OF VILLOUS ADENOMA OF THE COLON

Villous adenoma of the colon is not an uncommon condition. There is some disagreement as to the classification of this lesion and the designation of adenocarcinoma grade I is sometimes used instead of the term villous adenoma. It is generally agreed that the lesion is potentially malignant but that treatment prior to obvious malignant transformation carries a considerably better prognosis than the common varieties of carcinoma of the colon and that excessively radical operative procedures are not indicated. It is therefore of some importance to differentiate this type of lesion from the usual colonic carcinoma.

On roentgen examination, we have observed a number of cases of villous adenoma in which the diagnosis could be suggested. The roentgen features (Figs. 1, 2, 3) consist of a large, sometimes extremely large, apparently multilobulated,

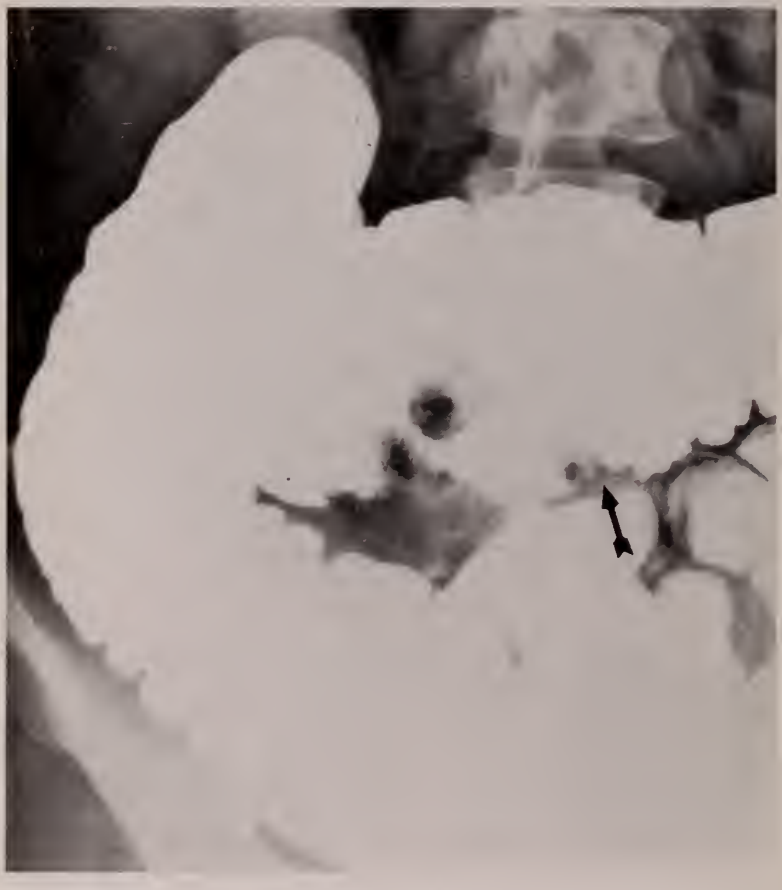


Fig. 3. Huge villous adenoma in the transverse colon. A large part of the intraluminal defect is obscured by surrounding barium but the irregularly lobulated contour and a broad base are evident. Adjacent satellite lesions (arrow), smaller but of similar nature may be present forming one conglomerate mass.

intraluminal, polypoid defect with a broad base which does not produce any obstruction to the retrograde flow of barium. The surface of this lesion has an irregular cobblestone appearance with small and larger, sharply drawn rings of barium. This surface pattern is the result of the entrance of barium into the fine interstices or clefts of the filling defect. It is not due to visualization of the "villi" which can be seen only microscopically. No discrete central excavation or ulceration is present. Intussusception, usually of limited extent, may be present. Large lesions may involve the entire circumference of the bowel but rarely produce obturation of the lumen. The reason for this is the fact that the diameter of the bowel at the site of the lesion is greater than normal, i.e., local dilatation is present. The presence of dilatation is of prognostic significance since it is indicative of superficial spread rather than deep infiltrations into the wall of the bowel.

In these cases, it is important to search for other more typical polyps which are frequently present. After transformation into a carcinoma, the typical appearance is lost and the more characteristic roentgen findings of an ulcerating neoplasm become evident. Incidentally, villous adenoma may occur also in the stomach and show similar roentgen features.

The diagnosis of a villous adenoma should not be made on the basis of the roentgen examination without the qualification that malignant change cannot be excluded. In some instances in which the diagnosis has been suspected, microscopic examination did not demonstrate the typical villous stricture. Nevertheless, these cases were large irregular adenomatous polyps which should be treated in a similar fashion.

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