GASTROENTEROLOGY AND HEPATOLOGY AT THE MOUNT SINAI HOSPITAL 1852–2000

Edited by
Jeremy Hugh Baron, D.M.
and
Henry D. Janowitz, M.D.

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In Memoriam:

Fenton Schaffner, M.D.

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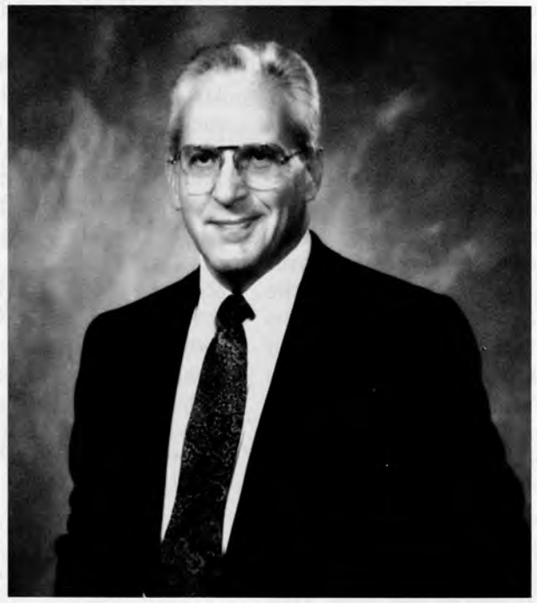

Dr. Fenton Schaffner.

DR. FENTON SCHAFFNER, an internationally renowned hepatologist who made pioneering discoveries in the field of liver diseases and was a distinguished member of the Mount Sinai community for more than forty years, died at his home in Washington, Connecticut, on January 24, 2000.

Born in Chicago, Dr. Schaffner earned BS and MD degrees at the University of Chicago and an MS degree from Northwestern University. After serving as a physician in the United States Navy, he returned to Chicago, where he joined the faculty of Northwestern University School of Medicine and practiced internal medicine. He also began an extraordinarily productive collaboration with Hans Popper that lasted for four decades and brought hepatology to the forefront of the intellectually active disciplines of medicine. Following his friend and colleague, who had been appointed to the directorship of the Department of Pathology at The Mount Sinai Hospital, Dr. Schaffner accepted a position at Mount Sinai, in 1958, to establish the Division of Liver Diseases and to serve as its first director. Mount Sinai opened its medical school in 1968, and Dr. Schaffner was among its first distinguished faculty members. During his exceptional career at the Mount Sinai School of Medicine, he held full professorships in both medicine and pathology, and was acting chairman of the Department of

Medicine from 1972 to 1974. Dr. Schaffner was named the George Baehr Professor of Medicine in 1973 and held that distinguished chair until his retirement in 1991.

Dr. Schaffner was an astute clinical observer, and his extensive clinical practice was the source of many of his insights, which were amplified by his expertise in light and electron microscopy. Although his clinical knowledge was virtually encyclopedic, he was especially interested in primary biliary cirrhosis, chronic hepatitis, and hepatic injury from drugs, areas to which he made important scholarly contributions. A clinician-scientist, he never lost sight of the primary responsibilities of a physician. His commitment to patient care was evident in his extraordinary devotion to each of his patients. A master clinician who attended to the needs of individual patients from around the world, he was also devoted to advancing the delivery of quality health care and held the position of governor of the New York Downstate Chapter of the American College of Physicians.

As a founding member of the American Association for the Study of Liver Diseases (AASLD) and an early supporter of the International Association for the Study of the Liver, Dr. Schaffner's impact on the field of hepatology has been global and enduring. He served as secretary of AASLD for fifteen years and was elected its president in 1976. He was also a vigorous supporter of the American Liver Foundation (ALF). His early support and leadership came at a critical time in the evolution of ALF, and continued throughout his life. Working to bridge the inter-institutional rivalries that had characterized the New York scene, he was one of the founders of ALF's highly successful Greater New York Chapter. The Chapter honored him in 1997 with the Mary Lea Johnson Richards Research Institute Award.

The author or co-author of more than 400 papers and books, Dr. Schaffner was recognized as an exceptional educator, teacher, and innovator in the study of liver diseases. His devotion to the dissemination of knowledge and specifically to the education of physicians was exemplified by his role in co-editing the classic series *Progress in Liver Diseases* over a 29-year period. He was also appointed one of the first associate editors of *Seminars in Liver Disease* when that journal was founded in 1980, participated regularly in its annual editorial board meetings for two decades, and remained active in this capacity virtually until his death. Dr. Schaffner's legacy, however, is not measured solely by the extraordinary volume of his scholarly contributions. It survives in the many fellows whom he trained, and who now represent a community of senior hepatologists both at Mount Sinai and around the world.

Dr. Schaffner is survived by his wife, Rosanne Kerby Schaffner, and four children, Roberta Schaffner of Dallas, Texas, Dr. John Schaffner of Rochester, Minnesota, Dr. Andrea Schaffner of Madison, Connecticut, and Marjorie Schaffner of Chicago, Illinois. He is also survived by five grandchildren, and a brother, Gerald Schaffner of San Diego, California.

Paul D. Berk, MD
Henry C. Bodenheimer, Jr., MD
Franklin M. Klion, MD

Introduction

JEREMY HUGH BARON, D.M., F.R.C.P., F.R.C.S., F.R.C.P.G.,
AND HENRY D. JANOWITZ, M.D.

This publication began as two independent initiatives. After Dr. Janowitz became Chief of Gastroenterology at The Mount Sinai Hospital in 1958, he made inflammatory bowel diseases the main interest of the division. He had long intended to write the history of this topic after he retired as chief. Dr. Baron was a fellow in this division in 1961–1962, and after he retired (in 1996) from his national health and university service in London, he decided to devote his energies to the history of gastroenterology and to spend his winters in New York. Therefore, we joined forces to coedit this history of gastroenterology and hepatology in time for the millennium in 2000 or the sesquicentenary of The Mount Sinai Hospital in 2002. We produced a list of topics, wrote some chapters, and invited colleagues to contribute their expertise. We express here our gratitude to all of them and to our secretaries, Sharon Nieman and Octavia Paul, for deciphering the illegible scripts; Jamie Kail, for the medical records data; and Al Lyons, Richard Steele, and Barbara Niss the Mount Sinai Archivists, for their skilled assistance.

Additional Note by Editor-in-Chief Sherman Kupfer, M.D.

All of the material incorporated into this book has previously been published in three separate issues of *The Mount Sinai Journal of Medicine*:

issue #1 January 2000; v67
issue #3 May 2000; v67
issue #2 March 2001; v68

These three issues constitute the entire theme issue devoted to Gastroenterology and Hepatology at The Mount Sinai Hospital, 1852–2000. We have taken the liberty of correcting several inadvertent errors in the names of some of the individuals, relevant dates, and some citations previously shown as "In Press." Dr. Fenton Schaffner, author of Chapter 16, is deceased. In addition, with respect to Chapter 27, Dr. Scott L. Friedman has replaced Dr. Paul D. Berk as Chief, Division of Liver Disease.

1

The Mount Sinai Hospital

A Brief History

JEREMY HUGH BARON, D.M., F.R.C.P., F.R.C.S., F.R.C.P.G.

Abstract

In 1852, The Jews Hospital was founded for the increasing number of Jews in New York. It opened in 1855 with 45 beds on West 28th Street; 92% of the patients were indigent. In 1864, the hospital formally became nonsectarian and, in 1866, changed its name to The Mount Sinai Hospital. The medical staff was primarily Jewish, because until relatively recently, it was difficult for Jewish doctors to obtain postgraduate training or specialist posts at major New York hospitals. As the Jewish population moved uptown, so did The Mount Sinai Hospital: in 1872 to 66th Street, and in 1904 to 100th Street, with 456 beds, growing with new buildings and services to the current 1100 beds, 50,000 discharges, 400,000 inpatient days and 300,000 outpatient visits each year.

Services increasingly became specialized, and then subspecialized. Key innovations included the choice of interns by competitive examination (1872), an advisory Medical Board (1872), the Nurse Training School (1881), the library (1883), the Alumni Association (1896), a professional medical hospital administrator (1903), research laboratories (1904), clinicopathological conferences (1905), the Social Services Department (1906), postgraduate teaching programs (1923), full-time chiefs of clinical services (1944), the dedication of the Mount Sinai School of Medicine (1968), and the merger in 1998 into the Mount Sinai-New York University Medical Center. **Key Words:** Mount Sinai Hospital New York, history.

THIS CHAPTER HIGHLIGHTS some of the main events of the first hundred years of Mount Sinai (1–13). In the 1850s, the increasing population of New York City, frequently subject to overcrowding, poverty and disease, signaled the need for new hospitals to complement the older voluntary ones (New York Hospital, 1771; Lincoln, 1839; St. Vincent's, 1849) and the older municipal institutions (Bellevue, City). The increasing number of Jews in New York (16,000) led the Hebrew Benevolent Society in 1850 to plan a Jewish hospital. In 1852, they and the Young Men's Hebrew Association, the German Hebrew Benevolent Society, and the Assistance and Education Society formed Articles of Association (1). Land was bought on the south side of then-rural West 28th Street between 7th and 8th Avenues, ground was broken in 1853, and The Jews Hospital was opened May 17, 1855 with 45 beds (2). The hospital's services were intended primarily for the indigent, and of the 216 patients admitted in 1855–1856 only 16 could pay (3).

In the 1852 Articles of Association, the hospital was established for "medical and surgical aid to persons of the Jewish persuasion" (1) but from the beginning accident cases were admitted from all ethnic groups. In 1862, the Jews Hospital admitted soldiers from the Civil War. The following year, those injured during the Draft Riots were admitted (4). In 1864, a formal nonsectarian policy was adopted, but this policy was not widely recognized (5). To emphasize this change in policy, the hospital was renamed, in 1866, The Mount Sinai Hospital (5). Nevertheless, this change did little to diminish the anti-Semitism prevalent at the time.

In the 19th century and much of the 20th, Jews were not readily accepted into medical schools (14). Moreover, it was more difficult for them to obtain postgraduate training and even more difficult to become specialists at a university hospital. Some medical schools did not take any Jews, while some of the better schools, such as the College of Physicians and Surgeons ("P & S") Medical School at Columbia University, had a quota of only 10% Jewish students (14, 15). When Crohn qualified at P & S in 1906, he came to The Mount Sinai Hospital as an intern (16). When Janowitz qualified at P & S in 1939, second in his class, he was given a message that he should not expect an internship at Columbia, but should contact Dr. George Baehr at Mount Sinai, as should his friend (third in the class), whose "accent was too thick for the Harkness Pavilion" (16).

Some social exclusions were blatant. When Crohn attended to a patient vacationing in a hotel in Maine, he could not spend the night there, and when he went to an executive board meeting of the AGA in Pittsburgh, he found that he alone was lodged in a hotel because he could not stay with the other board members at the Fort Duquesne Club (17, 18). When Winkelstein went to meetings of the AGA in the 1920s, he could not stay in the main conference hotel (19). In 1962, I visited Dr. Morton Grossman's department in Los Angeles and one day was invited to have lunch with Stuart Tuttle at his country club. Dr. Grossman learned where I had visited and remarked that I had been entertained where Dr. Tuttle could never have take him (20).

As the Jewish population of New York progressively moved uptown, The Mount Sinai Hospital followed. In 1872, it relocated to Lexington Avenue between 66th and 67th Streets (6), and then again in 1904 to Fifth Avenue at 100th Street (11). At the time of this second move, Mount Sinai had 456 beds. By 1875, when a separate outpatient dispensary was opened, gynecology and pediatrics cases were treated separately. From 1872, interns were chosen by a competitive examination and served two years (8). In 1877, the beds were divided into Medicine and Surgery. The Association of the Alumni of The Mount Sinai Hospital was created in 1896. The Mount Sinai Training School for Nurses was incorporated in 1881 (8). The medical library opened in 1883. The first sub-specialist, an ophthalmologist, was appointed in 1879 and a pathologist (Henry Heineman) and a neurologist (Bernard Sachs) in 1893 (10).

Sachs (21) enunciated the ethos of a Mount Sinai Hospital specialty service: "The chief aims . . . should be the considerate treatment of the patient, making use of the most recent methods, the training of an adequate House Staff, and, above all, the development of a group of able associates and assistants . . . . who would be certain in the course of time to contribute materially to the advancement of neurological science. . . . Incidentally I stressed the importance of the doctor looking neat, being scrupulously clean, using good English, and articulating distinctly."

In 1903, Mount Sinai appointed Dr. S.S. Goldwater as the first professional medical hospital administrator in the U.S. (1). Dr. Goldwater maintained that health was not a privilege but a right, and he fought throughout his long career in New York to ensure that its citizens should be warm, well fed and sheltered. Under Dr. Goldwater's administration, The Mount Sinai Hospital's Social Service Department was opened in 1906.

The development of a medical school in The Mount Sinai Hospital took almost one hundred years. In 1873 the Board was asked, but considered it not expedient then, to start a medical school. In 1908, when the decision was made to take medical students from Bellevue and Columbia, the titles of clinical professor of medicine and clinical surgery were awarded to senior hospital staff. Clinical pathological conferences were held occasionally from 1905 and regularly from 1919. Formal postgraduate teaching programs began in 1923.

Research, too, flourished at Mount Sinai. When the Pathology Department was formally instituted in 1906, the 15 staff members were all engaged not only in routine clinical testing but in "active research work in . . . higher problems of modern medicine" (12). The philanthropist Adolph Lewisohn (a Mount Sinai Hospital trustee from 1898 to 1938) insisted that a firstrate hospital must be a first-rate research center; he therefore financed both with capital and revenue the laboratories built in 1904 and 1916. By 1923, there were 22 professional laboratory staff members. The laboratory directors became full-time salaried employees in 1926, Klemperer for morbid anatomy, Shwartzman for bacteriology and Heidelberger for chemical pathology. But there were also 60 volunteer researchers-clinicians who maintained an active clinical practice, seeing patients, but who also devoted more than 20 hours per work to research (22, 23). They were motivated by being associated with progress in scientific medicine, which was thought to lead to a higher level of clinical care. They also knew the Mount Sinai policy of promoting clinicians with a scientific background. Thus, over its first hundred years, The Mount Sinai Hospital evolved from a small community hospital into a major medical center which was recognized internationally for its excellence in clinical care, research and postgraduate teaching.

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As an aside for the overseas reader, an explanation of the usual staffing structure of a major hospital may be helpful. In the 1850s all, and in the 1990s almost all, of the senior clinicians (consultants) were 'voluntary attending'; that is, they earned their livelihood in private specialist practice in their outside offices. They used the hospital only for the admission of patients to private beds. They were not paid for their hospital work in caring for patients in the wards, for operative procedures, or for research or undergraduate or postgraduate teaching. The post of attending was keenly sought, because even a voluntary staff position at a major hospital encourages other doctors to refer patients to the attending, or patients to refer themselves, and also because hospital privileges permit admissions of private patients whose care is facilitated by the "house staff" (interns, residents and fellows). Today there is also a large "full-time" salaried staff, but earlier this century only a few senior academic staff members, such as departmental or divisional chairmen, were salaried.

As early as 1872, the Hospital trustees were advised by a medical board. To avoid conflicts of interest or the diversion of funds to research activities, separate financing for research was instituted after 1925, with the encouragement of scientifically minded clinicians and pathologists. By 1937, joint committees were set up for research, administration, education, and the residency and fellowship program. In 1944, full-time chiefs of the clinical services were appointed, George Baehr directing the first medical service and medical research, followed by Isidore Snapper for the second service and graduate medical education. In the 1950s, the Board considered again the question of establishing a medical school, but these plans did not materialize until 1963, when the Mount Sinai School of Medicine of the City University of New York was incorporated. It now has about 400 medical students, 50 M.D./Ph.D. students and 130 Ph.D. students. The Mount Sinai Hospital now has more than 1100 beds, with approximately 50,000 discharges, 400,000 inpatient days, and 300,000 outpatient visits each year. In 1998, The Mount Sinai Hospital and New York University Medical Center agreed to merge into the Mount Sinai-New York University Health Services Organization, with NYU awarding degrees for two separate medical schools, the NYU School of Medicine and the Mount Sinai School of Medicine.

Thus, in a century and a half, The Mount Sinai Hospital grew from a tiny, 45-bed sectarian hospital serving an almost wholly indigent community into today's giant academic medical center, known for its clinical, scientific and teaching excellence.

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2

Gastroenterology and Hepatology as Subspecialties

JEREMY HUGH BARON, D.M., F.R.C.P., F.R.C.S., F.R.C.P.G.

Abstract

Gastroenterology grew as a subspecialty in Germany in the 19th century. In the 1880s and 1890s, Austrian and German clinics were attended by American physicians who, on returning to the U.S., founded the American Gastroenterological Association in 1897. The creation of a subspecialty board, however, had to wait until 1941. At The Mount Sinai Hospital, Dr. A.A. Berg was appointed Surgeon in 1899. His practice focused on the alimentary tract, which in 1910 became one of the four surgical specialties. In 1914, further subdivision led to the stomach and duodenum becoming additional specialties. In 1917, wards were endowed for Dr. Berg's specialty. The first Mount Sinai physician to have an interest in gastroenterology was Morris Manges, but the first to limit his practice to gastroenterology was Dr. Edward Aronson, for whom a specialist outpatient division was formed in 1913. Aronson died in 1922 and was succeeded by Dr. Burrill Crohn, who was followed in 1934 by Dr. Asher Winkelstein; all three collaborated closely with the surgeons, physiologists and biochemists. In 1958, Dr. Henry Janowitz became chief of the Division of Gastroenterology; he was succeeded in 1983 by Dr. David Sachar, who was followed in 1999 by his associate Dr. Steven Itzkowitz. In 1958 Dr. Fenton Schaffner became chief of the Division of Hepatology (now headed by Dr. Paul Berk), and in 1979 Dr. LeLeiko became chief of Pediatric Gastroenterology. **Key Words:** Gastroenterology, hepatology, history.

Germany

THE SUBSPECIALTY OF GASTROENTEROLOGY was created in Germany in the late 19th century, following the scientific advances in German clinics (1). To take the stomach as an example, Tiedemann and Gmelin measured the concentration of hydrochloric acid in 1824, the year after Prout's seminal presentation to the Royal Society, London. Muller and Schwann described pepsin in 1835, Enderlin found HCl in the stomach of a decapitated criminal in 1843, and Leube introduced the test meal in 1871 (1).

Ewald wrote the first textbook of gastroenterology in 1879, and his pupil Boas started the first gastroenterology clinic and laboratory, in Berlin, in 1886 (2). Boas called himself "specialist in gastrointestinal diseases" and in 1895 founded the first gastroenterological journal, *Archiv für Verdauungs-Krankheiten* (later *Gastroenterologia* and then *Digestion*). Meanwhile Ewald and Boas introduced the first fractional test meal in 1886, the year Jaworski and Gluzinski measured gastric secretion of HCl as the equivalent amount of a standardized concentration of NaOH/100 cc gastric juice used to titrate a 100 mL volume of gastric juice. In 1892, Ewald measured free and total acidity with Congo red and phenolphthalein indicators.

United States

The United States followed the German pattern (3, 4). In the 1880s and 1890s, many American physicians went to Austrian and German gastroenterological clinics and practiced this subspecialty when they returned. Moreover, many German gastroenterologists had emigrated to the United States. There were 17 founders of the American Gastroenterological Association in 1897. Einhorn was born in Poland. Hemmeter's

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parents were German and he was sent to school in Wiesbaden. Seven of the 17 learned their gastroenterology in Austria and/or Germany: Aaron, Eisner, Friedenwald, Hemmeter, Manges, and Stuckey visited Vienna; Friedenwald, Aaron, Einhorn, and Manges studied in Berlin; and Stuckey visited both Leipzig and Strasburg.

In Germany, academic physicians and clinicians, and even gastroenterologists like Leube and Ewald, opposed the efforts of Boas to detach digestive diseases from internal medicine. Unlike Einhorn and Pavlov, they refused to support Boas's journals, so that Boas was unable to convene a national conference on gastroenterology until 1914. There was similar opposition in the U.S., but the 17 physicians of 1897 did found the first national gastroenterological society in the world. A subspecialty board of gastroenterology came only in 1941. The American Gastroenterological Association formed its research group in 1956.

The first American textbooks on the stomach came in 1896 (Einhorn) and 1897 (Hemmeter). The first journal was *Transactions of the AGA* (1903–1908); *Digestive Diseases and Nutrition* appeared in 1934 and *Gastroenterology* in 1943 (1). Meanwhile, gastroenterological clinicians founded the Society for the Advancement of Gastroenterology (1932), which was renamed National Society for the Advancement of Gastroenterology in 1934, then the National Gastroenterological Association in 1938, and finally the American College of Gastroenterology in 1954 (5); its 1934 journal, *Review of Gastroenterology*, has been known as the *American Journal of Gastroenterology* since 1954.

Mount Sinai

Crohn was rarely reticent: "Without boasting, it is a fair statement to make that the profession of the country, or for that matter, the world over, look with expectation to the staff of this hospital when problems of a gastroenterological nature are up for discussion" (6). A clinically and scientifically organ-based specialty, to be successful, needs high-quality, multi-faculty components which work together. At The Mount Sinai Hospital, gastroenterology as a subspecialty actually began with Dr. A.A. Berg's appointment as surgeon in 1899 and his subsequent concentration on the alimentary tract. The first internal medicine physician to have an interest in gastroenterology was Morris Manges, one of the founders of the American Gastroenterology Association in 1897 (3). In 1910, surgery was formally divided into four specialties, one of which covered the abdomen; this specialty was further subdivided in 1914 into stomach and duodenum. In 1917, The Wimpheimer Wards for the Surgical Treatment of Diseases of the Stomach and Intestines were endowed for A.A. Berg. A separate proctology surgical clinic began in 1936 and was directed by Dr. Sylvan Mannheim.

In 1913, through Berg's influence on the medical board, a specialist outpatient division of medical gastroenterology was formed in Mount Sinai, to be headed by Edward A. Aronson, who was the first Sinai physician to limit his practice to gastroenterology. In this division, clinicians and laboratory staff worked on biochemical problems, especially variations in gastric and pancreatic secretion in health and disease, and in response to drugs.

Thus, at the time of the First World War, Aronson had a clinic but no beds, and Berg had beds on both adult and children's wards, biochemical support from Dr. Samuel Bookman, and physiological studies by Dr. Eugene Klein. Sunday morning grand rounds began at 9.30 A.M. when Berg's team (Richard Lewisohn, Paul Aschner, A.O. Wilensky, Eugene Klein) and Aronson's team (Burrill Crohn — "sometime conformist, often belligerent," Samuel Goldfarb "an amateur radiologist," Samuel Weiskopf, Eddie Hollander, S. Winfield Kohn, Asher Winkelstein) met in the Reception Ward (6, 7). There they saw special follow-up patients, especially those who had been given a gastroenterostomy for duodenal ulcer and cecostomy for ulcerative colitis. At 10:30 A.M., the teams moved to Berg's wards, M and N, where with the house staff, nurses and visitors they made rounds with open discussion until lunchtime.

Aronson died young in 1922 and was succeeded by his first assistant, Burrill Crohn, even though he was in bad grace with some of the senior staff for his unorthodox work and heretical criticism of gastroenterostomy (8, 9). In 1926, Crohn was given the title associate-in-medicine and the responsibility both of an attending and of clinical research. Crohn was succeeded by Asher Winkelstein in 1934. Their careers are outlined in chapters 3–5. When Dr. Ralph Colp became an attending in the 1930s, the multidisciplinary team continued. "Attached to the service was an internist, Dr. Samuel Averbuck; a psychiatrist; a gastroenterologist, Dr. Asher Winkelstein; and a gastrointestinal physiologist, Dr. Franklin Hollander. Ward grand rounds were formal, crowded with staff and visitors. After presentation of the case by the house surgeon, demonstration of the pertinent X-rays and the surgical specimen, the case was open for discussion, which included medical, psychiatric and physiological aspects. Later these were conducted off the ward at a formal conference" (10).

Henry D. Janowitz founded the first division of gastroenterology in the Department of Medicine in 1958 and headed it until 1983. Other associated divisions were created, such as Hepatology (Fenton Schaffner, 1958) and Pediatric Gastroenterology (Neal LeLeiko, 1979). Thus, gastroenterology became one of the new separate groups of internal medicine, each of which was headed by a physician ranked as an associate attending in medicine with responsibility for an outpatient clinic and, usually, a laboratory. Today The Dr. Henry D. Janowitz Division of Gastroenterology (named in 1992), headed by Dr. Steven Itzkowitz of the Department of Medicine, has a faculty of fifty. Dr. Paul Berk's Division of Liver Diseases has three, and Pediatric Gastroenterology has five attendings.

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3

Morris Manges and Edward Aronson

JEREMY HUGH BARON, D.M., F.R.C.P., F.R.C.S., F.R.C.P.G.

Morris Manges (1865–1944)

MORRIS MANGES (Fig. 1) (1–3), the first trained gastroenterologist at The Mount Sinai Hospital, was born in New York City on May 10, 1865 and graduated Phi Beta Kappa from City College in 1884. He graduated in medicine from the College of Physicians and Surgeons, Columbia University in 1887. Manges then interned at the Charity Hospital on Blackwell Island (later renamed City Hospital on Welfare Island), including six weeks at the Maternity Hospital with Dr. Henry Garrigues, who had immigrated from Denmark in 1875 (4). Manges was greatly impressed by the total lack of deaths from puerperal sepsis in the four years before he had arrived. This was entirely due to Garrigues' application of the doctrines of Semmelweiss (isolation and antisepsis with careful cleanliness), which led in 1883 to the reduction of maternal mortality from puerperal sepsis from 25% to zero.

Manges spent 1888 and 1889 first with Ewald in the Königin Augusta Hospital in Berlin, and then in Frankfurt and Vienna. On his return to New York, he attracted a large practice, with patients coming from all over the U.S. because he had a sympathetic manner and good diagnostic skills, and because he spoke fluent German and had a wide knowledge of European medicine, so that he could recommend health resorts for his wealthier patients to attend (1).

In 1892, Manges became visiting physician to The Mount Sinai Hospital and was promoted to attending in 1898. At that time, he joined A. Merger, J. Rudisch and N.E. Brill. He also served as consultant physician to the Hospital for Joint Diseases and the Hebrew Orphan Asylum. In 1892 and 1896, he published his most lasting works, translations into English of Ewald's two-volume classic, *Diseases of the Stomach*. His other singular contribution to American medical history was to purchase from the Curies in 1902 the first specimen of radium for therapeutic use in the U.S.; he later presented it to the New York Academy of Medicine (5). He retired in 1921 but remained a consultant until his death on January 6, 1944.

Fig. 1. Dr. Morris Manges.

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Key Words: Morris Manges, Edward Aronson.

Manges was a founding member of the American Gastro-enterological Association in 1897 and presented papers at its first two scientific meetings (Carcinoma of the cardia; A case of dilation of the stomach due to latent ulcer of the pylorus; and Operation by Halsted) as well as a detailed survey of stomach diseases at The Mount Sinai Hospital from 1898, at the seventh AGA meeting in 1904. Subsequently, he practiced and taught internal medicine. Crohn (6) commented: "He was really an internist and he contributed nothing to gastroenterology itself."

His non-gastroenterological publications, covering three decades (1890–1921) were protean in subject matter (7): a new rapid tubercle bacillus stain, quantitative estimation of sugar, mucous casts in the urine, treatment of typhoid fever, heart disease in the 18th century, therapeutics of heroin, treatment of coughs with heroin, secondary carcinosis in bone, rheumatism and gout, heart failure, pharyngeal diphtheria, exophthalmic goiter, pneumonia with pericarditis, ulcerative endocarditis, aneurysm, lysol in the treatment of meningitis, cholesterin pleurisy, rectal hypnotics, treatment of pneumonia, meningitis, adherent pericardium, aortic stenosis, abuse of water drinking, liberal diet in typhoid, typhoid fever in the aged, perforation in typhoid, the physician and the medical press, tuberculous pericarditis, lateral thoracic glands, prolonged fevers, whispered bronchial voice, heart disease and epigastric symptoms, mouth, diabetes, eventration of the diaphragm, early diagnosis of cancer, lung abscess, non-tuberculous pulmonary suppuration, pulmonary endarteritis, pulsating spleen, roentgen ray diagnosis, and periarteritis nodosa.

Outdoor recreation and the environment were important to him. He loved the arts, painting in watercolors outdoors, exhibiting at the American Physicians' Art Association, and collecting engravings, etchings and French bronzes. He had a fine scientific and archaeological library, and he was a member of the Archaeological Institute of America and the Oriental Institute of the University of Chicago.

Manges was an excellent lecturer, and from 1898 to 1908 he was professor of clinical medicine at the New York Polyclinic Medical School. From 1911 to 1922, he taught at New York University and Bellevue Medical College. He strongly supported the role of science and research at Mount Sinai, then a non-university hospital. In the 1890s, he was also compassionate enough to break the City Board of Health's rigid quarantine rules by smuggling a child with scarlet fever out of a well-known New York hotel into a building at The Mount Sinai Hospital used to quarantine patients. He ensured total secrecy of the doctors, nurses and attendants, which led to the child's grateful and wealthy mother buying land on East 16th Street to establish the Minturn (later Willard Parker) Isolation Hospital in 1896 (8).

For his era, Manges was unusual in his modesty; when he cited Ewald's book, it was in the format "see Ewald's *Diseases of the Stomach*, American translation, p. 47," thereby concealing his own role as translator (9).

Edward Aaron Aronson (1874–1922)

Edward Aronson (Fig. 2) was born in New York and qualified at Columbia University in 1899 (10). He followed the custom of seeking postgraduate training in Germany; like Manges, he worked with Ewald at the Königin Augusta

Fig. 2. Dr. Edward Aronson.

Hospital in Berlin (11) and also with Theodor Rosenheim for esophagoscopy (12).

On returning to New York, he served as instructor in the Medical Schools of Fordham University and the College of Physicians and Surgeons, as well as the New York Polyclinic. He came to Mount Sinai to join Dr. Bookman in the physiological chemistry department of the pathological laboratory, and investigated the chemical composition of the urine in such diseases as typhoid, pernicious anemia and tetanus (13).

Presumably as a result of his scientific training, he was appointed in 1913 as Mount Sinai's first chief of gastroenterology. In his 11 years as chief, he built a small team of clinical investigators and began that close cooperation with the gastrointestinal surgeons which has been such a strong feature of hepatogastroenterology at The Mount Sinai Hospital during this century (see chapter 2). However, he appears to have done little or no research, and his few papers are mostly clinical case reports or reviews. He died on June 24, 1922, at the age of 47, during an operation for pancreatitis.

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4

Burrill B. Crohn (1884–1983)

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Burrill B. Crohn (1884–1983)

BURRILL B. CROHN (Fig.) was not the first or only Mount Sinai Hospital physician to have a disease named after him. But "Crohn's disease" continues to resonate worldwide and probably will continue to do so even after the etiology of this enigmatic illness is discovered.

Burrill Crohn was one of twelve children born into a German-Jewish immigrant family. His father settled in New York City and earned a livelihood as a stockbroker. The children never lacked the necessities of life, but had to forego its luxuries. At age 13 (1907), Burrill entered the City University of New York; he graduated at age 18. He obtained his medical degree from Columbia University's College of Physicians and Surgeons after four years. Having passed a comprehensive examination, he was appointed to The Mount Sinai Hospital for a two-year rotating internship and a year's fellowship in a clinical laboratory under the direction of Emmanuel Libman (of Libman-Sachs endocarditis). This was the conventional pathway of bright young men at that time at The Mount Sinai Hospital.

In later years, Crohn wrote a short personal biography entitled *Notes on the Evolution of a Medical Specialist 1907–1963* (1). It is delightfully written and gives a picture of his development as he saw it. I had met him, of course, when I entered Mount Sinai for my own internship just seven years after the publication in the *Journal of the American Medical Association* of the paper on regional enteritis, and was amused by the slightly skeptical medical atmosphere which surrounded the importance of this curious entity of 14 cases. (Hugh Baron's account of the discovery of this disease, which can be found in chapter 19, is in my opinion, the most even-handed and detailed account of the road that led to its discovery.) When I returned to

Fig. Dr. Burrill B. Crohn.

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Key Words: Burrill B. Crohn

Mount Sinai in 1948, after World War II, I got to know him more closely. Indeed, when I needed office space to moonlight during the eight years I spent in Frank Hollander's laboratory, Burrill graciously allowed me his office in the evenings and on weekends. For a period of six months, I helped him in the morning sessions when he saw his patients. It became clear that his persistent and scholarly recording and substantive writing about regional enteritis had convinced his institution that his subject was going to be an important one.

Even Nobel Laureates make only one important observation. It should be noted that Crohn had already established himself as a clinical investigator in his early work on "Affections of the Stomach" (2) long before his ileitis studies. Burrill had contributed to the joint venture with the observations of Leon Ginzburg and Gordon Oppenheimer. I recall the efforts that Dr. Richard Marshak, his radiologist, made to convince Burrill that regional enteritis could also occur in the colon, but without success. Burrill eventually accepted this concept after it had been accepted by the entire world.

In 1935, he was elected president of the American Gastroenterological Association. During the brief period of my daily contact with him, he enjoyed a great clinical practice and was becomingly modest about his role in the discovery of regional enteritis. In my presence, he never used the term "Crohn's disease" which he ascribed to the writings of the English surgeon Brooke (3). He was a good general practitioner of gastroenterology, not a master of internal medicine, but his intuitive grasp of a patient's psychology made him outstanding in the handling of functional disorders of the GI tract. His approach to Crohn's disease was firmly based on detailed records of his experience, and he was an ardent exponent of steroids for Crohn's disease as well as ulcerative colitis. He thought these disorders were infections, probably of viral origin, and saw no reason why a patient might not have both diseases, although he considered this rather rare.

He enjoyed taking care of the famous, but was compassionate and supportive of his poor patients. He looked for a son in the young men who worked for him and had difficulty in realizing why they could not accept this role. He was educated, cultured and a well-read physician. His second marriage, to Rose, was a happy and fulfilling one. After his death, his family founded the Burrill B. Crohn Research Foundation to support the research in the disease at The Mount Sinai Hospital. Shortly before her death, Mrs. Crohn endowed the Burrill B. Crohn Chair in Gastroenterology for the head of the service. David Sachar was named to be the first in the line of future holders of the chair. Mrs. Ruth Dickler, his daughter, continues to play an important part in the work of the Crohn's Foundation and his son, Sylvan (Woody) Crohn, practices medicine in upstate New York. I was particularly happy that Burrill, along with Leon Ginzburg and Gordon Oppenheimer, accepted the role of honorary chairman of the National Foundation for Ileitis, Crohn's and Colitis (NFIC) of America (now known as the CCFA) (see chapter 32).

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5

Asher Winkelstein (1893–1972)

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Asher Winkelstein (1893–1972)

ASHER WINKELSTEIN (Fig.) was born in Syracuse into a music-loving, prosperous, middle class business family and spent his medical career at The Mount Sinai Hospital in a transitional period (1920–1950) just before the renaissance of modern gastroenterology. Educated at Syracuse University and the college of the medical school there, he served a two-year rotating internship at Mount Sinai and spent a year in a clinical laboratory, essentially a clinical pathology laboratory, under the volunteer direction of Dr. Emmanuel Libman. Dr. Winkelstein went into private practice after a preparatory period of $3\frac{1}{2}$ years.

I first met him in 1939, when I arrived at Mount Sinai for my internship, and got to know him more closely after returning to Mount Sinai after World War II in 1950. Dr. Winkelstein's scientific training may have been fragmentary, but his curiosity was endless and he was intelligent, active and gifted. These qualities enabled him to make numerous significant clinical observations in gastroenterology. I never found out what directed him to gastroenterology, but I am sure two outstanding chiefs of surgery, Ralph Colp and John Garlock, who were interested in surgery for the treatment of peptic ulcer and diseases of the esophagus respectively, were major influences in his choice of a nonsurgical gastroenterology course.

It is necessary to realize the low status of gastroenterology in those years and understand that it took a considerable amount of courage to enter the field. The chief of medicine during my years at Columbia University's College of Physician and Surgeons (1935–1939) made clear his disdain for the field. Furthermore, from its founding, The Mount Sinai Hospital had never had an independent GI service, only a GI clinic, until the establishment of the current division in 1958 by Dr. Alexander B. Gutman, the first full-time head of medicine. Such distinguished clinicians and gastroenterologists as Burrill B. Crohn and Asher Winkelstein never made active medical ward rounds in the hospital, but served as chiefs of the

Fig. Dr. Asher Winkelstein.

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Key Words: Asher Winkelstein.

GI clinic. Winkelstein, succeeding Crohn, was my own clinical chief during the years 1950 – 1958.

In his oral history, recorded by Dr. Albert Lyons, archivist of the hospital, in October 1965, following his retirement in 1958, Asher Winkelstein rated his most important findings in this order. The first was the invention of the milk drip therapy for ulcer and peptic esophagitis (chapter 14). The second was the description of peptic esophagitis, reported in 1934 at the Cleveland Meeting of the AMA in a paper entitled "Peptic Esophagitis: A New Clinical Evidence" (chapter 8). The third was his role, along with the young, soon-to-die Eugene Klein, in persuading Dr. Ralph Colp to perform anterior vagotomy along with gastroenterostomy for peptic ulcer disease (this occurred long before Dragdstedt had published his paper on bilateral vagotomy [chapter 10]). Finally, his studies of nocturnal acid secretion in peptic ulcer disease were a considerable advance (chapter 9). I would rate the description of peptic esophagitis as the most important of this group and outstanding in itself.

Dr. Winkelstein died in 1972. I am certain that, had he been alive today, Asher would have easily accepted the Helicobacter pylori theory of gastric and duodenal ulcer and gastritis. He greeted with enthusiasm the new advances that were just being made. He suffered from not having a laboratory under his control, and he proposed more experiments in an afternoon than a team of workers could accomplish in a lifetime, but he was never discouraged for long. Music was a great solace to him; Asher had been a talented amateur violinist and supported himself during college as head of a musical group.

According to his son, Asher felt his professional career had been a successful and a happy one, climaxed by his appointment as clinical professor of medicine and gastroenterology when the new medical school was founded at Mount Sinai. He was survived by his wife, Celia, for six years until she died at the age of 75, and also by his children, Charles, a Mount Sinai professor of psychiatry, and his daughter, Clara, an academic professor of education teaching at Roosevelt College in Chicago.

6

Franklin Hollander (1899–1966)

JEREMY HUGH BARON, D.M., F.R.C.P., F.R.C.S., F.R.C.P.G.,
AND HENRY D. JANOWITZ, M.D.

FRANKLIN HOLLANDER (Fig.) was born in New York on January 19, 1899 and educated there (1–3). While studying for his B.S. in mathematics and chemistry at Columbia (1919), he worked as an assistant and instructor in chemistry (1917–1923); he received his Ph.D. in physical organic chemistry in 1924 after a year as a research chemist in the petroleum industry. After spending a further year as a consultant in chemistry, he began a 40-year career in physiology and physiological chemistry. Hollander became a medical fellow of the National Research Council with Lafayette Mendel at Yale from 1925–1927, studying gastric secretion. He then did a five-year stint as assistant professor in physiology at New York Medical College, taking his pouch dogs every summer to the biology laboratory of Cold Spring Harbor, Long Island.

From 1934–1936, Hollander was research associate and secretary of the Columbia University Dental Caries Research Group. With his mathematical skills and the statisticians of the Metropolitan Life Insurance Company, he studied the incidence of dental caries in a control population of more than 12,000 persons and in a group presenting for dental treatment. He found that the total number of decayed tooth surfaces per person was a more sensitive index of the extent of dental disease than the number of decayed teeth per person (4).

Hollander's final 30 years were spent at Mount Sinai, as chief of the gastrointestinal physiology research laboratory. During these years, he had many outside scientific commitments, as lecturer (later assistant clinical professor) at Columbia and as research adviser on chemical warfare (1943–1944), working on the therapeutic use of aerosols in gas casualties.

Fig. Dr. Franklin Hollander.

From 1954–1959, he was consultant in gastric physiology to the cancer center division of the New York City Department of Health, and from 1960, a member of the NIH Research Grants general medicine study section. He was associate editor of the *American Journal of Digestive Diseases and Nutrition* from 1940–1943, when

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Key Words: Franklin Hollander.

he took a similar position with the new journal, *Gastroenterology,* becoming its abstract editor in 1953. From 1961, he was on the editorial board of the *Journal of Applied Physiology* and the *American Journal of Physiology*, and from 1963, the section editor for the latter for gastrointestinal physiology.

Hollander saw his role at The Mount Sinai Hospital as many faceted (5), but his first priority was research into physiological problems of immediate clinical importance in the hospital. His laboratory, in conjunction with the clinical staff, helped evaluate the efficacy of the intragastric drip for peptic ulcer, a new statistical procedure for assessing the results of ulcer surgery, a new bioassay for male sex hormone in urine, a study on the effect of artificial fever on gastric secretion, his insulin test for vagus nerve continuity, and a synthetic diet for jejunal feeding. His second aim was to pursue basic long-range physiological problems, in light of John Dewey's maxim that "it does not pay to tether one's thoughts to the post of usefulness with too short a rope." With this purpose in mind, Hollander studied the mechanism by which hydrochloric acid is produced in the stomach, and the role of mucus in gastritis, peptic ulcer, stomach cancer, and human sterility. His third role was in postgraduate education, teaching classes in normal and pathological physiology, and in statistical methods, as well as taking part in the various conferences, grand rounds and seminars. Fourthly, he gave both general and specific advice to other departments in the construction of their own formal research projects.

Despite his many activities, Hollander always considered his role as director of the gastrointestinal physiology laboratory as his principal one. Recruited by Drs. Ralph Colp and John Garlock, each director of a surgical service, Hollander arrived at Mount Sinai at a time when gastroenterology was a branch of surgery. Thus, he was a Ph.D. in a sea of M.D.s. By his influence, gastroenterology at The Mount Sinai Hospital took its place as a scientific discipline. Although unable to deal with patients in the hospital directly, he soon attracted a group of young, eager and talented physicians and surgeons with whom he carried on a fruitful collaboration and in whom he took pride. These included Albert Cornell, Asher Winklestein, Vernon Weinstein, Henry Janowitz, David Dreiling, and Lawrence Werther.

Of his own achievements, it is clear from his writings and private comments that he valued most his description of the composition of the two components of gastric juice (the parietal and the nonparietal; see chapter 9), and the two components of the gastric mucosal barrier (see chapter 11).

Hollander was a strict and firm mentor who demanded clear hypotheses and supporting statistics before allowing a new research project to go forward. His wit was a dry one, but his personal support was generous. For thirty or more years, his tact in managing the conflicting demands of administrators, physicians, surgeons, and would-be scientists allowed him to maintain the integrity of his research laboratory, which could not continue without him after his untimely death from cancer of the pancreas.

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7

Gastroenterology and Hepatology

The Diagnostic Data

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Abstract

The Annual Reports of the Mount Sinai Hospital from the 1850s, and the *Mount Sinai Hospital Reports* for 1897–1906, make it possible to trace the discharges of gastroenterological inpatients, and (for a few years) of outpatients. Fully computerized diagnostic data have only been available since 1986. In the 19th century, about 20% of the outpatients had digestive disorders, the commonest of which were gastralgia/gastritis/dyspepsia, gastroenteritis, oropharyngeal complaints and constipation. A similar proportion of inpatients had digestive diagnoses, but the four disorders listed above decreased markedly in the second half of the 19th century, so that by the turn of the century the commonest diseases were typhlitis (appendicitis), hemorrhoids and other anal problems. By the 1990s, digestive diseases accounted for only 5% of total admissions, hepatobiliary diagnoses being the commonest group. Some cancers such as gastric and esophageal showed little change, while colorectal increased markedly. Some newly recognized diseases, such as peptic ulcer, waxed and then waned, while colitis and regional enteritis came and have continued to increase. Other new diagnoses, such as autointoxication and visceroptosis, flashed into prominence and then disappeared totally, presumably because they were nondiseases. **Key Words:** Gastroenterology, hepatology, diagnostic data.

THIS CHAPTER DISCUSSES the numbers and diagnoses of patients with digestive and liver diseases in The Mount Sinai Hospital from its founding. In this hospital, as in other medical centers, patients were treated by internists and general surgeons until the subspecialties were recognized. For example, the first patient to be admitted to Mount Sinai, on June 5, 1855, was operated for (and cured of) fistula-in-ano (1, 2), and the first paper in Volume 1 of the bound *Miscellaneous Writings by the Attending Staff of Mount Sinai* is on gastrotomy for esophageal stricture (3).

Many of the great hospitals in the 19th century published detailed annual reports. Fortunately, it is possible to extract from most of the *Annual Reports of Mount Sinai Hospital* from 1855 complete lists of the diseases of inpatients and in some years also of outpatients. These lists were at first in Latin, but English terms soon appeared, and all the diseases were in English by the 1870s. Fatalities were usually noted and there were separate listings for surgery, and for children from 1877. Surgery was divided into 1st and 2nd divisions in 1900, as was medicine, in 1906. The short-lived *Mount Sinai Hospital Reports* (1897–1906) give remarkably full details of the gastrointestinal conditions of the inpatients of the medical, pediatric and surgical services during these ten years, classified by sex and outcome (cured, improved, unimproved, died). Such detailed data did not become available again until 1986, when the records were fully computerized by diagnosis.

The data extracted from the reports from 1855–1995 have been collated to provide total admissions and deaths at Mount Sinai, together with the total number of hepatogastroenterological diagnoses and fatalities irrespective of department, and the proportion of total admissions in these years, so that trends in incidence and fatality of the various diseases over the 140 years can become apparent. For simplicity, the data from both sexes have been combined.

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Clearly, there have been problems in disassembling the original data and then reassembling the figures into useful tables. Patients were often transferred between departments in one admission and may have been counted twice. Some patients may have had more than one diagnosis, so the sum of diagnoses may be greater than the number of admissions. Moreover, the changing pattern of diseases and the changing nomenclature required certain clarifying decisions.

In the 19th century, alcoholism and oropharyngeal diseases were classified as digestive diseases and have therefore been included in all tables. Alcoholism includes delirium tremens, inebriation and intoxication. Diseases of the oropharynx include dental caries, odontalgia and periodontal disease; mouth abscesses, gingivitis, palatal ulcers, pyorrhea, stomatitis; croup, pharyngitis and tonsillitis/amygdalitis (acute, follicular, hypertrophic, suppurative). Gastric and gastroduodenal catarrh, dyspepsia, gastrorrhagia and indigestion are included in gastralgia, which is a neutral word I have chosen to indicate any upper abdominal discomfort, now often called non-ulcer dyspepsia. In 1902, Brill (4) concluded that "an attack of gastralgia terminates with the eructations of gas and the pain is usually relieved by pressure in the epigastrium. [However,] there can be little doubt that many of the so-called cases of gastralgia or stomach cramp are really attacks of gall-stone colic." Lilienthal, in 1911, found that 55% of 82 of his private patients with gall bladder disease, and an even higher proportion of the 100 ward cases a year at Mount Sinai, had been previously diagnosed as having stomach trouble (5). Gastritis has been classified as in the original reports, but in the absence of endoscopy, histology and radiology, all these patients should be considered as having gastralgia, although some must have had peptic ulcers. The diagnosis "stomach (functional)" includes gastric neurosis, neurasthenia, hysteria, and hyperchlorhydria nervosa. Infective hepatitis includes catarrhal jaundice. Constipation includes fecal impaction and obstipation. Enteralgia was defined in 1879 by Wardell (6) as a painful affection of the intestines of neuralgic character, generally accompanied with constipation and flatus. Enteritis includes diarrhea, enterocolitis, dysentery, gastroenteritis and (gastro)intestinal catarrh. Abdominal pain, colic, enteralgia, functional pain, gas, mucous and neurasthenic colitis are included in "irritable gut," a neutral phrase chosen to indicate any lower abdominal discomfort, with or without bowel disturbances. Included in this diagnosis is the ancient term "intestinal colic," defined by Begbie in 1879 (7) as "severe pain in the abdomen (in a restricted view, in the colon), occurring in paroxysms, not stationary, but on the contrary moving from place to place, accompanied by a sense of constriction and tearing, for the most part also by that of expulsion." In 1902, Brill categorized this colic: ". . . the pain is usually centered about the umbilicus, is not as agonizing as in gall-stone colic and is relieved by the passage of flatus and by firm pressure" (4). Ulcerative (entero)colitis includes acute, catarrhal, chronic, croupous, membranous, necrotic, subacute and ulcerative colitis. Appendicitis includes cecitis, typhlitis and perityphlitis. The term "autointoxication" was used at Mount Sinai only between 1898 and 1906 and does not correspond to any modern diagnosis. In 1905, Brill (8) defined it as "an infectious disease of definite clinical aspects . . . having somewhat the picture of typhoid fever. . . ." and cited Cumston's 1898 paper, "Autotoxaemia" (9, 10). Although that paper refers to toxins produced by most organs in the body, including the stomach and intestine, with little or no resemblance to the Mount Sinai term, Koplik (11) embraced the concept of gastrointestinal autointoxication when he attributed transitory attacks of renal failure to episodes of alternating constipation and mucus diarrhea (mucous colitis) in which intestinal toxins are absorbed. Hemorrhoids and anal diseases have been included, but other purely surgical conditions have been excluded. Visceroptosis includes enteroptosis, gastroptosis, and hepatoptosis.

Clinical Data

Any history of a clinical speciality must first try to identify the patients' complaints and the doctors' diagnoses during a particular decade. Today there are national surveys of samples of whole populations, of visits to primary care physicians and clinics, and hospital admissions. The data presented here are of digestive disorders extracted from the *Annual Reports of The Mount Sinai Hospital*.

Deaths in New York

In 1852, there were 21,601 reported deaths in the city of New York (Manhattan), of which only 3137 were in hospitals or public institutions, and 5281 were deaths of infants under the age of one year. The city's population was then 558,412. The commonest cause of death, numbering 3397, was from some diarrheal illness, of which 1774 were certified either as diarrhea, dysentery or inflammation of the bowel, 1527 as cholera, and 96 as typhoid. The other conditions killing more than 500 were consumption (2487), convulsions (1680), stillbirths (1405), inflammation of the lungs (1062), marasmus (971), dropsy of the heart (882), typhus (662), apoplexy (653), scarlet fever (613), and croup (595).

Outpatients

For the general population served by the hospital, the least biased data are those of the outpatients seen in the Dispensary, where any sick person, however poor and irrespective of ethnic origin, would be seen and if necessary given medication. There are detailed diagnoses for two periods, the nine years of 1860 and 1864–1871, between which total attendance increased from 90 to 981 and gastroenterological attendance increased from 20 to 159. For the three years 1877–1879, total attendance averaged 10,159 annually, of which 2156 were gastroenterologic (Table 1).

Thus, the proportion of outpatients with gastroenterological problems increased by one-third from 15% to 20%, between the 1860s and 1870s. Their ten commonest complaints, expressed as proportions of total attendances or of gastroenterological diagnoses, are shown in Table 2.

The commonest GI complaint of outpatients in the 1860s as in the 1990s was upper abdominal pain (40%), which was only slightly less common (31%) in the late 1870s. Enterohepatological infections, probably mostly bacterial but some certainly due to worms or viral hepatitis, increased from 28% to 41% in this period, probably from overcrowding with poor sanitation, contaminated water and food. Constipation and hemorrhoids were together about as frequent as oropharyngeal disease (13%), mostly pharyngitis and tonsillitis (probably bacterial); all are rarer today with less overcrowding and the availability of antibiotics. In the 1990s, one of the commonest diagnoses by a gastroenterologist is some form of irritable gut, which was probably underdiagnosed in the 1860s (5%) and 1870s (2%).

TABLE 1
Outpatients. 1860-1871, 1877-1879.

Year	1860	1864	1865	1866	1867	1868	1869	1870	1871	Annual Mean 1860-1871	1877	1878	1879	Annual Mean 1877-1879
Total	90	310	437	459	619	743	906	1064	981	623	10,996	9,858	10,727	10,519
GI	20	54	71	67	113	88	122	170	160	96	2,308	2,227	1,923	2,156
GI%	22	17	16	15	18	12	13	16	16		21	23	18	20
Alcohol			2					2		–	4	19	8	
Oropharynx	5	7	2	0	13	11	20	35	19	12	380	203	245	275
Esophagus — misc.											3	3	2	
(Gastro)enteritis		12	22	20	26	27	31	29	50	24	795	778	541	705
Internal Obstruction											3	8		4
Peritonitis				2		1	2	1		1				
Peritoneal Malignancy								1		–				
Liver Abscess													2	1
Cirrhosis											22	22	44	29
Enlarged		2						1		–		1		–
Misc.		1								–		2	1	1
Catarrhal Jaundice		2	2	2	1		1	1	6	2	39	32	28	33
Gallstones												2		1
Parasites — Ascaris	1									–	181	112	70	121
Taenia		1		1		2			1	1	17	16	39	24
Stomach Cancer											3	5		3
Gastralgia	8	19	31	34	49	22	39	80	62	38	672	729	570	657
Gastric Ulcer											6	14	21	14
Colon Carcinoma							1	1	2	–				
Constipation	5	7	9	6	11	11	6	5		7	34	175	191	133
Colitis											17	34	5	19
Irritable Gut					8	8	8	7	10	5	6	40	70	39
Typhlitis	1			1			3			1	2	3	3	3
Hemorrhoids		2	3		5	6	9	5	9	4	101	32	34	56
Anal		1		1			2	2	1	1	23	19	37	26

TABLE 2

Outpatients (OPD). Ten Most Common Diagnostic Groups.

	1860, 1864-71		1877-1879	
	% total OPD	% GI OPD	% total OPD	% GI OPD
1. Gastralgia	6.1	40	6.2	31
2. Gastroenteritis	3.8	25	6.7	33
3. Oropharynx	1.9	13	2.6	13
4. Constipation	1.1	7	1.3	6
5. Irritable Gut	0.7	5	0.4	2
6. Hemorrhoids	0.7	5	0.5	3
7. Infective Hepatitis	0.2	2	0.3	2
8. Worms	0.1	<1	1.4	7
9. Cirrhosis	0	0	0.3	1
10. Anal	0	0	0.2	1
HGI infections 2 + 7 + 8	4.2%	28%	8.3%	41%

TABLE 3

Annual Admissions and Deaths (in Parentheses) for Total Cases and for Digestive Diseases.

Decade	1855-1865	1866-1876	1877-1886	1887-1896	1897-1906	1986-1995	1996*
Total Admissions/year	397 (35)	825 (55)	1709 (141)	2635 (236)	3541 (396)	41,841 (1246)	47,929 (1264)
Fatality %	9%	7%	8%	9%	11%	3%	3%
1. Alcohol excess	3	3 (1)	2	1	0	14	1092 (31)
2. Oropharynx	7	13	28 (1)	15	1	3	246 (13)
3. Esophagus Cancer		<1	1	1	8 (3)	8 (2)	54 (8)
4. Esophagus — misc.†		1	1	1	5	130 (4)	1443 (114)
5. Gastric Cancer	<1	1	3 (2)	6 (2)	23 (8)	13 (3)	178 (20)
6. Gastric — misc.†	25	28	50	85	44 (2)	89 (1)	797 (40)
7. Gastric / Peptic Ulcer†		<1	4	3	10 (1)	73 (3)	490 (22)
8. Duodenal / Jejunal Ulcer†					1	72 (4)	254 (27)
9. Hematemesis — ?site		<1	<1			120 (10)	446 (70)
10. Pancreas Cancer			<1		2 (1)	20 (5)	479 (34)
11. Pancreas — misc.†					3 (1)	87 (3)	420 (29)
12. Liver Cancer 1°		1	3 (2)	3 (2)	7 (4)	18 (6)	292 (33)
2°						16 (8)	753 (76)
13. Liver — Cirrhosis†		1	4	5 (1)	8 (2)	155 (28)	878 (211)
14. Liver — misc.†	2	6 (1)	10 (1)	12 (4)	16 (7)	159 (28)	1823 (328)
15. Biliary†		<1	3	8 (1)	59 (10)	107 (4)	1278 (51)
16. Gastroenteritis†	11 (1)	17 (1)	52 (7)	29 (6)	33 (8)	29	1537 (99)
17. Enteritis, e-colitis†						220	544 (6)
18. Int. Obstruction		<1	<1	4 (2)	11 (6)	65 (2)	1081 (60)
19. Worms		<1		1	1	1	4
20. Peritonitis†	2 (1)	3 (2)	8 (5)	10 (4)	7 (3)	15 (2)	291 (20)
21. Colorectal Cancer		1	4 (1)	6 (2)	14 (6)	50 (4)	509 (19)
22. Irritable Gut	<1	1	1	3	5	8	144
23. Colitis		1	2	17 (2)	17 (2)	193 (1)	320 (3)
24. Constipation	<1	1	4	21	17	13	239 (9)
25. Hemorrhoids	2	7	17	81	55	7	105 (3)
26. Anal	2	4	22	63	73 (1)	25	226 (4)
27. Appendicitis	<1	2	5 (1)	42 (9)	221 (27)	8	234
28. Diverticulitis						140 (4)	428 (11)
29. Visceroptosis					2		
30. Autointoxication					19		
31. Abdomen — misc.						6 (2)	
32. Colon — misc.†						28	370 (17)
Total GI admissions	55 (2)	95 (5)	226 (20)	418 (35)	676 (92)	1902 (124)	16, 955 (1358)
GI Deaths %	4%	5%	9%	8%	14%	6%	
GI Adm. as % Total	14%	12%	3%	16%	19%	5%	
Fatality Ratio	0.4	0.7	1.1	0.9	1.3	2.3	

The number of deaths is shown in parentheses.

* The 1996 GI figures are for diagnoses, not for individual patients.

† Diagnoses so marked are further analyzed in the following Notes.

TABLE 3

Notes for GI Diagnoses 1996.

4. Esophagus — misc., 1443 (114),
diaphragmatic hernia 297 (6), esophagitis 97 (9), reflux 408 (15), stricture 61 (7), ulcer 64 (9); achalasia 27, diverticulum 20 (1), dyskinesia 26 (1), dysphagia 230 (20), foreign body 6, hemorrhage 15 (4), perforation 3, varices 193 (41); other 16 (1).

6. Gastric — misc., 797 (40),
angiodysplasia, 27 (1), anorexia nervosa 3, bulimia 6, eating disorder 3, benign tumor 17 (1), dilation 4 (1), functional 33; Gastritis 60 (8), acute 35 (2), alcoholic 8, atrophic 60 (3), gastroduodenitis 148(3), + hemorrhage 124(8). Mallory-Weiss 39 (9), nausea/vomiting 174, pyloric spasm/stenosis 56 (4).

7. Gastric/Peptic Ulcer, 490 (22),
gastric ulcer 67 (4), + hemorrhage 101 (7), + obstruction 3 (1), + perforation 4 (1); peptic ulcer 300 (6), + hemorrhage 14(3), + perforation 1.

8. Duodenal /Jejunal Ulcer and other Duodenal Diseases, 254 (27),
duodenal ulcer 68 (4), + hemorrhage 104 (15), + obstruction 2, + perforation 7; jejunal/marginal ulcer 12 (1). There were additional patients with duodenitis 45 (3), and other 16 (4).

11. Pancreas — misc., 420 (29),
pancreatitis acute 193 (18), chronic 76 (2); cysts/pseudocysts 18 (2), other 133 (7).

13. Liver — Cirrhosis — 878 (211),
cirrhosis 563 (89) - alcoholic 273 (121), - biliary 42 (1).

14. Liver — misc., 1823 (328),
abscess 14 (4), alcoholic 61 (8), Budd-Chiari 14 (3), chronic (unspecified) 112 (21), chronic persistent hepatitis 55, coma 230 (94), echinococcus 5 (1), hepatomegaly 5, hepatorenal 60 (43), jaundice 15, necrosis 103 (36), portal hypertension 102 (15), portal vein thrombosis 60 (12), viral hepatitis 805 (79), other 183 (12).

15. Biliary, 1278 (51),
carcinoma 15 (2), cholecystitis 582 (6), cholelithiasis 278 (5), cholangitis 110 (11), cholangiocarcinoma 62 (7), obstruction biliary ducts 125 (12), other 106 (8).

16. Gastroenteritis and other Small Intestine, 1537 (99),
gastroenteritis 384 (6), gastroenteritis bacterial 475 (32), - radiation 15 (1), - toxic 7; benign tumor 14 (1), blind loop 3, celiac 7, functional diarrhea 162 (6); ischemia 106 (27), malabsorption 98 (4), malignant 26 (1), perforation/fistula 116 (16), ulceration 15, other 209 (5).

17. Enteritis, enterocolitis, 544 (6),
regional enteritis 135 (2), small intestine 198 (3), small and large intestine 116 (1), large intestine 95.

20. Peritonitis, 291 (20),
peritonitis 280 (19), peritoneal malignancy 11 (1).

32. Colon — misc., 370 (17),
angiodysplasia 81 (3), benign tumor 137 (4), foreign body 5, hemorrhage 111 (10), megacolon 7, other 29.

Inpatients

In the last century and a half, annual admissions to The Mount Sinai Hospital each year have increased from 113 in 1855 to 47,929 in 1996. The diagnostic data go back only to 1860. Over this period the proportion of gastroenterological admissions decreased steadily from 14% of total admissions to 6% in 1995. However, the severity of gastroenterological cases, as assessed by their fatality, increased from 5% (compared with total mortality of 8%) in 1860 to 6% in the most recent decade (compared with the current all-case mortality of 3%).

The commonest admitting diagnoses in the early decades of Mount Sinai were similar to those in outpatients: gastralgia, (gastro-)enteritis and oropharyngeal diseases (Tables 3 and 4). In the later decades of the 19th century, these were overtaken by the proctological components of perianal disease, hemorrhoids and constipation. (Peri)typhlitis (later to be called appendicitis) increased from 1 patient in 1860, 7 in 1870, 9 in 1880, 15 in 1890, 217 in 1900 and 458 in 1906, falling to only 9 in 1995. Oropharyngeal disease declined rapidly, with only one admission in 1906 and two in 1995.

No patient was diagnosed as having gall bladder disease at Mount Sinai until 1875, but by the 20th century such patients were one tenth of all hepatogastroenterological admissions. Gastric carcinoma was and remains uncommon. In the mid-19th century, patients with colorectal carcinoma were admitted less than once a month, but have become more frequent and 4% of digestive admissions, partly from improved investigational techniques, and (probably) partly from a real increase in incidence. The frequence of colitis, as it became diagnosed separately from (gastro)enteritis-dysentery, increased in this century, so that patients with colitis now represent 10% of digestive admissions, second only to regional enteritis at 11% (see chapter 14). Other disease diagnoses such as autointoxication and visceroptosis suddenly appeared, rose to a peak within a decade, and then effectively disap-

TABLE 4

Commonest Hepatogastroenterological Diagnoses, 1855-1996, of Inpatients by Decade and as Percentage of All GI Diagnoses.

	1855-1866		1867-1876		1877-1886		1887-1896		1897-1906		1986-1995		1996*	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
GI Admissions %	553		932		2258		4179		6759		20,114		16,955	
Gastralgia/Gastritis	248	(45)	264	(28)	502	(22)	826	(20)	381	(6)	890	(4)	797	(5)
Gastroenteritis, Inf. Hepatitis, Worms	113	(20)	225	(24)	572	(25)	342	(8)	365	(5)	534	(3)	1690	(10)
Oropharynx	70	(13)	134	(14)	284	(13)	1477	(4)	99	(1)	29	(<1)	246	(1)
Anal / Hemorrhoids	40	(7)	113	(12)	403	(18)	1438	(34)	1278	(19)	315	(2)	331	(2)
Alcohol Excess	28	(5)	27	(3)	15	(<1)	9	(<1)	0	(0)	137	(<1)	1092	(6)
Peritonitis	18	(3)	26	(3)	77	(3)	96	(2)	71	(1)	154	(<1)	291	(2)
Constipation	5	(1)	7	(1)	46	(2)	205	(5)	173	(3)	132	(<1)	239	(1)
Typhlitis / Appendicitis	5	(1)	24	(3)	46	(2)	420	(10)	2211	(33)	76	(<1)	234	(1)
Gastric Carcinoma	3	(1)	8	(1)	33	(1)	56	(1)	233	(3)	258	(1)	178	(1)
Irritable Gut	3	(1)	19	(2)	10	(<1)	27	(<1)	45	(<1)	75	(<1)	144	(1)
Liver Cancer 1°	3	(1)	10	(1)	29	(1)	31	(<1)	67	(1)	183	(1)	292	(1)
2°					2	(<1)	4	(<1)			163	(1)	753	(4)
Liver Cirrhosis			11	(1)	40	(2)	46	(1)	71	(1)	1552	(8)	878	(5)
Liver — misc.			10	(1)	85	(4)	116	(3)	127	(2)	858	(4)	1823	(11)
Colitis			10	(1)	16	(<1)	168	(4)	172	(3)	1926	(10)	320	(3)
Colorectal Carcinoma			8	(1)	36	(2)	63	(2)	136	(2)	630	(3)	509	(3)
Esophageal — misc.			6	(1)	9	(<1)	4	(<1)	46	(<1)	1301	(6)	1443	(9)
Gastric Ulcer			3	(<1)	37	(2)	35	(<1)	96	(1)	733	(4)	490	(3)
Biliary			1	(<1)	28	(1)	80	(2)	589	(9)	1070	(3)	1278	(8)
Intestinal Obstruction			1	(<1)	2	(<1)	36	(<1)	112	(2)	651	(3)	1081	(6)
Esophageal Carcinoma			1	(<1)	7	(<1)	11	(<1)	76	(1)	84	(<1)	54	(<1)
Pancreas Carcinoma					2	(<1)	4	(<1)	15	(<1)	200	(1)	479	(3)
Duodenal Ulcer					1	(<1)	1	(<1)	11	(<1)	716	(4)	193	(1)
Autointoxication									190	(3)	0	(0)		
Pancreatitis									26	(<1)	856	(4)	287	(2)
Visceroptosis									16	(<1)	1	(-)		
Regional Enteritis											2202	(11)	544	(3)
Diverticulitis											1398	(7)	424	(3)
Hemorrhage - upper											1346	(7)	446	(3)
Hemorrhage - lower											130	(<1)	111	(<1)

* The 1996 data are for diagnoses in that year.

peared. No doubt, a historian of the 21st century reviewing Mount Sinai gastroenterology will consider similarly obsolete some of our current diagnostic labels, such as gastro-esophageal reflux disease, non-ulcer dyspepsia, biliary dyskinesia, irritable bowel syndrome and inflammatory bowel diseases.

The 1996 digestive data are presented in Tables 3 and 4 by diagnoses, and not as in 1855 to 1995 by individual patient, who may today have a dozen different diagnoses. Of the 16,955 hepatogastroenterologically coded diagnoses, 34% were hepatobiliary. The commonest gastroenterological diagnoses included 8% for esophageal miscellaneous (mostly gastroesophageal reflux disorders); 5% for inflammatory bowel; 3% each for gastric ulcer, gastric miscellaneous (mostly gastritis and gastroduodenitis), colorectal and pancreatic carcinoma; and 3% each for diverticulitis and hematemesis from unspecified site. The number of upper gastrointestinal hemorrhages from specified or unspecified sites was 1072; that is, 6% of all hepatogastroenterological diagnoses.

The changes in absolute and relative frequencies of these diagnoses will be presented in the following chapters, which cover the individual disease groups.

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8

The Esophagus

ELLEN L. WOLF, M.D.

Abstract

Original investigations and descriptions of the radiographic findings and techniques of evaluation of the esophagus and esophagogastric junction were made at The Mount Sinai Hospital by Drs. Bernard S. Wolf and colleagues in the third quarter of the 20th century. These included basic descriptions of peptic ulceration of the esophagus, the gastric lined esophagus, definitions of hiatus hernia, terminology of the esophagogastric junction, use of the barium pill and correlations of cineradiology with manometry. **Key Words:** Esophagus, radiology, motility, esophagitis, hiatus hernia, esophagogastric junction.

DR. BERNARD S. WOLF, chief of Radiology at The Mount Sinai Hospital from 1949–1977, and his colleagues made original investigations and descriptions of the radiographic findings in many esophageal diseases. In the 1950s, advances in fluoroscopy and cineradiography techniques allowed more detailed study of the esophagus and its motility, and allowed correlative study with esophagoscopy and manometry.

An increase in clinical interest in diseases of the esophagus, particularly in benign inflammatory conditions associated with hiatus hernia, led them to refine and amplify special procedures, maneuvers and technical factors designed to demonstrate such lesions. The consistency of the barium used for the examination of the esophagus was altered. Recommendations were made for patient positioning and the projections for routine studies and those for demonstrating particular diseases (1). They used a radiolucent bolster during continuous drinking in the prone right anterior oblique (RAO) position, to demonstrate minimal herniation of the esophagus and maximal size of the hernia (1, 2).

Various methods for demonstrating reflux were in use. However, Wolf's group recommended a more physiologic evaluation, with the patient in a moderate supine Trendelenburg position (1). It was noted that a fair amount of air was swallowed along with the barium, and by continued drinking through the straw after completion of a cup of barium, additional swallowed air would lead to a "double contrast" effect. This was the basis for the primary double contrast study in use today (1).

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Peptic Esophagitis

In 1934, Winkelstein described to the annual meeting of the American Medical Association (AMA) a new clinical entity which he called peptic esophagitis (3). His five cases all had symptoms typical of the recently established disease of peptic ulcer of the esophagus, especially pain and dysphagia, but radiology showed only irregular narrowing, esophagoscopy only congestion and inflammation, and biopsies only acute and/or chronic inflammation; there were no ulcers. Three of the five had a previous duodenal ulcer, one a previous esophageal ulcer and one a subsequent incisural gastric ulcer. Acidities were high. All five responded to ulcer therapy and Winkelstein attributed the peptic esophagitis to erosion by gastric juice rising into the lower part of the esophagus. Similar cases were reported at the same time both in Europe and elsewhere in the U.S. The presence of a hiatus hernia was not emphasized in the 1930s, and it was only in the 1940s that Allison attributed the esophagitis to reflux with hiatus hernia.

The 1950s saw the first basic radiologic descriptions of peptic ulceration of the esophagus (4–8). In 1954, Winkelstein, Wolf, Som and Marshak recognized that the triad of duodenal ulcer, hiatus hernia and peptic esophagitis is of special clinical significance (5). In 1957, Winkelstein presented twenty cases: "Peptic esophagitis probably commences with a more or less continual transcardial reflux from the stomach of a highly acid peptic secretion. This reflux may result from the hypersecretion associated with the duodenal ulcer or from the unexplained decrease in the tone of the cardiac sphincter. Perhaps the characteristic nocturnal hypersecretion with the patient in the horizontal position leads to prolonged bathing of the lower esophagus by the highly acid gastric contents" (8). Complications included stenosis, massive hemorrhage and perforation. Although Winkelstein continued to distinguish his peptic esophagitis from reflux esophagitis, it is the latter term or the more inclusive "gastro-esophageal reflux disease" which now prevails.

The radiographic findings in peptic esophagitis and peptic ulceration in association with gastric lined esophagus (Barrett epithelium) were described in detail in subsequent papers (9, 10). It had been stated previously that esophagitis occurs in one-half to three-quarters of patients with sliding hiatus hernia and that radiologic findings are frequently absent. Wolf and his colleagues identified subtle abnormalities that would suggest the presence of mild esophagitis, such as mild functional disturbances with inefficient peristaltic stripping action, mild nondistensibility and subtle fold and mucosal abnormalities.

Hiatus Hernia and the Esophagogastric Junction

The radiographic anatomy of this region was studied extensively and defined by Wolf and colleagues (2, 11–21). These descriptions were supplemented by many illustrations which captured the dynamic changes observed fluoroscopically in this region (2, 11–21). The terminology of the esophagogastric junction had long been disputed and correlations with anatomical and surgical findings were unsatisfactory. They were able to correlate radiographic observations and manometric measurements, and classified the rings seen in the distal esophagus as A rings (contraction) and B rings (the B rings representing the esophagogastric [EG] or squamomucosal junction). They then defined and redefined the radiographic diagnosis of sliding hiatus hernia.

Conclusions reached by studying large numbers of patients helped to clarify confusing terminology and correlated radiographic findings with manometric and autopsy descriptions of the EG junction. By 1958, it was possible to make the following authoritative conclusions (12) (Fig. 1):

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 (22), 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 the distal half of the vestibule normally 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 sphincter activity in this area is less commonly seen than contraction of the vestibule as a whole. The description of 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

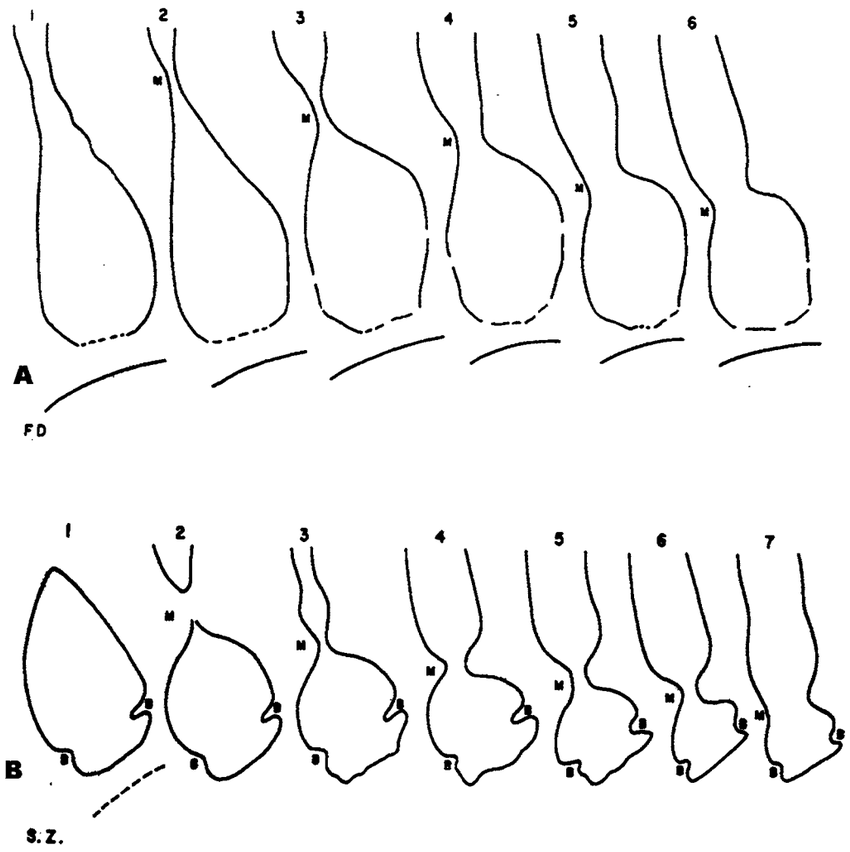

Fig. 1. The Gastroesophageal Vestibule. Reproduced with permission from *The Journal of The Mount Sinai Hospital* (12).

A. 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.

B. In this patient, 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 demonstrate 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.

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 corresponds 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.

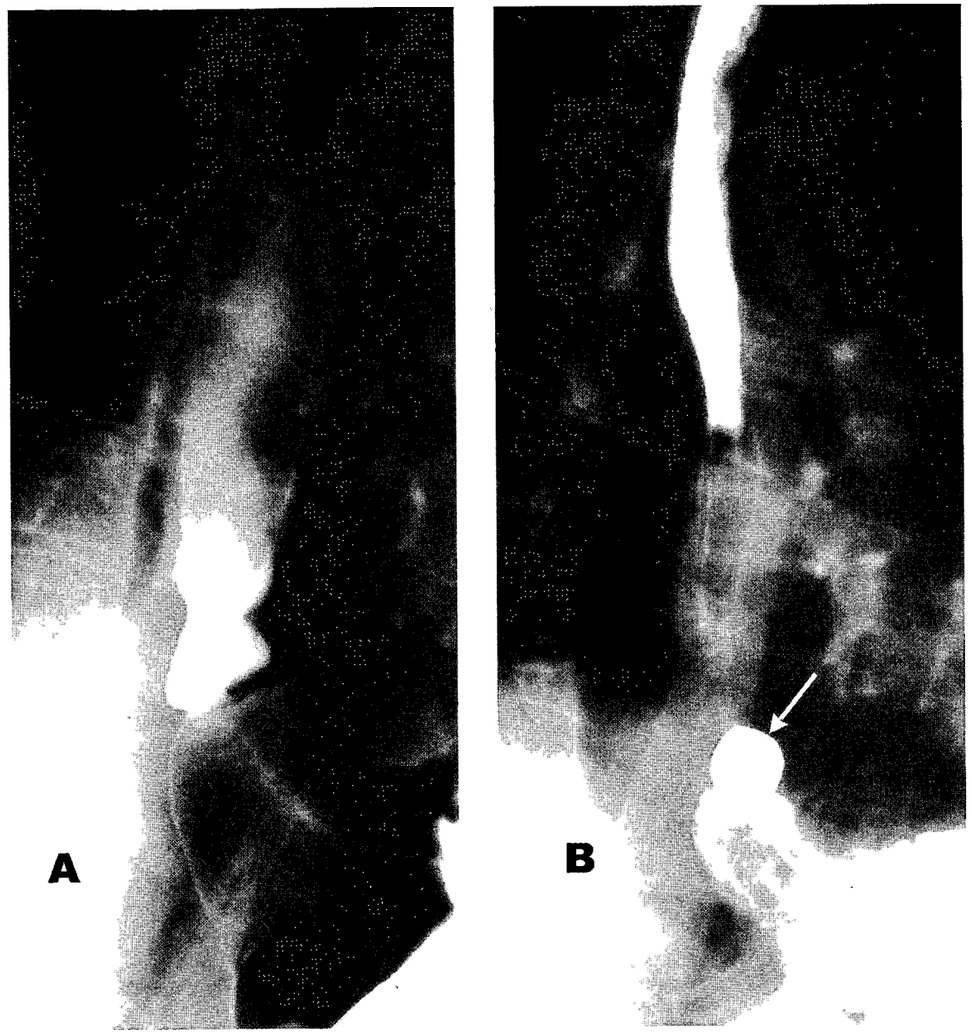

Fig. 2. Barium esophagram demonstrates (A) a hiatus hernia with A and B rings and (B) impaction of the barium pill (arrow) at the level of the ring. Symptoms could therefore be attributed to the ring.

The first report of a B ring treated endoscopically was made in 1960 by Som, Wolf and Marshak (23). The patient had a symptomatic B ring, measuring 1 cm in diameter as measured in comparison with an impacted 1.25 cm barium pill. A 1.6 cm (48F) esophagoscope was passed and through it an esophageal forceps with right angle punch distally. The ring was grasped between the cutting jaws of the punch and severed. The patient had successful relief of symptoms.

The Barium Pill

In 1956, Wolf reported the use of a half inch barium tablet to detect minimal esophageal stric-

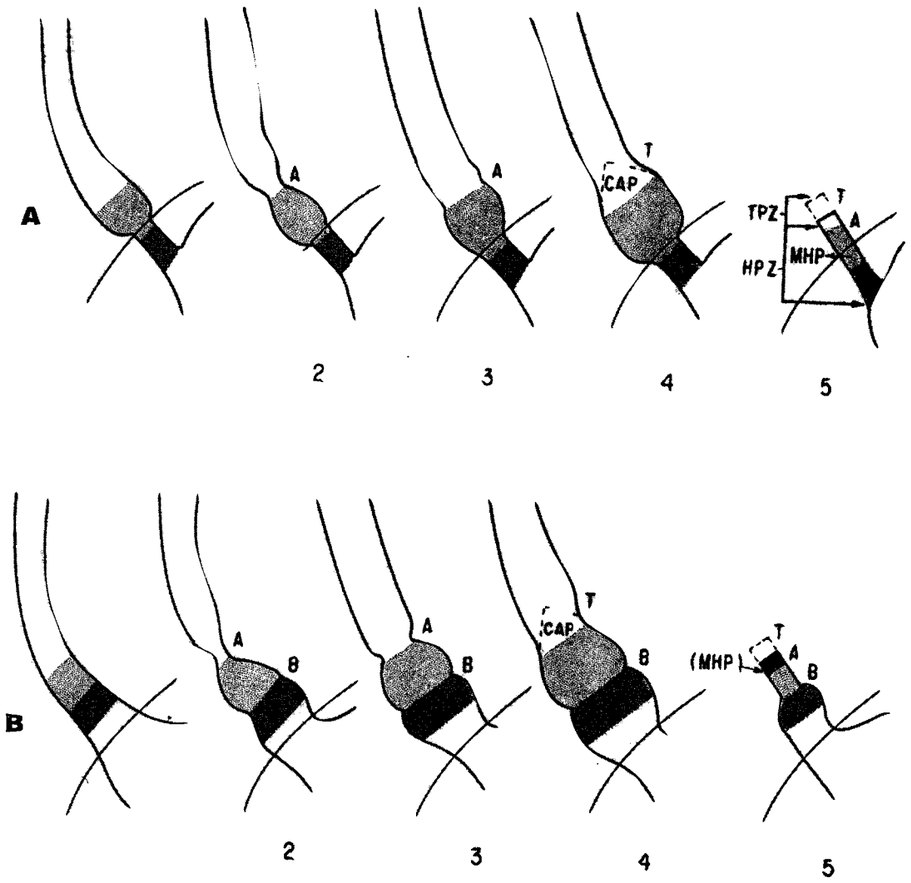

Fig. 3. The inferior esophageal sphincter. Reproduced with permission from the *American Journal of Roentgenology* (28).

A. Diagrammatic representation of vestibular and cardiac canal segments under normal circumstances in filled and empty phases. The vestibular segment is dotted and the cardiac canal cross-hatched. The proximal margin of the vestibule and the site of a potential functional ring is indicated by A. The cap in Panel 4 indicates the appearance in the transitional zone when the peristaltic wave reaches this area. Panel 5 represents the resting state. The transitional pressure zone (TPZ, unshaded) is shown as extending from the end of a tubular esophagus proper to the A level. The sharp distinctions in the resting phase diagram do not actually exist. The high pressure zone (HPZ) extends from the A level to the cardiac orifice. The peak or maximum pressure (MHP) of this zone is below the level of the hiatus.

B. Diagrammatic representation of the vestibule and "cardiac canal" in hiatal herniation. The A and B levels are indicated. The dotted region represents the vestibule and the cross-hatched regions the incompetent persistently dilated cardiac canal. The sling fibers which normally contract completely to form a short tubular segment now act as if they were part of the fundus of the stomach. Panel 5 shows diagrammatically the possibility that, in some cases, a discrete zone of resting, or maximum, high pressure zone may appear corresponding to an A ring. Pressure at this site may equal or exceed the maximum of the normal HPZ. The resting pressure in the vestibule itself may be somewhat higher than or equal to fundic pressure. In other cases, there is no region between fundus and tubular esophagus in which resting pressure exceeds fundic pressure, i.e., the cardiac canal and vestibule are incompetent and no compensatory A ring is present.

tures (24, 25). These tablets are often referred to as "Wolf pills." The assumption was that if a tablet of this diameter passes through the esophagus, dysphagia is not likely to be of an obstructive basis. The diameter of 1.25 cm was selected to correspond with the diameter of a 36F esophagoscope. The pill is of use in patients who complain of difficulty in swallowing but in whom no apparent or definite abnormalities are identified by conventional methods, and to confirm that findings such as rings or apparent strictures are indeed responsible for symptoms (Fig. 2). The pill is shaped so that obstruction is not increased even though the tablet may be prevented from passing. If obstruction is present and the pill is unable to pass through a stricture or a ring, it will disintegrate within 15–20 minutes. The pill is also helpful in identifying hypopharyngeal or cervical esophageal webs that may be overlooked in conventional studies. If a pill is impacted at that level, it is usually regurgitated after a short interval.

Motility Studies

Working in conjunction with the gastroenterologists, primarily Dr. Bernard R. Cohen, correlations with cineradiology and manometry of the pharynx, hypopharynx and esophagus were made (14, 16, 19, 26–28). More detailed and more physiologic understanding of the radiographic findings were possible using these techniques (Fig. 3). In 1960, intraesophageal pressure determinations were performed and correlated with the radiographic findings during the swallowing of barium using modifications of previously described techniques (14). The findings demonstrated that the junction of the phrenic ampulla and the narrow or "empty" segment in barium filling of the esophagus corresponds to the position of the hiatus and that the junctional segment therefore lies entirely within the abdomen. Refinements in the technique and additional observations were subsequently made, and a series of pressure inversion points were identified during the course of inspiration which corresponded to the posterior region of the physiologic hiatus (16). Manometric features were then correlated with the cineradiographic findings at the esophagogastric junction in patients with hiatal hernias and rings (18, 26–29). Clinical applications of esophageal motility studies and the radiologist's role in the evaluation of patients with heartburn evolved from these physiologic-roentgenographic studies (30, 31).

Conclusions

The radiographic techniques described above and the barium pill are still in wide use today, as are the definitions and terminology of the esophagogastric junction.

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9

Gastric Secretion

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Abstract

The European gastric test meal was widely used in The Mount Sinai Hospital in the 1890s and early 1900s, but was then abandoned diagnostically after the introduction of gastroscopy and radiology. The fundamental methodological advances of Franklin Hollander led to his quantitative formulation of the ionic concentrations of the gastric acid parietal and nonparietal components, followed by his insulin test for completeness of vagotomy. **Key Words:** Gastric secretion, acid, biochemistry, components, insulin test of completeness of vagotomy.

IN THE LAST 150 YEARS, measurements of gastric acid have developed from the test meal to measurements of basal, insulin-stimulated and maximal acid output.

Test Meals

Morris Manges (see chapter 3) brought to Mount Sinai the latest German concepts, equipment and tests in gastroenterology. He could not obtain an Ewald tube in the U.S. and had some made by the Davidson Rubber Company, 24 inches long, and in large sizes, 29, 31, 34 (French) gauge. He emphasized the precise details of intubation of the fasting patient for the Ewald Test Breakfast (a dry roll and a cup of hot water or tea) followed by evacuation of the gastric contents one hour later (1). Measurements were made by litmus paper, then titration with decinormal soda using Congo red and phenolphthalein as indicators for free and total acidity, with Uffelman's reagent for lactic acid (2). Manges saw little point in routinely testing for pepsin, rennet, ptyalin and other ferments (3).

On the basis of the hard data, Manges warned against routine use of test meals because "distinct pathological processes do not produce corresponding sharply defined changes in the chemistry of the stomach" (2). He considered the main value of the test meal to be in the differentiated diagnosis of gastric cancer when hydrochloric acid was absent and there was an excess of lactic acid (from fermentation in the stomach) (4).

Manges brought to Mount Sinai other new European diagnostic equipment. Einhorn's gastrodiaphane was a small incandescent lamp attached to the end of a stomach tube, allowing a red area to be seen normally on the abdomen giving some impression of the position and size of the stomach and colon (2). Bianchi and Bazzi's phonendoscope combined auscultation and percussion to ascertain the positions not only of the heart and lungs but also of the stomach, colon and even gall bladder (5).

Edward Aronson was assistant physiological chemist before being appointed as the first gastroenterologist at The Mount Sinai Hospital (see chapter 3). He came to Mount Sinai with considerable experience of the various test meals from Ewald's clinic in Berlin. One sophisticated test meal was the Sahli flour and butter meal, which allowed the fat to be used as a dilution indicator to calculate how much meal had been emptied into the intestine, how much remained in the stomach, and how much of the aspirated meal consisted of gastric secretion (6). A dilution indicator could therefore distinguish between hyperacidity and hypersecretion. However, the com-

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plexity of the test, the analyses and the calculations made the Sahli test impractical, and the Ewald-Boas meal remained in use at Mount Sinai until the 1950s. Another of Aronson's papers on gastric secretion (7) had an almost 18th century air, because it analyzed 81 samples of vomit, mostly post-anesthetic.

In about one in ten test meals, fragments of gastric mucosa large enough for histology were sucked into the tube. Boas had considered these specimens a means of distinguishing neurosis and a catarrhal condition (gastritis). Aronson found either congestion or gastritis in these fragments, but again the clinical utility was minimal (8). By 1912, Aronson was sharing Manges' disappointment with the diagnostic value of the test meal and was optimistic that the new techniques of gastroscopy and radiology would give better answers in due course (9).

Nevertheless, in 1915, 400 patients in the GI clinic still had a test meal each year, effectively "every patient in whom there is no contraindication to the passage of a stomach tube" (8). However, by 1916, Aronson was beginning to rely on the radiologic demonstration of a niche of barium or bismuth as pathognomic of an ulcer crater. Yet, "for the diagnosis of a simple gastric ulcer the . . . use of the stomach tube and stool examination gave much more information" (10).

Gastric Analysis

Measurements of Titratable Acidity

Prout (11) probably, and Jaworski and Gluzinski (12) certainly, used litmus as the indicator for their titrimetries. However, Ewald used either litmus or phenolphthalein as well as Congo Red paper to measure what was then called free acid. Once pH scales became available, it became possible to titrate to a specific end-point, but there was no agreement as to which single end-point, or whether to use two end-points, one for "free acidity" and one for "free alkalinity" ("total acidity").

The most comprehensive study of these methods of titrating gastric juice was made by Hollander in 1931 (13). Using a modified microburette allowing accuracy better than one percent (14), he found that while there was no difference in the acidities obtained by titration with phenol red (pH 6.8 – 8.4) and phenolphthalein (pH 8.3 – 10) for pure acid gastric juice from animal fundic pouches, this was not the case for human stomach contents which contained protein. In 1938, Hollander (15) showed that the mean difference in titratable acidity between the two indicators phenol red and phenolphthalein was 5 mmol/L (range 2 – 11), and concluded that "based on the theory of titration of buffer-containing solutions, there can be no doubt that an end-point of 7.0, precisely determined by comparison with a buffer standard, is more correct than an end-point of considerably higher pH value and determined by a gross color change." Hollander discussed electrometric titration, and "the simple and cheap commercial set-ups" which he lacked are now in routine use for his now universally accepted end-point of 7.0 or 7.4 as an alternative to colorimetric titration using phenol red.

Parietal and Nonparietal Components

A specimen of gastric aspirate is a mixture of the acid secreted by the parietal cells of the stomach, the alkaline juice secreted by the nonparietal cells, and contamination of these gastric components by regurgitation of intestinal, pancreatic and biliary secretions from below and by swallowed saliva from above. Both Heidenhain and Pavlov postulated an acid component of fixed ionic concentration. Hollander's two-component hypothesis (16) explained the varying composition of gastric juice by the assumption that two components of fixed ionic composition are secreted by the stomach in varying volumes, as opposed to the Teorell hypothesis of an exchange-diffusion of ions across the mucosa (17).

Hollander (16) postulated that "the parietal solution is essentially an isotonic solution of hydrochloric acid" and is admixed with an alkaline component of sodium chloride and bicarbonates (18), a buffer secretion of composition similar to blood plasma (19). Since then, there have been various formulas for calculating the acid parietal and alkaline nonparietal components, especially those of Fisher and Hunt (20), Hunt (21–23), Thompson and Vane (24), and Whitfield and Hobsley (25). After Hollander moved to Mount Sinai in 1936, he and his first research fellows, Penner and Saltzman, showed that the nonabsorbed phenol red (26, 27) was preferable to phenolphthalein as a dilution indicator in gastric analysis (28). Hollander had worked with Pavlov and Heidenhain pouch dogs from his time at Yale (29), and his unit now reassessed the evidence that the vagal innervation of the Pavlov pouch was intact: it was not (30), and they therefore designed a new stomach pouch without interruption of its vagal supply (31). They were then faced with the problem of differentiating those stomach pouches innervated by the vagus and those which had been denervated. They sought advice from seven experts, all of whom used the psychic and/or chemical stimuli of a meat meal, but found these tests unreliable (32). Hollander's group then devised a new stimulus, insulin hypoglycemia (32, 33), the future "Hollander Test." However, although the Heidenhain pouches were clearly denervated, the test did not distinguish "degrees of vagality" between the Hollander and Pavlov pouches.

Nevertheless, the Hollander test was used to assess the completion of vagotomy in six patients in Dr. Colp's service; all were incomplete with definite acid response to the insulin (34). The test then became "a standard routine procedure in [Mount Sinai] hospital for all cases in which a division or excision of the vagus nerves has been performed" (35), with a standardized protocol of 15 units of insulin injected intravenously after fasting gastric and blood glucose samples, followed by eight gastric samples collected at 15-minute intervals and three more blood samples during this two-hour period. Adequate hypoglycemia was defined as < 50 mg/100 mL but no precise levels of acidity were stated. Not all of the unoperated patients showed acidity rises, which were seen in all the unilateral vagotomy patients and in at least 10 of the 21 patients after bilateral vagotomy (35).

The subcommittee on vagotomy of the American Gastroenterological Association did a national survey concerning the gastric function tests used in connection with this operation. Hollander (36) recommended the overnight acid measurement and the insulin test, if performed, and the need to interpret the results by his criteria. Soon the "Hollander test" (an eponym disclaimed by Hollander [37]) was used universally, despite inconsistencies in technique and interpretation and the fact that there was no correlation between clinical results and postoperative insulin test data (38, 39).

Dose Response Relationships of Insulin Hypoglycemia and Gastric Acid

Hollander's group (32), in their original study, concluded that "it is impossible . . . to establish any quantitative relation between the magnitude of the insulin dosage or the hypoglycemia on the one hand, and the volume-rate of secretion or the acidity on the other." However, Jemerin, Hollander and Weinstein (33) claimed "a rough parallel between the degree of hypoglycemia and the magnitude of response that was obtained. . . ." This discrepancy may be related to Hollander's group having measured volume and acidity separately while omitting the calculation of their product, the acid output. When their data on dog 77 was recalculated (40), there was a significant inverse linear correlation of gastric acid output with the lowest blood sugar concentration, similar to the results in humans (41, 42), which established that insulin hypoglycemia provides a quantitative glycopenic stimulus producing quantitative vagal acid response (43). The criteria for an adequate insulin test in the unoperated subject were then established: "An insulin dose of about 0.2 U/kg may be optimum in producing sufficient hypoglycemia (blood glucose below 30 mg/100 mL; 1.7 mmol/L) to guarantee initiation of gastric secretion in an individual, to ensure a near maximal vagal acid output, but not to allow blood glucose to fall so low (< 15 mg/100 mL; 0.8 mmol/L) that hypoglycemic inhibition of gastric secretions or dangerous side-effects be produced" (43).

The insulin test became an essential tool for the assessment of the vagotomies (truncal, selective, proximal gastric/highly selective), which became for almost half a century the most frequently performed operation to reduce acid secretion. It was shown that in patients before (40–42) and/or after vagotomy (44–46), the same dose of insulin, 0.2 U/kg, was found optimal. In the last twenty years, potent acid inhibitors, and then eradication of *Helicobacter pylori*, replaced surgery in the elective treatment of peptic ulcer.

However, even when Hollander's qualitative acidity criteria were replaced by quantitative acid measurements, more than a dozen alone or in combination were recommended to refine the interpretation of the test (43). These absolute criteria were all based on a common fallacy, that an insulin test gave a positive or negative answer, and that vagal innervation is either present or absent. We no longer accept, as Dragstedt did (47), that insulin-stimulated gastric acid after vagotomy is an all-or-none phenomenon, with acid secretion unchanged if a single vagal fiber remains intact. We no longer assume that a surgeon cuts either all or none of the vagal fibers to the stomach. Nor do we accept Hollander's denials that an acidity increase is an indicator of the number of intact vagal fibers, i.e., "degrees of vagality" (33).

Instead we believe that "If peak acid output after insulin in the intact stomach represents the sum of the secretory output stimulated by the individual vagal fibres, then the reduction in insulin-stimulated peak acid output after a vagotomy is an index of the proportion of efferent

vagal fibers which have been divided" (43). The final methodological advance was to correct measurements of insulin-stimulated secretion for pyloric loss and duodenal reflux by Hobsley's formulas (48).

It is now accepted that Hollander was correct in believing that the insulin test should not be used in the individual patient to predict who will develop or has already developed recurrent ulceration after vagotomy, nor which patients with recurrent symptoms have indeed re-ulcerated. However, Hollander's insulin test, and its safer successor, sham-feed, chew and spit, often supplemented by measurements of basal and pentagastrin-stimulated acid, were once essential tools in the systematic assessment of the various vagotomies and of different vagotomists (49), and in the evaluation of residual innervation in patients with recurrent ulcer, in order to plan revision surgery (re-vagotomy and/or antrectomy) (49).

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Acid Secretion after Gastric Operations

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Abstract

In the early 20th century, the commonest surgical treatment of peptic ulcer was gastroenterostomy. Crohn and Wilensky demonstrated that this operation did not achieve its aim of markedly reducing gastric acidity or of accelerating motility. These results were highly controversial, but led to Lewisohn visiting Haberer in Austria in 1922, and convincing Dr. A.A. Berg to abandon gastroenterostomy and use partial gastrectomy as the standard ulcer operation, with additional vagotomy in those patients with duodenal ulcer with high acidity. In 1929, a few patients were treated by vagotomy and gastrojejunostomy by Dr. Ralph Colp, with discouraging results. It was only in the 1940s that Mount Sinai surgeons adopted transthoracic or subdiaphragmatic vagotomy and gastroenterostomy (or later, pyloroplasty) as their standard, effective acid-lowering treatment of peptic ulcers. **Key Words:** Gastric acid, gastroenterostomy, partial gastrectomy, vagotomy, pyloroplasty.

IN 1916, CROHN, REISS, AND WILENSKY began studies on gastric acidity after gastroenterostomy (1), using a heavy oatmeal gruel test breakfast (2) and motility by kymography (3). Neither test was novel, but the results of their studies on 37 patients, on whom Dr. Berg had performed a posterior retrocolic gastrojejunostomy, were new and important. The patients were divided into three groups. Group A consisted of 11 patients with few or trivial symptoms and Group B consisted of 14 patients who had developed new symptoms after their operation. Seven patients of the 12 in Group C had similar symptoms to Group B, but 2 had developed gastrojejunal ulcers and the other 5 had stomal constrictions. Wilensky and Crohn were careful, however, to point out that most of the patients were examined because of their symptoms and did not constitute a representative selection of patients after gastrojejunostomy. Their results suggested that this operation did not achieve its aim of markedly reducing gastric acidity or of accelerating motility.

Around the same time, Dr. William Mayo was making one of his regular visits to Mount Sinai; he was invited to the laboratory by Libman to listen to these results. This prompted an invitation to Crohn and Wilensky to present a paper at the American Gastroenterological Association (AGA) in Atlantic City in May 1916, where it was well received by a standing ovation, according to Crohn (4).

Standing ovation or not, the discussion was critical and occupies ten pages of the published transactions (5), although it is not appended to the later paper (which does however provide graphs and kymograms) (1). Some discussants (5) claimed that in their centers, 85–90% of their patients "have been injudiciously chosen for operation and various surgeons good and indifferent have performed them." Others advised pyloroplasty rather than gastroenterostomy. One speaker cited a non-American authority, Mathieu in Paris, where "very few, if any, of their cases of gastro-enterostomy, if followed over a sufficiently long time, failed to show some pathological symptoms, gastric or intestinal." Crohn's lengthy reply to his critics was so diplomatic that he was

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elected a member of the AGA in 1918 on the recommendation of Max Einhorn, Jacob Kaufman and Morris Manges (6). He became the first staff member of The Mount Sinai Hospital to serve as president of the AGA, from 1932 to 1933.

Despite the preaching by Manges and Aronson that the fractional test meal should not be used as a routine test, it was still so used (5). The use of such tests caused prolonged discussions on the postulated diagnosis of gastric hypersecretion (gastrochronorrhoea) (5), which in retrospect was clearly a non-diagnosis, since the test meal only provided qualitative measurements of gastric acidity. Quantitative measurements of juice volume, basal or stimulated, were yet to come (6).

Partial Gastrectomy

In 1922, Lewisohn returned from visiting Haberer in Innsbruck, Austria, with details of the new operation for peptic ulcer, namely partial gastrectomy, to replace gastroenterostomy for duodenal ulcer because of the unsatisfactory results seen in Europe after this drainage procedure (7). Lewisohn convinced Berg to change his practice, and Berg was soon able to perform hundreds of these new operations, because he operated mornings and afternoons six days a week, and sometimes on Sundays. Clinical efficacy was measured by meticulous follow-up involving Social Service. The physiological effects consisted of the anticipated abolition of postoperative free acidity in almost all cases, together with increased gastric emptying.

Thus, Lewisohn and Feldman (7) were able to persuade 88 patients to have a repeat Ewald test meal years after their gastric operations. They were the only patients to consent from the 191 surviving patients (out of a total of 213) who were operated on at Dr. Berg's service between 1915 and 1920. Simple gastroenterostomy (n = 13) changed acidity little and never abolished free acid; even with pyloric exclusion in addition (n = 50), only 2 patients lost their free acid. However, after partial or subtotal gastrectomy for gastric ulcer, free acid persisted in only 2 patients, and after gastrectomy for gastrojejunal or recurrent duodenal ulcer, each of 8 patients lost free acidity (7). Klein confirmed the different results with the various types of peptic ulcer (8). Every patient with a gastric ulcer lost free acid within 6 months of partial gastrectomy, compared with only one-quarter of patients with duodenal ulcer and one-half of those with gastrojejunal ulcers. These data were cited by Berg in his classic 1930 paper (9), which finally convinced the next generation of American surgeons that subtotal gastrectomy was the rational and effective operation of choice for peptic ulcers. An update in 1933 by Winkelstein (10) of 122 patients after partial gastrectomy showed absence of free acidity in 55% of patients who originally had a duodenal ulcer, but in 88% of those operated on for gastric ulcer.

Ulcer Recurrences at Mount Sinai and the Jewish Question

Critical reassessment of gastroenterostomy at The Mount Sinai Hospital, begun by Wilensky and Crohn in 1916 (5), and continued by Berg's group in the 1920s, met with considerable opposition by advocates of the then-standard operation, both at Mount Sinai (4, 11) and elsewhere (12, 13). Surgeons claimed that "their" patients did well after "their" operations: "I have been able to follow 60 cases from 12 years to 3½ months. . . . In 88.33%, the result was satisfactory" (12). From 1905–1922, the Mayo clinic performed 7000 operations, but saw only 37 patients with recurrent gastric or duodenal ulcer (13).

Thus, the bad results at Mount Sinai were blamed not on the operation but on the poor selection of cases and/or poor operative techniques. However, the most bizarre explanation was Woolsey's attribution of the high Mount Sinai recurrence rate to their high proportion of Jewish patients (12), citing Eusterman from the Mayo Clinic: "There is a third type of case in which there is a tendency toward recurrence, in some instances repeated, over a short period. The Hebrew and the person with a hyperirritable nervous system who smokes excessively are illustrative of this type" (13).

Lewisohn rejected these disparaging suggestions to explain the high Mount Sinai gastrojejunal ulcer rate of 34% (14). "The large percentage was explained by the accuracy of our follow-up system, which included very careful personal examination of the patients."

Lewisohn submitted this question to Haberer and received the following answer: "The statement that gastro-enterostomy is followed by worse results in Jewish than in other patients is absolutely incorrect. I have among my patients less than 2 per cent of Jews; among those there are a number of gastrojejunal ulcers. These patients are as healthy today, following a subtotal gastrectomy, as the Gentile patients. I have never noticed any difference as to operative results between Jewish and Gentile patients. Professor Raffaele Bastianelli of Rome told me recently that

he was under the impression that 25% of his gastro-enterostomy patients developed trouble, probably as a result of gastrojejunal or jejunal ulcers. He states that there are almost no Jews among his patients."

Vagotomy

Nevertheless, there were still patients with duodenal ulcer who developed jejunal ulceration even after partial gastrectomy, so that in 1938 Winkelstein and Berg (15) reconsidered the operative approach with their hypothesis that the problem lay with patients with high preoperative acidity. They found that patients with gastric ulcer or with duodenal ulcer with preoperative normal free acidity (20–40 mmol/L) had postoperative low or nil free acidity and negligible ulcer recurrences. Those with duodenal or juxtapyloric ulcers with high preoperative free acidity (> 60 mmol/L) were the group in which postoperative recurrent jejunal ulcers occurred, because of inadequate reduction of acidity. Recalculation of the data in their chart V shows that 13 patients who later developed jejunal ulcers had a reduction of free acidity from a mean and range of 76 (24–130) only to 61 (20–110) mmol/L after the partial gastrectomy.

The new Mount Sinai protocol (which Winkelstein [16] states was the idea of Dr. Eugene Klein) was to add subphrenic anterior vagotomy to partial gastrectomy in patients with duodenal ulcer with high free acidity (> 60 mmol/L) (15). After this operation, in a group of 31 patients, free acidity disappeared immediately in 16 and within months or years in another 10; all 26 remained well after 4–9 years' follow-up. However, there were 5 patients whose free acidity was not abolished by the new radical operation, but was reduced immediately from a mean (range) from 96 (74–135) to 25 (20–36) mmol/L, and within months or years to 23 (10–30) mmol/L; these 5 were without recurrences for up to 6 years (15).

According to Winkelstein, he had speculated in 1929 that if the addition of an anterior vagotomy to a partial gastrectomy further reduced acidity, then gastroenterostomy plus vagotomy should be tried for duodenal ulcer (16): "This operation was then carried out on the service of Drs. Berg and Lewisohn in two cases of rather severe duodenal ulcer with pyloric obstruction (one case operated by Dr. S. Hirshfield and the second by Dr. P. Klingenstein)." In case 1, free acidity was reduced from 70 to 10 mmol/L at 2 months after operation and at 3, 4, 5 and 7 years were 10, 0, 20 and 60 mmol/L, respectively. In case 2, acidity was reduced from 50 to 10 mmol/L at 3 months after the operation and after 3 and 4 years were 40 and 10 mmol/L, respectively. Both patients remained well. Three other patients were treated similarly, but no follow-up was reported (17).

These patients operated on in 1929 were probably the first patients with duodenal ulcer to be treated by vagotomy and gastrojejunostomy to reduce their gastric acidity, as distinct from reducing their pain by cutting vagal afferents. Two further patients were studied at Mount Sinai by Klingenstein on Dr. Colp's service. In one, in 1942 (case 6 of Weinstein et al. [18]), posterior gastroenterostomy and anterior vagotomy had little effect on alcohol- and insulin-stimulated acid. With the other patient, in 1939, there are discrepancies between the descriptions of case 5 of Weinstein et al. (18) and the case report of Cornell (19) as to whether the patients ever had duodenal ulcer. The latter patient was published (19) as "probably the first known case of attempted 'complete' subphrenic vagotomy for duodenal ulcer performed without any other operation." There were marked motor effects (no gastroenterostomy was added) but the acidities were little altered. Clearly, only partial vagotomy had been achieved.

Thus, deliberate partial vagotomy had been mostly unsuccessful in reducing gastric acidity; the one attempt at complete vagotomy had also been unsuccessful in lowering acid. Moreover, the Mount Sinai surgeons were reluctant to attempt the rational transthoracic or subdiaphragmatic vagotomy because of the added risk (18). After Dragstedt's epoch-making supradiaphragmatic bilateral vagotomy in 1943, Colp's group (20) reported 101 poor-risk patients with duodenal ulcer in whom gastroenterostomy and vagotomy led to an operative mortality of 5% compared with 0.7% for subtotal gastrectomy. Moreover, the recurrent ulcer rate was 15% for gastroenterostomy alone, 10% for gastroenterostomy and vagotomy, 8% for subtotal gastrectomy, and 0.6% for subtotal gastrectomy and vagotomy.

Nevertheless, Dragstedt's truncal vagotomy, or the later selective or proximal gastric (highly selective) vagotomies, became the standard operation for reducing acid in patients with ulcer for the rest of the 20th century. The operation of truncal vagotomy and pyloroplasty was used extensively at Mount Sinai from 1959 (21), with 76% mean reduction of maximal histamine-stimulated acid (22). Thus, over these decades, Mount Sinai had produced evidence that the efficacy of operations for ulcer was related to their acid-lowering results, allowing later gastroenterologists at Mount Sinai to aim at healing ulcers by acid-lowering drugs (see chapter 14).

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The Gastric Mucosal Barrier

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Abstract

Most gastroduodenal ulcer disease results from a weakness in the normal gastric mucous barrier against the penetration of acid secreted by the stomach. Based on meticulous and insightful research, the distinguished physiologist Franklin Hollander hypothesized that the stomach is protected against its own acid secretion by a dynamic two-component mucus-mucosal barrier. Hollander and his co-workers defined the physical and chemical characteristics of the mucus components of this barrier, as well as the defense provided by the surface epithelial cell layer, which he viewed as the second line of defense (the second component). Barrier investigators at Mount Sinai demonstrated the effects of impairment of barrier function with resultant increased back-diffusion of acid, and they defined the consequences of this acid penetration into the gastric epithelium. The contribution of these workers included important observations on the natural impermeability of the gastric corpus and fundus as well as the normally increased permeability of the antrum. They also presented evidence on the role of bile in duodenogastric reflux in gastric ulcer disease and the presence of impaired barrier function in patients with gastric ulcer and pernicious anemia. Further studies included demonstration that stress and carcinogens could disrupt the gastric mucosal barrier. Disruption of the barrier, in turn, was shown to allow carcinogenesis to occur by permitting the absorption of certain carcinogens which otherwise are warded off by the barrier. The Hollander two-component gastric mucosal barrier hypothesis has, in recent years, been increasingly validated by experimental data coming from other laboratories.

Key Words: Gastric mucus, gastric mucosal barrier, gastric epithelium, gastric acid.

The Gastric Mucosal Barrier

IT IS NOW GENERALLY AGREED that almost all gastroduodenal ulcer disease results from an abnormality in the mucosal barrier. In recent years, attention has focused on *Helicobacter pylori* and ASA/NSAIDs as important causes of this failure of barrier function. Uncommonly, ulcer disease of the upper GI tract is attributable to excessive secretion of hydrochloric acid rather than to a primary failure of the barrier itself.

Background

An early hypothesis on the inherent resistance of the stomach to autodigestion was that of John Hunter in 1772 (1). On observing the rapidity of post-mortem gastric autolysis, he ascribed the ability of the stomach not to digest itself during life to the presence of a "living principle." This "living principle" depended, in Hunter's view, on the continuing circulation of blood through the gastric tissue. In 1853, Virchow (2) refined this hypothesis, proposing that the acid in the gastric juice diffused back into the mucosa, where it was neutralized by circulating alkaline blood. Gastric ulcers were considered to be secondary to a restriction in local blood supply, with resultant ineffective neutralization of absorbed acid, leading to localized areas of autodigestion. Pavy agreed, publishing strong endorsements in 1863 (3) and 1869 (4).

Beaumont's epic observations provided a meticulous account of the dynamic nature of the gastric lining of his patient, Alexis St. Martin, a gunshot victim with an open gastric fistula (5). Beaumont described the inner lining of the stomach to be "constantly covered with a very thin transparent viscid mucus lining the whole interior of the organ." Beaumont documented this mucus layer to be a distinct alkaline entity of widely varying appearance and physical characteristics, often dependent on the general state of his patient.

An earlier reference to the protective quality of the gastric mucus layer itself was published by Glover in 1800 (6). Glover believed the function of the mucus to be "lubricating and that it must likewise defend the internal surface of the stomach and the intestines from the action of the gastric juice." Some 60 years later, Harley (7), who is usually credited with the initial hypothesis regarding the protective nature of the mucus layer, stated: "It is chiefly, if not solely, the mucus which protects the stomach from the chemical action of its own gastric juice." In 1855, Claude Bernard (8) recognized the apparent impermeability of the gastric lining to pepsin. Bernard also pointed out the importance of the dynamic quality of this gastric surface epithelium: "the epithelial layer is destroyed and renewed with great ease."

Bernard described the gastric lining: "The epithelium of the gastric mucosa, especially the glutinous mucus which covers the inner wall of this viscus, and which is seen very well when one opens the living animal, encloses the gastric juice as in a vase as impermeable as though it were made of porcelain." This view regarding the one-component nature of the protective barrier dominated physiologic thinking until the 1940s, when the importance of a dynamic two-component barrier was proposed by Hollander.

Hollander's Two-Component Barrier

During the first half of the 20th century, the prevalence of peptic ulcer disease increased alarmingly. The thinking of most clinicians and investigators turned to excessive secretion of HCl as the major causative factor in this disease. However, despite this consensus, Hollander proposed that the stomach's primary defense against peptic ulcers was the mucus-mucosal barrier. Hollander's insight into the functioning of the mucus-mucosa as a virtually impenetrable barrier to the acid which the stomach itself secretes grew out of his fundamental studies on the mechanism of gastric acid secretion. It became apparent to him, early on, that the parietal cell secretion consisted of nearly pure concentrated HCl; he was able to demonstrate that it remained almost unchanged within the gastric lumen over long periods of time. He also pointed out that peptic ulcer is a localized disease, rather than one diffusely affecting the gastric or duodenal lining, i.e., if hypersecretion of the acid were the sole cause of ulcer disease, then that disease should be more diffuse. He also drew attention to the fact that most individuals with hypersecretion of acid did not suffer from peptic ulcer disease and that many patients with peptic ulcer disease did not demonstrate hypersecretion of acid. To Hollander, the conclusion was obvious: some localized defect or weakness in the protective mucus-mucosal barrier must be primary in the causation of peptic ulcer disease. By 1944, Hollander presented his early ideas of the "mucous barrier" as a two-component, self-renewing system.

Franklin Hollander

Franklin Hollander had come to The Mount Sinai Hospital as director of the Gastrointestinal Physiology Research Laboratory in 1936, and he continued there until his death in 1966 (see above, chapter 6). His studies on gastric physiology began a decade earlier in the laboratory of Lafayette Mendel at Yale. In all, he published a total of 272 scientific papers. His final days were spent painfully but quietly at home, continuing almost daily meetings with those of us whom he was guiding through ongoing studies on gastric pathophysiology. In accordance with his request, his name did not appear on any papers published after his death. Hollander devoted the bulk of his time and energies to basic science rather than to clinically oriented research, yet he was always looking for direct clinical applications of his work and gave generously of his time and support to clinicians and trainees. It was Hollander's conviction that a grounding in bench research and in basic gastrointestinal physiology was essential to the development of the complete gastroenterologist.

In his earliest publication (9), Hollander reported that gastric juice collected from isolated canine gastric pouches had a pH of less than 1, provided special care was taken to avoid irritation of the pouch during collection of juice, thereby avoiding any stimulus to the stomach to secrete diluting or neutralizing substance. Hollander's new technique involved the construction of a sphincter at the mouth of the pouch. Although he left it unstated at the time, Hollander later referred to this observation as a crucial one, indicating to him that there must be very little (or virtually no) loss of acid via back-diffusion into the mucosa; otherwise, such low pH values could not have been achieved. When he published this observation in its final form (10), Hollander was able to report the pouch juice to have a constant pH value of less than 1.

His early interest in the barrier was already apparent in 1929 (11). Commenting on the high

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concentration of hydrochloric acid in the gastric secretion, "about 0.15 N.," Hollander stated: "Even more remarkable are the intracellular organizations which permit the existence of living normally functioning tissue in intimate contact with so corrosive a liquid. True, the fluid contents in the lumen of the stomach is much less acid, by reason of the neutralizing action exerted by food stuffs, saliva, and regurgitated intestinal juices. Nevertheless, even this less acid fluid will exert a marked digestive action on many tissues which may be immersed in it, even though these tissues are living organs transplanted into the stomach. The acid secretion, however, unaffected by admixture with the above-mentioned alkaline fluids exerts no such corrosive action on the cells which are immediately concerned in its elaboration. While the effective agent in the protection of these cells may be the mucus, no one has yet conclusively demonstrated that it is so, and thus, the stability of these tissues in the presence of digestive juices which they themselves manufacture remains as great a mystery as ever."

In the 1930s, Hollander continued his studies on the nature and mechanisms of gastric acid secretion (11–19). His observations refined and extended the views of Pavlov, and he formally proposed a two-component acid secretory process: (1) the parietal cell secretion, containing isosmotic HCl (160 mM) and no other ions except for "perhaps a little potassium," and (2) an alkaline component comprised of mucus, enzymes and a transudate of interstitial fluid. These were conceived to be relatively invariant physiologic entities with all alterations in the concentrated (isosmotic) primary HCl secretion resulting from dilution and neutralization by the non-parietal cell alkaline component. Absorption or back-diffusion of H^+ was, in Hollander's view, not a factor.

The major evidence supporting an opposing viewpoint was presented by the renowned physiologist Torsten Teorell (20, 21). Based on experiments in pylorus-ligated cats, as well as in an *in vitro* membrane preparation, Teorell concluded that the hydrogen ions of strong acids diffuse out of the stomach quite easily, and that this hydrogen ion loss occurs via an exchange diffusion for Na ions across the surface mucosa. He viewed the gastric mucosa as an ion exchange membrane whose function it was to reduce the intraluminal gastric acidity. Teorell's back-diffusion model received some support (22). One of the more interesting aspects of Teorell's 1939 report (21) was his observation that weak acids disappear from the stomach even more rapidly than do strong acids, a phenomenon ascribed to entry of un-ionized acid molecules via paths (solution in the cell membrane) other than those open to ions. The inflammatory effects upon the mucosa of the entry of these weak acids were noted, but better appreciation of their significance awaited the work of later investigators (23).

Hollander (24) objected to Teorell's hypothesis: "The notion that the concentration of HCl within the stomach may be reduced by a physical process of absorption is one which as yet has not acquired many adherents." Hollander pointed out that Teorell had not demonstrated directly the existence of an ionic exchange in the mammalian stomach, but rather had utilized *in vitro* nonvital membranes, as an "analogous" model. Hollander held Teorell's views to be "worthy of consideration and even of experimental examination," but they received little of either by that time.

Hollander's own early observation that highly acidic gastric secretions can be retained within canine gastric pouches up to 9 hours without any significant diminution in acidity cast considerable doubt on the likelihood of any such process of absorption or ionic exchange (12).

Hollander's studies on the physical and chemical properties of gastric mucus began with publication of an abstract written with Robert Felberg in 1941 (25). In it, they stated that "previously published data on mucus are too scant and divergent to yield criteria of purity of the secretion or quantitative correlations among its chemical characteristics," and then described their earliest efforts to obtain mucus secretion from canine fundic pouches. The abstract ends with: "these studies will be extended"; and, so they were.

In 1943, Hollander and Stein published their first joint paper on some of the characteristics of gastric mucus (26). They reported that a major part of the mucus secreted after pilocarpine administration is squeezed out of the surface epithelial cells by muscular activity. In particular, they saw oozing of blood from the mucosa after pilocarpine, a finding later featured in a study by Davenport (23). Seven years later, Janowitz, Hollander and Jackson (27) found that topical application of acetylcholine resulted in secretion of alkaline, cell-free mucus, confirming Hollander's previous conclusion that the exfoliation of gastric-surface epithelial cells is not an essential part of the process of mucus secretion.

Hollander first mentioned a "two-component barrier" in 1941 (28), when he suggested that such a barrier provided laboratory animals with their normal resistance to the induction of gastric

cancer by topical application of carcinogens. He presented his concept of the barrier more formally in an editorial in *Gastroenterology* in 1944 (29) "Mucous secretion (including desquamation of affected surface mucosal cells) constitutes the most effective protective agent for the healthy mucosa — against tumor formation, as well as peptic ulceration. Some such modification in (mucus) secretory activity may obtain in the human precancerous stomach."

Hollander amplified this view in 1945 (30): "The one aspect of gastric physiology that might prove to be of fundamental importance in relation to gastric carcinogenesis is mucus secretion. This importance derives from its function as a protective agent against all forms of irritation, but particularly the chemical ones. Hence, any deficiency in output of mucus or in its essential physical properties might well serve to predispose the gastric mucosa to attack by an exogenous carcinogenic agent. This barrier involves not only the viscous mucus secretion, but also the mucous cells themselves. Mildly irritating solutions result in a flow of thick, jelly-like mucus. Histologic examination smears reveal considerable quantities of desquamated columnar epithelium. Spontaneous secretion, to the contrary, is frequently free of such desquamated columnar cells. . . . Obviously, if any cancerous change is induced, when these columnar cells make contact with a carcinogen, it will immediately elicit a shedding of these cells so affected making the development of an adequate tumor impossible."

Seeking confirmation of this view, Hollander and co-workers studied the effects of mild irritants and noted that the occurrence and volume of mucus and of desquamated surface epithelium increased with the irritating power of the agent applied (31). Hollander credits Pavlov (32) with stating that the copious flow of mucus after application of irritants to the gastric mucosa does not reflect serious pathologic condition but only a normal physiologic reaction to an irritant which "wards off danger which threatens the more important elements of the mucus membrane beneath."

Hollander and Lauber, studying multiple stimuli, found that clove oil water emulsion is the most effective stimulus of gastric mucus secretion (33). However, clove oil is a mixture of several compounds, including 80% eugenol (4-allyl-2-methoxyphenol). Therefore, they investigated pure eugenol as a topical stimulus and concluded that it is as effective a stimulus as clove oil and "has the advantage of being a single chemical individual." After exhaustive studies on the effects of many irritants and other stimuli, Hollander proposed that eugenol be adopted as a standard stimulus for study of the gastric mucus (34).

Hollander and co-workers explored the effects of repeated eugenol instillation in isolated canine gastric pouches (35). In these "fatigue experiments," striking changes occurred, with an initial flow of opaque jelly-like mucus decreasing, to be replaced by large volumes of secretion of clear alkaline fluid. These studies formed the basis for the later works of Code (36) and Davenport (37). In a companion paper (38) with Sonnenblick and Sober, Hollander documented cytologically the progressive desquamation of layers of epithelium after eugenol.

Hollander and Goldfisher (39) then described (by histology) a remarkably rapid 3-stage regenerative process after repeated eugenol applications: (1) the preliminary resurfacing of the denuded mucosa with flat cells, evident 30–60 minutes after removal of eugenol from the pouch, (2) the transformation of these new cells into low and tall columnar cells, and (3) the reformation of crypts in these areas of smoothly resurfaced mucosa. This entire process occurred within 36 hours following deep shedding of the mucosa as far down as the bottoms of the foveolae.

The definitive paper by Sober, Hollander, and Sonnenblick on the effects of topical eugenol application (40) established a new experimental approach to some stomach diseases — notably gastritis, peptic ulcer and carcinoma of the stomach. Hollander and co-workers looked at the possible beneficial effect of topical application of eugenol to the gastric lining of patients with peptic ulcer via increased mucus secretion (41). Ten out of 14 patients had complete or partial relief of symptoms, suggesting that prolonged stimulation of mucus secretion might be beneficial.

Formulation of the Two-Component Barrier Theory

After a decade of study on the nature of the gastric mucus and the underlying epithelium, Hollander formally proposed the concept of a two-component, self-regenerating barrier (42). According to his hypothesis, the gastric mucous barrier is a composite of two integrated structural units. The layer of viscous mucus constituted the first line of defense and the second was the layer of columnar and cuboidal cells of the surface of crypt epithelium. "The mucus layer constitutes a first line of defense in the gastric wall by reason of its tenacious adherence to the underlying tissue, and its ability to maintain considerable thick-

ness and its impermeability to destructive chemical agents." Hollander looked upon the cellular layer as providing defense by immediately shedding the injured columnar cells and concomitantly reinforcing the secreted layer (mucus) with material of extra-high viscosity. He documented the rapidity with which this cellular layer regenerates itself and pointed it out as a crucial element in this hypothesis. Hollander commented that "it is curious that although Claude Bernard anticipated the importance of this dynamic quality of the surface layer in protecting the stomach against autodigestion, its role in this regard has almost completely been neglected during the intervening century." The facts suggested to him that ulcer etiology was more closely dependent upon predisposition to autodigestion than on secretion of excessive gastric juice, and he stressed the need for a shift of emphasis in research, holding this position long before any understanding of *H. pylori* or the role of NSAIDs in altering the mucosal barrier and in the causation of peptic ulcer disease.

Hollander proposed the gastric "mucus-mucosa" to be a virtually impenetrable barrier to the diffusion or absorption of HCl or to the exchange of H^+ for other ions across it. Therefore, all alterations in the concentration and composition of HCl collected from the gastric lumen resulted from neutralization and dilution. Support for Hollander's hypothesis came from Cope and co-workers (43, 44), who in 1943 demonstrated in dogs a strong gastric "epithelial barrier" to the diffusion of H^+ and other ions, as did Reitmeier et al. in humans, in 1957 (45). In 1963, Code and co-workers reported that the presence of acid within the gastric lumen led to a striking, almost complete, restriction of the movement of Na^+ ions across the membrane (46).

It remained unclear, however, whether this barrier to diffusion of ions (most notably H^+ and Na^+) was at the level of the surface epithelium or at the mucus layer, or both. Nevertheless, most authors began to refer to the epithelium as the site of restriction of ionic diffusion. This view arose in part from the apparent ease with which HCl secreted by the parietal cells found its way across the mucus layer and into the gastric lumen, as well as experiments which demonstrated the free movement of H^+ in both directions across refined films of gastric mucus *in vitro*. This objection to the mucus layer as being the protective barrier against acid in the lumen was met by Hollander with an educated speculation (42): "This seeming inconsistency in behavior might result from the formation of short-lived channels in the mucus layer. Immediately thereafter, the uncoagulated mucus surrounding the minute hole, by reason of its high surface tension, will flow over the opening and seal it."

Breaking the Barrier

This next stage in barrier research began in 1955 with a brief abstract (47) in which Hollander drew attention to Davenport's report that acid secretion by mouse stomachs *in vitro* was inhibited by the enzyme inhibitors iodoacetamide and N-ethyl maleimide (48). Hollander stated that "at Davenport's suggestion, we have attempted to confirm this effect *in vivo*." Hollander found that topical application of these substances to the mucosa, followed by parenteral histamine stimulation, resulted in a marked increase in volume rate of secretion without a drop in pH (49). Surprisingly, neither Hollander in this study (49), nor Davenport in his (48), considered the possibility that this finding might have resulted from a disruption of the mucous barrier, and that hydrochloric acid continued to be secreted by the parietal cells only to back-diffuse across this impaired barrier and be lost before it could be recovered for titration. This possible explanation may have been obscured by the fact that, in the absence of histamine, these enzyme inhibitors led to the output of significant volumes of viscous alkaline mucus secretion. Similarly, in 1952, when Janowitz, Colcher and Hollander concluded that secretion of HCl by canine gastric pouches in response to repeated injections of histamine had been markedly inhibited by acetazolamide (a new and powerful carbonic anhydrase inhibitor), they too ignored the possibility that acetazolamide might be causing a disruption of the barrier, with loss of secreted hydrogen ions by back-diffusion rather than by true inhibition at the parietal cell level (50). In support of their conclusion, Janowitz, Colcher and Hollander referred to a paper by Davies and Edelman (51), who studied tied tubes of frog mucosa and found "acid already secreted began to leak back through the mucosa" after application of carbonic anhydrase inhibitors. They ascribed this result to damaged parietal cells (51). Janowitz and Hollander also failed to make the connection and did not mention the possibility that the gastric mucosal barrier was being impaired by acetazolamide.

This oversight was corrected, quite by accident, in the fall of 1960. Mario Altamirano, a brilliant young physiologist from Santiago, Chile, who had established an international reputation with his studies on the permeability of the gastric

mucosa, came to work with Hollander. He brought with him his ingenious lucite chamber device, in which a segment of gastric fundus with intact blood supply was mounted between two layers of lucite so that the mucosa formed the bottom of a cup. This so-called *vivo-vitro* preparation allowed for nearly quantitative instillation and collections, as well as continuous direct observation of the gastric mucosa itself (52). I borrowed Altamirano's chamber and in the course of a pilot experiment on the effects of acetazolamide on potassium in gastric secretion, I noted the sudden appearance of striking gross mucosal damage after intravenous acetazolamide when HCl was in the chamber in contact with the mucosa. This unexpected observation prompted a series of experiments designed to evaluate the degree to which mucosal damage might have contributed to the apparent inhibition of acid secretion following administration of this compound. Test solutions were placed in the chamber to control the acidity of the fluid bathing the mucosa, and acid secretion was stimulated by histamine. Administration of acetazolamide to preparations with high concentrations of HCl in contact with the mucosa resulted in prompt gross damage, with hemorrhage and edema. When the acidity of the chamber fluid was reduced by the addition of a buffer (glycine), the degree of damage and the degree of acid inhibition diminished proportionately to the reduction in acidity. The resulting paper (53) was the first to describe the consequences of impairment of the gastric mucosal barrier function leading to back-diffusion of H^+. It was also the first to point out that what appeared to be inhibition of stimulated acid secretion was in fact a consequence of H^+ loss by back-diffusion. When this paper was presented, Charles Code questioned the results, because the experiments had been done using a chambered gastric segment preparation, which in his view might have led to damage of the mucosa even though the blood supply was thought to be intact. He proposed that the experiment needed to be repeated in isolated canine pouches and emphasized that Janowitz, Colcher, and Hollander had not found any such damage or impairment of the barrier (50).

In 1962, Horace Davenport, chairman of the Department of Physiology at the University of Michigan, spent a sabbatical year at the Mayo Clinic with Dr. Code. At the Mayo Clinic, he held the title of visiting professor, but he asked Code (36) to "treat him as a post-doctoral fellow and assign a research project to him." Early in the fall of 1962, Hollander received a telephone call from Code and Davenport, asking his advice. Hollander beamed as he recounted to me the details of the long conversation: Code would assign Davenport a study on acid and sodium movement across the mucosa in canine gastric pouches damaged by eugenol, in accordance with Hollander's eugenol experiments. By Hollander's account, information was freely shared, and he was delighted at the prospect of these highly regarded physiologists starting a project so close to Hollander's heart, and so much derived from his ideas and previous work.

In 1981, at the time of his presentation of the Friedenwald Medal to Davenport, Code spoke (36) of the arrival of Davenport at Code's laboratory, and of the barrier research project: "The investigation, I thought, was one for which he was uniquely qualified. I had found a year or two earlier that when I washed out canine gastric pouches with an emulsion of eugenol, the active ingredient of the oil of cloves, the secretion of the pouch in response to histamine changed from hydrochloric acid to sodium chloride. Was the eugenol altering the product of the parietal cells, or was the hydrogen ion they secreted escaping after its formation?" The rest is history. To quote Code, "Davenport took off like a jackrabbit. . . . He had two papers published before I had ours written!"

In his early publication on the subject in 1964, Davenport and colleagues followed Hollander's lead, using eugenol to alter the barrier, and showed that eugenol damage did not alter acid secretion but rather that secreted hydrogen ions back-diffused across a damaged barrier more rapidly (37). Davenport's important and highly regarded body of work from 1962 through 1982 enlarged and enhanced our understanding of the gastric mucosal barrier. As part of his quest to locate the site of the barrier, he went on to publish many papers documenting the effects of a variety of barrier breakers. Davenport clearly can be credited with the reawakening of interest in the gastric mucosal barrier, for it was these many critical and concise reports, published in popular clinical journals, which caught the attention of the medical world. At the same time, the Mount Sinai group continued its own studies on the barrier. Multiple publications by Hollander, Altamirano, Werther, Chapman, Dycke, Rudick, Janowitz, Himal, Lindner, and Berkowitz *(vide infra)* followed.

Interest in the gastric mucosal barrier was not only reawakened: it flourished. In fact, it became an exciting subject for research and filled many a program at national meetings. By this time, how-

ever, Hollander was terminally ill. Although treated with respect, Hollander and his work were generally met with a polite indifference and at times went unrecognized. Even the eloquent article by Johnson (54) stated that "all of those papers, written by numerous physiologists, pharmacologists, gastroenterologists, surgeons, anatomists, and probably others as well, on acetic acid, bile acids, aspirin, and ethanol damage to the gastric mucosa were prompted by Davenport's original studies." When Davenport's paper (37) was published in *Gastroenterology*, its editor, Dr. Morton I. Grossman, wrote that it would revolutionize the physiology of the stomach and added, without references: "Substances which break the gastric mucosal barrier cause desquamation of cells which are quickly replaced."

The final paper on the gastric mucous barrier co-authored by Hollander and published in his lifetime was the definitive report of the effects of barrier disruption by acetazolamide (55). The apparent inhibition of acid secretion after acetazolamide was in fact shown to result from increased loss of secreted H^+ from the luminal fluid by back-diffusion. Even very prolonged contact (5 hours) of the mucosa with strong HCl (160 mEq per liter) never resulted in damage. This remarkable ability of the mucosa to maintain solutions of high acidity within the gastric lumen was abruptly lost after acetazolamide administration. H^+ losses accelerated over time, and the increase in H^+ penetration caused more mucosal damage. Furthermore, mucosal damage did not depend upon active HCl secretion *per se* and therefore was not due to the accumulation of alkali within oxyntic cells, as had previously been thought (51). Microscopic examination of the tissues did not show early damage to the oxyntic cells, but instead found it to be in the surface mucosal cells.

Davenport initially suggested that the increase in Na^+ gain and H^+ loss associated with impairment of the mucosal barrier resulted from an acceleration of the normally minimal equilibration of these ions across the membrane. Opposing this view, the Mount Sinai group showed that a large part of the increased Na^+ output from damaged mucosae was associated with net water movement into the lumen (55). In later publications, Davenport accepted these findings. The second Mount Sinai group of barrier investigators (working apart from Hollander), Lindner, Cohen, Dreiling and Janowitz, studied the effects of acetazolamide in humans and also agreed (56). Altamirano (57) confirmed the absence of a transport mechanism involving Na^+ for H^+ exchange across the gastric mucosa and concluded that both ions diffuse independently, for which he suggested the term "interdiffusion."

Hollander died in 1966. At this point, Davenport (58) still disagreed strongly with Hollander's two-component theory: "It should be noted that Hollander included the epithelial cells as half the barrier. . . although the layer of mucus is equivalent to a thin sheet of unstirred fluid, it provides little chemical protection for the mucosa; its chief function is lubrication. . . . Acid quickly diffuses through it to reach the apical border of the cells."

Thus, Davenport dismissed the mucus layer as nothing more than a lubricant. He gave no direct evidence to support this view, but referred to the work of others using refined mucus films. Davenport proposed that most of the barrier function of the mucosa was at the level of the apical membrane of the surface epithelial cells and at the tight intercellular junctions of the gastric mucosa. The luminal surface of the epithelial cell has no carrier for the ionic transport (as do the basolateral cell membranes) and the tight junctions appear to be much tighter than those found elsewhere in the GI tract. However, the mucus layer was later shown to possess a notable pH gradient from acidic at its luminal surface to neutral at the mucosal surface (59). This near-neutrality was maintained at the epithelial membrane surface by bicarbonate secretion into the mucus layer from the mucosa itself.

It was not long before Davenport began to retract his opposition to Hollander's views. In February 1968 (60), two years after Hollander's death, he published a subscript dedication: "This paper is dedicated to the memory of Franklin Hollander in gratitude for early encouragement and in appreciation of his contributions to the physiology of the gastric mucosal barrier." In this paper, Davenport wrote, "Although the exact locus and nature of the barrier are unknown, one component must be the plasma membrane of the mucosal cells, and another component may be the mucus layer at the tips of the epithelial cells." In addition, he credited Hollander's 1954 paper (43) with defining the two-component barrier. Davenport speculated that detergents might loosen the tight junctions and/or disrupt the plasma membrane of cells, and he cited evidence (61) that urea is capable of dissolving gastric mucus.

After Hollander

In the post-Hollander period, the Mount Sinai barrier investigators continued their studies.

Some are presented here as representative of that group.

Previous studies showing a "tight" barrier to H^+ and Na^+ had utilized *vivo-vitro* preparations (55) or isolated canine pouches, which consisted of oxyntic gland area only (62). Studies on the intact human stomach indicated a more rapid movement of hydrogen and sodium ions across the membrane than would have been anticipated from the canine studies, which employed oxyntic gland area only (63). Citing this disparity, as well as the known physiological relationship between antral acidification and the inhibition of gastric release, Walter Dyck, then a fellow in Gastroenterology at Mount Sinai, working with Werther, Rudick and Janowitz, studied separated canine pouches constructed from antrum or corpus (64). The antral mucosa absorbed more H^+ and put out greater amounts of Na^+ and K^+ than did the oxyntic mucosa. Dyck continued his work on the barrier and on other aspects of gastric pathophysiology during his fellowship and later as chief of the Gastroenterology Division and director of Research and Education at the Scott and White Clinic and Texas A and M University Health Science Center.

At this point, it had been established that the administration of acetazolamide, as well as topical chemical injury to the gastric mucosa, resulted in a loss of resistance of the mucosal barrier to acid absorption. Practically nothing was known about the nature and importance of this process in the diseased human stomach. Perhaps the hypoacidity as well as the ulcers in patients with gastric ulcer disease resulted from an altered barrier. Therefore, Chapman, Werther, and Janowitz studied the responses of the normal and abnormal human gastric mucosa to an instilled acid load (65). The patients with larger and more proximal ulcers were found to have a greater gastric permeability to H^+ and Na^+, as did patients with pernicious anemia.

Increased bile regurgitation into the stomach occurs in gastric ulcer disease (66–68) and the concentration of bile salts within the stomach returns to normal after the ulcers have healed. Davenport had shown that dog bile and sodium taurocholate caused an increased permeability of the gastric mucosa to H^+ in oxyntic-gland-area canine pouches (60); however, peptic ulcers of the stomach occur in pyloric-gland-area mucosa, not oxyntic. Werther and colleagues therefore studied the effects of human hepatic bile on electrolyte movements across the pyloric gland area in canine pouches and compared them with oxyntic gland area in the same dog (69). Their findings indicated that brief exposure to human bile in relatively low concentration markedly increased the net flux of Na^+, K^+, and H^+ across the pyloric-gland-area gastric mucosa. These results supported the hypothesis that at least part of the mucosal abnormality in gastric ulcer disease may reflect damage from increased back-diffusion of H^+ through a functional barrier which has been diminished by contact with bile. In the same issue of *Gastroenterology*, in 1970, Ivey and colleagues reported similar effects of bile salts on the gastric mucosa of human subjects (70).

Jack Rudick was appointed assistant professor of surgery at the Mount Sinai School of Medicine in 1966. Before he arrived at Mount Sinai, he had been a research associate at the University of Washington School of Medicine in Seattle. In 1968, he joined Werther, Dyck, Chapman and Janowitz in their studies on the barrier. Rudick's surgical skills, intellect and high energy added importantly to the work of this group, which found that atropine administration in both fundic and antral pouches in dogs resulted in an increased H^+ diffusion into the mucosa (71). They concluded that some of the apparent reduction in secretory rate after atropine was, in fact, the result of these H^+ losses. Other investigators did not agree (72), finding to the contrary that atropine did not affect the permeability of the gastric mucosa.

From the earliest observations on the gastric resistance to autodigestion, investigators had suggested that impairment of blood flow (especially localized) might be responsible for decreased resistance. The Mount Sinai group then validated aminopyrine clearance as a measure of mucosal blood flow, but aminopyrine itself was shown in this study to alter the permeability of both antral and fundic mucosa for H^+ and Na^+ (73, 74).

The Mount Sinai barrier group also reported that pentagastrin infusion tightened the barrier (75) and others agreed (76). Overholt, a student of Davenport, had previously attempted to estimate H^+ back-diffusion rates by utilizing glycine to trap secreted H^+ in the gastric lumen in human subjects (77). However, glycine had been shown to stimulate acid secretion (78), negating Overholt's results. Chapman, Werther, Rudick and Janowitz applied this glycine technique to patients with gastric ulcer, duodenal ulcer and gastric cancer and found increased permeability of the stomach to endogenous and exogenous H^+ ions in gastric ulcer disease and diminished permeability in duodenal ulcer disease (79). They corrected the problem of glycine augmentation of acid secretion by utilizing the glycine trap against

a background of maximum acid output during full dose pentagastric infusion. Chapman was then a fellow in gastroenterology at Mount Sinai, later rising to associate clinical professor. He made important contributions to the work of the Mount Sinai gastric mucosal barrier study group and was lead author or co-author on seven papers relating to the gastric mucosal barrier.

Utilizing *vivo-vitro* chamber mounts of distal canine duodenum (80), the group then showed that the rate of movement of H^+, Na^+ and K^+ across duodenal mucosa was twice the rate for the antrum and 30–100 times that of the fundus of the stomach.

Werther and Horowitz clarified the controversial role of the gastric mucosal barrier to back-diffusion of H^+ in the pathogenesis of gastric ulcerations produced by restraint-stress in rats (81). Acid secretion did not decrease during restraint-stress, but there was a marked increase in hydrogen ion back-diffusion and loss across the gastric mucosa, which was clearly correlated with gross mucosal damage. They concluded that abnormal gastric mucosal permeability to hydrogen ions played an important role in restraint-stress-induced gastric ulceration.

Certain carcinogens, such as methylcholanthrene, are not absorbed by the normal stomach (82) and cause cancer experimentally only when they are surgically implanted in the gastric wall. Bile salts, which may reflux back into the stomach from the duodenum, promote absorption of such carcinogens by micelle formation. Horowitz and Werther showed that radiolabelled micelles of 3-methylcholanthrene, prepared *in vitro,* were absorbed by the gastric mucosa of the rat (83).

Some nitrosamines (N-methyl-N-nitro-N-nitrosoguanidine [MNNG]) are potent carcinogens site-specific for the stomach. Early inflammatory changes in the gastric mucosa occurred after administration of MNNG, followed by the occurrence of gastric cancer. Horowitz, Toth and Werther showed that the gastric mucosal barrier to hydrogen ions was markedly impaired after the administration of MNNG (84). Increased hydrogen back-diffusion was observed three hours after small doses of MNNG, both with carcinogenic, as well as with subcarcinogenic concentrations, so that barrier disruption by MNNG may play a role in gastric carcinogenesis by this agent.

The Mount Sinai group then reported (85) the effects of stress, aspirin and sodium taurocholate on the activity of MNNG in the stomach of the Buffalo rat, which is uniquely resistant to gastric carcinogenesis from any source, including MNNG. Adenocarcinomas and even greater numbers of gastric leiomyosarcomas were produced in these animals after barrier disruption by these agents. However, Buffalo rats receiving MNNG in the absence of restraint-stress, aspirin or taurocholate did not develop either gastric adenocarcinoma or leiomyosarcoma, so that at least part of the resistance of this unique strain to gastric cancer may be related to its mucosal barrier.

Mucus Revisited

The intense focus on gastric epithelium as a barrier gradually waned and was supplanted (in 1979) by a wave of interest in a phenomenon referred to as gastric "cytoprotection." This term related to the remarkable ability of gastric mucosa to resist gross injury by some extremely aggressive substances, such as boiling water, absolute alcohol, and concentrated corrosive solutions. Cytoprotection could be induced by prior exposure of the mucosa to a substance which would be irritating minimally injurious to the gastric lining. This gastric adaptation enabled the stomach to remain intact after exposure to these strongly aggressive agents. Since adaptive cytoprotection was blocked by inhibition of prostaglandin, it was suggested that exposure to a conditioning agent increased production of prostaglandin in the gastric mucosa, which in turn, in some mysterious way, was cytoprotective. However, there soon followed studies, utilizing both light and electron microscopy, which found that, in fact, the integrity of the surface epithelium was not maintained by this process. The term "cytoprotection" came into disfavor; however, the concept of mucosal protection by the effects of prostaglandins was documented and clarified. Increased thickness of the mucus layer provides most of the prostaglandin-induced cytoprotection (86–93). Recently, the mucus layer itself has been proposed as the site of the primary barrier (94).

If we accept the evidence that the mucus layer acts as a powerful diffusion barrier to hydrogen ions in the gastric lumen, how then does HCl secreted at the base of the gastric glands by the parietal cell traverse this mucus layer? Until 1990, the answer was obscure. Hollander had speculated on the possibility of short-lived channels but did not pursue this and presented no evidence. Fabry, working independently at Mount Sinai, provided the answer (95). Fabry described a process of viscous fingering, which is a hydrodynamic phenomenon by which fluids of low viscosity pass through fluids of high viscosity without mixing. In Fabry's model, pulses of hydrated HCl wind their way back through the mucus layer by means of short-lived channels or fingers. He proposed that surface tension makes the flat surface which the mucus layer presents to the lumen almost impermeable to the entry of hydrochloric acid. Driven by the secretory pressure of oxyntic cells, pulses of hydrochloric acid find their way through these channels in the mucus layer and into the lumen. After the secretory pressure drops, at the end of the pulse of acid secretion, the finger closes and disappears.

Lamont's group (96) confirmed Fabry's hypothesis. They documented viscous fingering patterns and showed the process to be dependent upon pH, so that "HCl secreted by the gastric gland can penetrate the mucus gel layer at the epithelial surface (pH 5–7) through these narrow fingers. Whereas, HCl in the lumen (pH 2) is prevented from diffusing back to the epithelium by the high viscosity of the gastric mucus gel on the lumenal side."

In the same year (1990), it was shown (97) that the mucus gel contained numerous phospholipids, and that its luminal surface was coated with a film of phospholipid. This surfactant layer accounts for the remarkably strong hydrophobic nature of the gastric luminal surface, which, in turn, provides protection against damaging agents. This phospholipid surfactant is a secretory component of the gastric surface mucosal cell.

Prostaglandin induces maintenance of the stomach's nonwettable surface properties protecting the underlying epithelium from aqueous acidic/proteolytic damaging agents in the lumen (98). This hydrophobic acid-resistant property of the gastric surface active phospholipid layer (SAPL) is rapidly attenuated by NSAIDs. As in humans, *Helicobacter* infection in mice is associated with a significant reduction in both gastric surface hydrophobicity and the phospholipid concentration of the oxyntic mucosa (99).

In a recent leading article in *Gut*, Hills emphasized that the stomach wall is strikingly hydrophobic (100). A droplet of water placed upon it "beads up as if on polyethylene." This hydrophobicity is largely eliminated by major "barrier breakers" such as bile salts and aspirin. A layer of hydrophobic surfactant transforms the hydrophilic mucoid layer into a surface so hydrophobic that the contact angle in many normal stomachs can exceed 90 degrees — that is, approaching that of polyethylene (93 degrees) or Teflon (108 degrees). The SAPL resides on the outermost layer of the gastric mucus (101). The source of this SAPL seems to be lamellar bodies found in parietal cells and mucus neck cells with some reported in chief cells.

The surfactant phospholipid is more permeable to lipids than to aqueous solutes. This finding fits well with the studies of discussed above in this paper. The Slomianys also found that stress ulcers are associated with a change in lipid profile of the gastric mucosa and that each of the known barrier-breakers displays some affinity for SAPL (102, 103). Bile salts form a chemical complex with SAPL, ethanol is a solvent for SAPL, while NSAIDs inhibit the production of prostaglandins controlling SAPL. Lichtenberger (99) has also shown that NSAIDs disrupt the surfactant phospholipid layer directly.

Recently, Hills (104), in a reply to a letter by Bernhard and Postle (105), agreed "on the major issue that surface active phospholipid (SAPL) protects the stomach wall from autodigestion by providing the gastric mucosal barrier to hydrated protons $H(H_20)_3{}^+$." However (104), "protons are far too polarizing to exist alone in an aqueous environment, the water of hydration being repelled by any hydrophobic domain."

Conclusion

Controversy over the locus of the gastric barrier has gradually faded and been replaced by disagreement. The importance of the mucus layer continues in its re-ascendancy; however, some physiologists continue to consider its major function to be lubrication (106). The importance of cytoprotection by prostaglandin-E_2 now receives considerable attention because of increasing concerns regarding NSAID-induced ulcers. However, these prostaglandins reduce gastric mucosal blood flow, which theoretically should be deleterious rather than helpful. Most would agree that enhanced mucus production, with thickening of the mucus layer, is the key to prostaglandin-induced cytoprotection. The apical cell membrane and the very tight gastric surface mucosal tight junctions are generally resistant to acid back-diffusion and may serve further to retard hydrogen ion back-diffusion. Some regard this membrane as the primary barrier. The layer of surfactant residing on the surface of the mucus layer is probably of great importance, but this is still being disputed. Most would agree that the pH gradient across the mucus layer exists and is important in the protective process. The problem with this latter hypothesis is that *H. pylori* may dwell close to the mucosal surface. *H. pylori* has very high levels of urease activity to make it an acid-tolerant neutrophil. This observation might lead one to the conclusion that the pH in the

deeper mucus layer is, in fact, more acidic than microelectrode problems would indicate.

So what is the view from Mount Sinai at this time? We interpret the published evidence to show that the key protective mucosal barrier resides in the mucus layer itself, and that this derives from the nonwettable surfactant layer on its surface. The physico-chemical effect of the very high viscosity of the mucus layer and its ability to retain bicarbonate secreted by the epithelium with maintenance of a pH gradient is real and an important factor in protection. Our view of the barrier includes the surface epithelial cell layer for: (1) its easy desquamation, (2) its remarkably rapid regeneration, and (3) production of its bicarbonate and phospholipid surfactant. Last but not necessarily least is the resistance of the apical membrane of the surface epithelial cells to back-diffusion from ions.

All the work of a multitude of investigators, including the Mount Sinai group and Davenport, on the "barrier breakers" was important in understanding the nature of the barrier and the consequences of its disruption. However, since all these barrier breakers may function to disrupt the SAPL and mucus layer, as well as the surface epithelial cell at the apical membrane, the data do not give us critical information regarding the locus of the barrier. Evidence from the predilection of *H. pylori* to colonize the mucus layer close to the epithelium is circumstantial and indirect and cannot yet be considered definitive negation of the importance of the surface mucosal resistance to acid penetration. From the Mount Sinai point of view, the preferred area for *Helicobacter* colonization is the gastric antrum (pyloric gland area), because of the increased permeability of the antral mucus layer to acid as opposed to that of the nearly impenetrable surface of the oxyntic gland area mucus. From this viewpoint, sufficient acid passes through the antral mucus layer to satisfy *Helicobacter* and to reach the acid-sensitive neuroendocrine cells residing in the antral surface epithelium. We speculate that factors which increase the permeability of mucus overlying oxyntic gland areas lead to back-diffusion of enough acid to encourage cephalad extension of *Helicobacter* colonization into the gastric corpus and fundus.

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12

Gastrointestinal Hormones

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Abstract

Solomon A. Berson, M.D., the first Murray M. Rosenberg Professor and Chair of the Department of Medicine at Mount Sinai from 1968 until his death in 1972, and Rosalyn S. Yalow, Ph.D., 1977 Nobel Laureate in Medicine or Physiology and Solomon A. Berson Distinguished Professor-at-Large, brought meticulous quantitation and new vistas to all of clinical medicine and biomedical science through the application of their technique of radioimmunoassay. I was fortunate to know and work with them for many years. In 1972, while I was an NIH Fellow in gastroenterology at Mount Sinai, Dr. Berson suggested that I pursue my research in their laboratory at the Bronx Veterans Administration Hospital. Dr. Berson died one month after I began my research in the Bronx. Yalow and Berson had already discovered big gastrin (G-34), but much work with gastrin remained to be done. Challenging work with secretin, cholecystokinin, and a host of other gut peptides, would keep the Mount Sinai group at the forefront of this exciting field. **Key Words:** Radioimmunoassay, gastrointestinal hormones, regulatory peptides, gastrin, secretin, cholecystokinin.

"Ros Yalow and Sol Berson were the Toscaninis of the field. . . . Most others were, if not organ-grinders, followers. . . ."

Rolf Luft, M.D.
Professor Emeritus of Endocrinology
Karolinska Institutet, Stockholm
Former Chairman, Nobel Committee (1)

Introduction

IN 1902, conceptual and practical endocrinology began in London when Bayliss and Starling discovered secretin in the duodenal mucosa of a dog. They coined the term "hormone," suggesting that there were more chemical messengers to be found. Within a year, Edkins discovered gastrin in the mucosa of the gastric antrum. This was a major advance in medical knowledge. And nearly sixty years later, a discovery made by members of the Mount Sinai community would revolutionize endocrinology, as well as gastroenterology, hematology, virology, clinical pharmacology, oncology, and virtually every other area of medicine and biomedical science.

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Berson and Yalow

The technique of radioimmunoassay (RIA) was introduced in 1959 by Solomon A. Berson, M.D., and Rosalyn S. Yalow, Ph.D. It is a method that can detect and measure extremely low concentrations of virtually any substance. They applied it first to the study of insulin, demonstrating that patients with Type 2 diabetes are resistant to its action. Subsequently, they and their younger colleagues studied many hormones and made the first RIA to detect an antigen, then known as Australian antigen, and now known to be a component of Hepatitis B virus. During their long association with Mount Sinai, their work was carried out in the Radioisotope Service of the Bronx Veterans Administration Hospital (VA).

Solomon Berson completed his residency training in internal medicine at the Bronx VA in 1950, and after a brief sojourn in private practice, he joined Rosalyn Yalow in the Radioisotope

Service during the same year. Rosalyn had established the service in 1947. She was a nuclear physicist and had never taken a course in biology. At that time, Sol had scant background in research, but by 1968, he was appointed to serve as the Murray M. Rosenberg Professor and Chair of the Department of Medicine at the Mount Sinai School of Medicine. His death in 1972 ultimately cut short a brilliant career and eligibility for the Nobel Prize. In 1977, Dr. Yalow was awarded the Nobel Prize in Medicine or Physiology.

The history of gastrointestinal hormones at Mount Sinai is the story of Berson and Yalow, and the following is a brief summary (2). As this is a historical rather than a scientific review, the emphasis is on the major figures within the context of Mount Sinai. Technical reviews of the work involving gastrointestinal hormones, especially the contributions of members of the Mount Sinai community, can be found elsewhere (3, 4).

In 1950, the High Flux Isotope Reactor at Oak Ridge Tennessee was firing neutrons into the nuclei of atoms. It was often said that a physicist looking into the "swimming pool" reactor could see the blue glow of the neutrons streaming out and believe that the intellectual creations of Albert Einstein, Hans Bethe, and Enrico Fermi were the greatest works of art of the century. Nuclear physics had been Ros' first love. Fermi inspired her when she heard him speak in 1939, along with many others "hanging from the rafters in Room 301 of the Pupin Laboratory at Columbia University." However, with her new Ph.D., she joined IT&T, in 1945, working outside the field she loved. Then, when the soldiers returned from the war, she found herself replaced by a man. She took a tip from her husband, Aaron Yalow, who was working as a medical physicist at Montefiore Hospital, and went to work creating a nuclear medicine service at the Bronx VA. But Ros needed a bright physician to work with, and the Chief of Medicine at the VA, Dr. Bernard Straus, suggested Sol Berson. Berson had recently opened a practice on Long Island, which Straus regarded as a mistake. When the young nuclear physicist came looking for a research partner, Straus got Berson and Yalow together and, through his department, funded their early efforts.

Their work first grew from the circumstance of the availability of radioisotopes. When these two individuals, one with no background or knowledge of biology or medicine and the other with no knowledge of research or radioisotopes, joined force, something just "clicked." They worked with an intensity beyond passion, with little regard for themselves, and little regard for its effects upon those around them.

Radioimmunoassay

By 1955, Yalow and Berson were already well known and respected for their quantitative work in the areas of iodine and albumin metabolism. Then came their ability to measure peptide hormones, the proteins that act as chemical messengers and regulate body functions. Hormones like insulin, glucagon, growth hormone, parathormone, ACTH, gastrin, secretin, and cholecystokinin (CCK), some of which circulate in the blood at concentrations as low as 10^{-12} M, equivalent to the concentration of one teaspoon of sugar dissolved in a lake which is sixty-two miles long, sixty-two miles wide, and thirty feet deep. This was quite an accomplishment. And they were quick to realize that RIA could be applied to a vast array of endogenous and exogenous substances, because antigenicity, the ability to elicit an antibody response, as they had shown for insulin, was a far more general characteristic of molecules than had previously been thought. The commercial possibilities for RIA were enormous. In fact, RIAs have made fortunes for commercial laboratories and producers of assay kits.

"We never thought of patenting RIA," Yalow once told me, looking down her nose as though a dead fish had been placed before her. "Of course, others suggested this to us, but patents are about keeping things away from people for the purpose of making money. We wanted others to be able to use RIA. Now some people assume that I'm sorry, but I'm not. Anyway, we had no time for such nonsense."

Suddenly, physicians and researchers wanted to go meet and learn from the masters. And they came from everywhere: Guillemin, Rosselin and Assan from Paris; Isidori and Negri from Rome; Samols and Hartog from London; Thomopoulou from Athens; Devlin from Dublin; Gomez-Mont from Mexico; Scott from Auckland; McGarry, McKenzie, Colle and Schucher from Montreal; Beraud from Lausanne; Brauman from Brussels; Pimstone from Capetown; and Jadresec from Santiago de Chile, to mention just a few.

The guests would stay for a few days, or a week, or a month, and leave The Bronx with the secrets of RIA, with hands-on experience using the new method that was changing the world, and with the blessings of the masters. Many also took with them some of Berson and Yalow's precious antisera, the small volumes of guinea pig plasma containing specific antibody molecules, to enable them to begin to work quickly when they got home; for many it was the gift of a new direction in their work. All returned with stories of what it was like to be around Berson and Yalow, where concepts and approaches to problems flew between them and around the lab like tennis balls. "It was like bouncing ideas around," say many of the people who worked in the laboratory. It was the free exchange of ideas and the opportunity to participate which excited the visitors and fellows alike. Berson and Yalow were overpowering in the defense of their data when controversy arose, but they did not try to stifle the competition. They did not try to sell their antisera, and the suggestion that they patent their methods, as Yalow indicates, was met with frank derision. It truly can be said that they gave of their knowledge and materials and bade the scientific community to go forth and multiply. It is also true that they were intensely competitive, disinclined to collaborate with others, and frequently harsh and unforgiving in their criticism.

Among those who came to visit Berson and Yalow was the outstanding gastrointestinal physiologist and doyen of gastrointestinal hormones, Morton Grossman. Grossman was a good friend of Henry Janowitz and both had studied with Andrew Ivy, the discoverer of cholecystokinin. It was Mort Grossman who influenced Sol to enter the field of gastrointestinal hormones, and he introduced Ros and Sol to Rod Gregory, Michlos Bodansky and Victor Mutt, the researchers who purified gastrin, secretin, and cholecystokinin.

Gastrin

In 1970, Yalow and Berson reported their assay for gastrin and discovered "big gastrin," or G-34, the 34-amino-acid gastrin peptide (5). The major discovery that gastrin is found in tissues and blood in both 17- and 34-amino-acid forms, energized the gastrointestinal hormone research community. They brought both their technical expertise and their cutting edge understanding of hormone physiology to the study of gastrointestinal peptides, and they shared these, along with their gastrin antisera, with many individuals who would advance the field. Indeed, so influential was their finding of heterogeneous forms of plasma gastrin that it inspired some to see "micro-heterogeneity," or a plethora of innumerable gastrin forms. Nonetheless, their view that G-17 and G-34 are the predominant biologically active gastrin peptides mediating meal-stimulated acid secretion prevailed.

Since the major stimulus of gastric acid secretion is the ingestion of a meal, Berson and Yalow performed extensive studies of meal-stimulated gastrin release. Their findings uncovered a fundamental pathophysiologic mechanism associated with duodenal ulceration. Acidification of the antral portion of the stomach causes "feedback inhibition" of gastrin release. Since groups of duodenal ulcer patients have lower mean fasting gastric pH and higher rates of meal-stimulated acid secretion when compared with normals, they hypothesized that mean fasting plasma gastrin concentrations and integrated meal-stimulated gastrin release should be lower in groups of duodenal ulcer patients. Their observation that groups of duodenal ulcer patients had normal mean fasting gastrin levels and greater integrated meal-stimulated gastrin release indicated that, as a group, duodenal ulcer patients have relatively insensitive acid feedback inhibition of gastrin release (3). They further demonstrated that when acid feedback inhibition becomes grossly insensitive, a patient may display pathophysiology that mimics the autonomous hypergastrinemia of a gastrinoma (3, 6). They called this condition "non-tumorous hypergastrinemic hyperchlorhydria," admittedly a bit of a tongue twister, allowing others to rediscover this pathophysiology and apply the names "hypergastrinemia of antral origin" and "antral G-cell hyperplasia."

Subsequent work with gastrin demonstrated that the hyperchlorhydria resulting from extensive small bowel resection is caused by hypergastrinemia due to the absence of a gastrin release-inhibiting factor (7). In addition, the Mount Sinai group studied the molecular structure of gastrins from a variety of mammalian species, discovered gastrinomas in dogs and cats, traced gastrin-like peptides back to mollusks, and determined the distribution and metabolic fate of heterogeneous gastrin peptides (8–10).

Secretin and Cholecystokinin

With respect to the first hormone, secretin, the Mount Sinai group constructed the first successful assays (11, 12). Secretin had proven difficult to measure because the molecule, lacking a tyrosine, was difficult to label with radioactive iodine, and because it circulates in very low concentration. Nonetheless, methods of labeling the amino-terminal histidine and extraction from plasma using reverse-phase cartridges allowed demonstration of postprandial secretin release and hypersecretinemic states.

The Mount Sinai group played a central role in working out the technical problems in measuring cholecystokinin and in determining its complex heterogeneity and distribution in plasma, gut,

and brain tissues (13–19). This group was the first to demonstrate that CCK is found in neurons of the cerebral cortex, that it is concentrated in synaptosomes, and that it is released by paradigms similar to those for nonpeptide neurotransmitters.

Conclusion

From the discovery of the first hormones, the regulatory peptides of the digestive system and the study of brain-gut peptides have been exciting and productive areas for the understanding of health and disease. We may take pride in the fact that members of the Mount Sinai community have contributed to this crucial area. In addition to Solomon Berson and Rosalyn Yalow, it is also worth mentioning Seymour Glick, Jesse Roth, John Walsh, and John Eng, each of whom has contributed greatly to this field both during and after their association with Mount Sinai. Those of us who have worked in the field are indebted to them all.

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Peptic Ulcer

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Abstract

Indigestion and heartburn have been described for thousands of years, but it was only in the 16th century that the disease peptic ulcer was established by autopsy. At first, only gastric ulcers were identified. In the 18th century, duodenal ulcers, most of which were fatal cases after perforation or hemorrhage, were seen. In the 19th century, when autopsy became a common, even routine, hospital procedure, uncomplicated acute and chronic ulcers were found and then correlated with symptoms. Thus, our current clinical understanding dates from the 1820s, by which time peptic ulcers were being reported in the U.S. It is unclear why gastric ulcers were not diagnosed at The Mount Sinai Hospital until 1873 and duodenal ulcers until 1885. However, after that time both conditions were diagnosed frequently, and they rapidly became common and were treated medically and surgically. **Key Words:** History, gastric ulcer, duodenal ulcer, U.S.

GASTRIC SECRETION AND THE MUCOSAL BARRIER have been described in chapters 9–11, and surgical and medical treatments for peptic ulcer in chapters 10 and 14. This chapter explores the story of peptic ulcer through the centuries, in the U.S. and at The Mount Sinai Hospital.

Until recently, peptic ulcer was, as inflammatory bowel disease still is (see chapters 19 and 20), of increasing incidence, unknown etiopathology, and without rational cures. Our current understanding of the causative roles of acid and *Helicobacter pylori* and anti-inflammatory drugs in peptic ulcer does not explain its explosive increase in this century, so that historical research is necessary.

Upper abdominal discomfort and pain are described in ancient medical texts, and some patients who complained of a sour taste of bitter liquid may have had gastroesophageal reflux. Others may have had peptic ulcer, gall bladder disease or pancreatitis, but such retrospective diagnoses can be made only on autopsy reports, which were rare before the 16th century.

In the 15th century, Beniviene (1443–1502) described 111 cases, but only 15 of his autopsies have been published (1). One was a typical clinical case of pyloric stenosis (xxxvi): "The body was cut open for reasons of public welfare. It was found that the opening of his stomach had closed up and it had hardened down to the lowest part with the result that nothing could pass through to the organs beyond. . . ." However, Beniviene did not report an ulcer (and he was familiar with perforations of the small intestine), so that the stenosis may have been due to linitis plastica rather than to ulcer disease. Morgagni described a similar case, in which the history of vomiting dated back to soon after birth and then again from age 33 to 57. Prepyloric contraction was found; it may have represented adult "congenital" hypertrophic pyloric stenosis rather than post-ulcer stenosis (2). The first pyloric stenosis in association with a gastric ulcer (which had perforated terminally) was reported in 1727 (3), and the first hourglass stomach in 1732 (4).

Goldstein (5, 6) cites early descriptions of gastric ulcer in 1479 (7), 1519 (8) and 1581 (9). One of the first autopsy-proven pyloric peptic ulcers was published in 1586 by Donatus of Mantua. The patient was a 59-year-old man of bilious disposition, who died after four days of acute and persistent vomiting (10). When Cardinal Caesar Boronius died in 1607 after intractable nausea, the autopsy showed three ulcers in the mouth (cardia?) of the stomach (11).

The Bolognese painter Elisabetta Sirani died suddenly in 1665 (at age 27) after a few months of abdominal pain and one day of severe pain and collapse. The autopsy showed that she had a perforation of the stom-

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ach; two doctors diagnosed an inflammatory ulcer. However, two other doctors attributed the hole to a corrosive poison, and a maidservant was tried for murder but not convicted (12). Charles I's daughter, Henriette-Anne, died suddenly in 1670 (at age 26) after a day of abdominal pain and tenderness. The autopsy, performed to see if she had been poisoned, showed peritonitis and a small hole in the anterior wall of the middle of the stomach. However, the doctors had never heard of a peptic ulcer, let alone a perforation, and attributed the hole in the stomach to the knife of the dissector (12, 13). An early report (about 1600) of perforated gastric ulcer in a doctor's wife, age 18, indicated that she died after four days of abdominal pain, vomiting and peritonitis; Bauhin, in 1679, concluded that inflammation of the stomach led to a gastric ulcer which then ruptured (14).

The first known gastric hemorrhage was reported in 1704 (15); it was thought to be iatrogenic: "It is clear that the stomach ulcer caused the large quantity of blood which had come from many open blood vessels but the cause of the ulcer one suspects could be due to the violent medicaments given the patient by a physician of little experience." Morgagni (16) described duodenal erosions (but not ulcer) (XXIX.20) in 1737 as well as gastric erosions and ulcers (in 1735), one of which (XXIX.14) had a hole which Morgagni was certain was a perforation and not a dissector's incision.

In 1791 in Padua, Jacob Penada saw an alcoholic butcher of 35 with a four-week history of abdominal pain, worse in the patient's final 24 hours, with vomiting and collapse. Autopsy showed, and Penada illustrated, a perforated ulcer on the anterior wall of the duodenum (17). Although he did a literature search, Penada was unaware of a similar case in 1746 (18) or Sir George Baker's case of hematemesis and melena from an ulcer in the first part of the duodenum, reported in a footnote in the second edition (1772) of his 1767 lecture on lead colic (19).

The first classification of stomach diseases came in 1793 from Matthew Baillie (20), with clear descriptions of acute inflammation (arsenic), trichobezoar, ulcer, perforation, pyloric stenosis, and scirrhous and ulcerated cancer. In 1817, patients with perforated gastric ulcer were reported in Dublin by Crampton (21), and patients with perforated duodenal ulcer were reported in London by Travers, who also noted bleeding, stenosing and penetrating gastric ulcers (22). Sometimes, in retrospect, early reports of ulceration or perforation of the duodenum appear to have been tuberculous (23) or malignant (24). Identification of the anatomy and pathology of *ulcus simplex chronica* of the stomach is usually attributed to Cruveilhier (25), but in various editions (26), Abercrombie had already covered symptomatology, pathology and complications of ulceration, both in the duodenum and the stomach, and had reviewed the literature, mostly French.

Proof that chronic stomach ulcers could cause pain came when patients with recurring, years-long chronic stomach pains died of another disease, and ulcers were found at autopsy (27), in contrast to such diagnosis being made after a fatal complication of the ulcer. Nevertheless, ulcers found at autopsy could have been coincidental, rather than causing the symptoms, as is suggested by the later report of a patient who died of heart disease who had never had stomach pains, yet was found to have a chronic gastric ulcer (28). Of Rokitansky's 79 cases of perforated ulcer, only 6 were duodenal, with 16 prepyloric, 15 lesser curve, 20 posterior, 5 anterior; 1 in the cardia and 16 multiple (29, 30).

Incidence of Gastric and Duodenal Ulcer

In 1857, Brinton (31) found a gastric ulcer or scar in 5% of all autopsies, whereas Perry and Shaw (32) found 70 duodenal ulcers in 17,652 routine postmortems (that is, 0.4%) at Guy's Hospital, London, 1826–1892. Of these 70 cases, 9 were fatal by hemorrhage, 8 by perforation, and 3 as the result of cicatricial narrowing either of the bowel or of the common bile duct (32). In the other 50 cases, the ulcer was found at routine autopsy.

Perry and Shaw (32) added to their own 70 cases another 81 from the British journals and hospital reports, to make a total 151 patients, 60 of whose complications included 32 with hemorrhage, 56 with perforation and 33 with obstruction. However, 91 of the 151 had been free of abdominal symptoms until complications or their death from other causes. Duodenal ulcer became more noteworthy after its convincing association in 1842 with burns, although Curling (33) was careful to point out that the association between burns and inflammation, congestion and ulceration of the intestine (but not specifically the duodenum) had previously been noted by Dupuytren (34) (and even earlier, in 1823 [35]). Moreover, three of John Hunter's six autopsies from 1755–1781 on patients with gastroduodenal erosions/ulcers (36) were acute, related to one patient with fever and two with fractured skull. A patient with gastric ulcers after burns was reported by Swan in 1823 (37), and one with both duodenal and gastric ulcers by Cooper in 1839 (38). Meanwhile, the 1st (1882) and 2nd (1892) series of the Index-Catalogue of the Library of the Surgeon-General both have three columns of citations, from 16 countries, of papers on duodenal ulcer (and 23 and 64 columns respectively on gastric ulcer), with 16 monographs on duodenal and 35 on gastric ulcers, mostly in German and French.

Peptic Ulcer in the U.S.

Goldstein (5) claimed that the earliest reference to a peptic ulcer in an American patient was in 1761 by Morgagni (16). However, Goldstein was relying on

Alexander's English translation of 1769 (16), where the "in an American" is a mistranslation of "in Marsupiali Americano," which was the opossum dissected by Tyson in 1698 (39); Morgagni had read of the dissection in a Latin report from that year (40) rather than in the English original (39). Nevertheless, Tyson was not only the first to report an animal with a (perforated) peptic ulcer, but he claimed to have seen three such perforated ulcers in patients, and in one he claimed he had foretold the diagnosis "before the *Patient's* Death" (41).

The first three Surgeon General's Catalogues list 64 reports on 101 patients with duodenal ulcer in the U.S. in the 19th century. It is interesting to compare their timing with the 68 reports from the U.K. on 211 patients, including the 201 cases collected by Perry and Shaw (32) (Table). It seems clear that, as in Britain, duodenal ulcer was increasingly reported in the U.S. from the middle of the 19th century, especially from the 1870s, after the diagnosis was made from fatal cases of hemorrhage and perforation.

With the advances in operative and anesthetic techniques, surgeons were able to perform laparotomy for gastric ulcer, at first for emergencies and then electively. Series of such operations with reviews of the literature were reported in the early 1900s, both from Leeds (42, 43) and the U.S. (44), and especially from the Mayo Clinic (45–47) which performed 2263 ulcer operations between 1906 and 1915 (48).

Peptic Ulcer at Mount Sinai

"Gastric Ulcer" appears in *Mount Sinai Annual Reports* continually from 1873, at first with about one case per year and increasing to five cases annually in the 1890s, but only with cases of perforation, stenosis or hemorrhage. Then, according to the 1901 report of the 1st surgical division, Fannie S., a woman of 18, was admitted with epigastric pain and massive hematemesis, which continued for six days while she was in a bed in a medical ward. When she was exsanguinated, the internist requested the surgeons to perform laparotomy, which showed a large prepyloric lesser curve ulcer with a large vessel pulsating underneath its floor. She died 14 hours later. "Epicrisis — A fundamental rule of medicine is the checking of dangerous hemorrhage. There is no reason why a dangerous hemorrhage issuing from the stomach should form an exception to this rule. It seems that in this case more prompt interference might have checked the hemorrhage and eliminated the ulcer."

TABLE

Reports of Duodenal Ulcer in the 19th Century in the U.K. and U.S.

Decade	U.K.		U.S.	
	Reports	Patients	Reports	Patients
1810–1819	2	2		
1820–1829	2	6		
1830–1839	1	10	1	1
1840–1849	9	31	2	3
1850–1859	7	20	6	9
1860–1869	7	23	5	8
1870–1879	11	42	9	10
1880–1889	9	26	13	13
1890–1899	20	51	28	57
Total — 19th century	68	211	64	101

Sources:
U.K. and U.S. reports Surgeon General's Catalogues of 1882; 3:953–955, 1899; 4:557–559 and 1923; 4:782–796.
U.K. patients: Perry & Shaw 1893–1894 (32):70 cases from Guy's Hospital, London, 1826–1892 and 131 reports published between 1810 and 1892, for a total of 201. The Surgeon General's Catalogues provided 10 more cases.

Duodenal Ulcer at The Mount Sinai Hospital

It remains unclear why duodenal ulcer was so rare at Mount Sinai until the early 1900s; possibly routine autopsies were not feasible on Jewish patients, but hemorrhage, perforation and stenosis would have been easily diagnosed while they were alive. "Duodenal Ulcer" appears in *Mount Sinai Annual Reports* as single cases in 1885 and 1893, with perforation in 1901 and 1902, as stenosis in 1903, as 5 cases of perforation in 1901 and 1902, as stenosing in 1903 and 1905, and as 5 cases of perforation in 1906, after which time the number of admissions increased each year. The 1901 admission was for right iliac fossa pain with pus found at incision at that site. However, no further exploration was done, and the autopsy showed perforations both in the duodenum 8 cm from the pylorus and in the ascending colon.

Admissions for peptic ulcer soon increased so rapidly that, in the two years 1903 and 1904, Berg's services operated on 1 duodenal ulcer and 18 gastric ulcers, of which 6 were uncomplicated, 3 each were after hemorrhage and perforation, 6 were with stenosis, and 1 was a recurrence after gastrojejunostomy (49). Such recurrences at Mount Sinai of peptic ulcer at the stoma after the then-standard operation led to the change in practice at Mount Sinai in the 1920s and 1930s from gastroenterostomy to partial gastrectomy (see chapter 10).

The commonest gastroenterological case at Mount Sinai in the19th century was calculated to be gastralgia, meaning upper abdominal symptoms (see chapter 7). In today's clinics and private offices, these symptoms are similarly frequent. Some patients are diagnosed after tests as having peptic ulcer, gastro-esophageal reflux, gall bladder ulcer or pancreatitis, but most are categorized with the neutral and unhelpful term "non-ulcer dyspepsia," because it is still unclear whether there is a disturbance of function of the stomach (dyskinesia) or a functional disturbance of the patient. In 1882, the *British Medical Journal* claimed that the cause of dyspepsia in the U.S. was ice water (50): "The prevalent dyspepsia from which Americans suffer so much, and which is so

apt to undermine the strength of the men and the bloom of the women of America, is in a large measure due, we believe, to the universal habit of drinking large quantities of ice-water. This essentially transatlantic habit has long been a speciality of which our American friends and travelers seem to be proud, complaining that they find the purest water in England undrinkable, from the difficulty of getting water to drink with lumps of ice floating about in it. Nothing can be more destructive to the utility of the process of digestion than this habit."

However, dyspepsia was and still is common in the U.K., where ice water is still uncommon, and the problem remains unsolved. The treatment of dyspepsia and peptic ulcer is discussed in the following chapter.

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14

Treatments of Peptic Ulcer

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Abstract

From the late 19th century, Mount Sinai gastroenterologists declared their scepticism of the efficacy of all recommended treatments of peptic ulcer, and looked forward to trials which could distinguish between sequence and consequence, between association and causation. The rationale of all the early studies was to reduce gastric acidity, but it soon became clear that any neutralization by single doses of antacids was brief and ineffective. Winkelstein's demonstration that patients with duodenal ulcer had higher acidities not only before and after meals but also through the night hours led him to introduce a new treatment, the alkalinized intragastric milk drip together with atropine. One of the earliest controlled clinical trials at Mount Sinai compared different antacid regimes and showed that pH values above 3.5 were achieved in only about half of the patients on the various drips. When the new anticholinergic drugs were developed in the 1950s, they were found to produce sustained hypoacidity and were tried as maintenance treatment, as an alternative to acid-lowering operations. The third Mount Sinai approach was to "attack the machinery of the acid-producing cell itself" by an inhibitor of the enzyme producing hydrogen ions. In 1939, this enzyme had been thought to be carbonic anhydrase, but when Janowitz and Hollander tested its inhibitor, acetazolamide, and showed marked but very brief acid inhibition, they concluded that its action was too brief to be therapeutically useful. The problem was to be solved decades later by H_2 receptor blockers from Britain and H^+K^+ATPase inhibitors from Sweden. **Key Words:** Acid inhibitors, antacids, anticholinergic drugs, acetazolamide, controlled trials.

IN THE LAST HUNDRED YEARS, Mount Sinai gastroenterologists have swung between critical caution and uncritical enthusiasm in their use of the countless new remedies periodically made available to the profession. Manges was particularly scathing about the use of ferments such as pepsin, rennet, papain, papayatin, papoid, caroid, bromelin, ptyalin, diastase, maltine, and takadiastase (1): "The prevailing idea is that the ferments exist in the body; therefore their administration, even if accomplishing no good, will surely do no harm. A most pernicious doctrine! . . . the sphere of usefulness of the ferments is a limited one, and although this fact is emphasized in every textbook on the diseases of the stomach, yet on account of the glamour which still surrounds the ferments, it is not practically accepted by the profession at large."

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In 1900, Manges reviewed "the unanimity which prevails among medical writers on the subject of the diet of typhoid fever," which then had to be liquid and bland. Manges was skeptical, and noted that a series of patients in Leeds, England had seemed to fare no worse when fed generously. More important, Manges then (perhaps for the first time at The Mount Sinai Hospital) cited a controlled clinical trial, in Russia, where in 1896–1897, 80 patients with typhoid admitted to one ward were well fed and, based on 12 criteria, did as well as 74 other patients who were admitted at the same time to another ward and kept on a liquid diet (2).

Although of limited value in diagnosis, the test meal was often used to assess therapy. In the early years of this century, dilute hydrochloric acid was widely used in the treatment of dyspepsia, but Crohn showed that conventional doses of HCl given infrequently had minimal effects on intragastric acidity; only large doses every 15–30 minutes were effective chemically, but in no way stimulated the mucosa (3). Similarly, Crohn confirmed that antacid neutralization depended on the

cation (sodium, magnesium) and anion (bicarbonate, oxide), the dose and the frequency of the dosage, and was followed by rebound hyperacidity (4). Crohn also studied olive oil, belladonna, bismuth and atropine, but again without any novel findings (4).

Diets were the standard treatment for ulcer for most of the 20th century, and Crohn and Reiss (5) investigated their clinical efficacy, together with their acid-lowering effect. For the first time in Mount Sinai gastroenterology, critical biometrical distinctions were drawn between sequence and consequence, and between association and causation:

> Medical treatment resulted in a net reduction of acidity in 13 out of a series of 34 cases (38 per cent). If we wish to consider only those cases with definite hyperchlorhydria, omitting all cases with iso- or hyposecretory curves, the percentage of net lowering of acidity is still lower (30.3 per cent). Of these 13 cases chemically benefited, 12 or 92 per cent, were discharged free of symptoms. Loose reasoning might lead one to see a relationship of cause and effect in these figures. But if we analyze those cases in which treatment failed to invoke chemical relief, and these comprise the larger proportion, we find, despite this fact, clinical relief in 13, or 62 per cent of them. . . .
>
> We can draw . . . inferences from these figures. . . . Only a small percentage of ulcer cases react to medical treatment by showing a reduction of acid produced during digestion (38 per cent) . . . clinical improvement can take place independently of whether the hyperacidity is relieved or whether the case remains acid-fast. . . . Medical treatment, consisting of restricted diet and rest in bed, causes the cessation of hypersecretion in 45 per cent of the cases, a fair proportion; clinical improvement takes place as often in cases with persistent hypersecretion as in those relieved of their excessive flow of gastric juice, and is apparently not dependent upon it.

In 1929, Crohn studied for the first time a proprietary antacid, colloidal aluminum hydroxide "Alusol" (Wander) and concluded that it:

> . . . seems to be the more desirable of the neutral nonabsorbable antacid salts in so far as it is an efficient agent in reducing gastric acidity to a point where symptoms are relieved but gastric digestion allowed to continue. It hastens gastric emptying; it is nontoxic and devoid of deleterious by-effects. It is clinically applicable in cases of gastric secretory disturbances characterized by hyperacidity and can be used in ulcer cases in moderate dosage over prolonged periods without the anxiety of producing or the production of alkalosis or the toxic symptoms such as may be due to the absorption of soluble alkaline salts. (6)

Winkelstein, Crohn's successor as chief of the gastroenterology clinic at The Mount Sinai Hospital, introduced several new treatments for peptic ulcer. Atropine was known to reduce gastric acidity for up to two hours after a single dose. However, when Winkelstein (7) studied 40 patients whose free acidity had been reduced after partial gastrectomy from 50–80 mmol/L down to 15–34 mmol/L, atropine immediately reduced acidity to zero for more than two hours. He concluded that with the removal of the second (chemical) gastric phase of acid achieved by the partial gastrectomy, any persisting acid secretion must be vagally driven and potentially suppressible either by a vagotomy (see above) or by atropine (7). It was only twenty years later that he pursued this antimuscarinic approach, because meanwhile he had devised a new therapy.

Winkelstein knew that patients with duodenal ulcer had higher-than-normal acidity basally, postprandially and after sham or psychic feeding (8). He then devised a new (for the U.S.) test measuring acidity every two hours from 7 PM to 7 AM and found that patients with duodenal ulcer also had high nocturnal acidity (8, 9). Measurement of acidity throughout the night, on waking and after a meal, was an important advance in testing gastric secretion, which testing needed only to be extended to hourly measurement of pH throughout the 24 hours. This was not attempted until twenty years later by James and Pickering (10) and is still one of the gold standard tests for assessing the effects of acid-lowering diets, drugs and operations (11).

Winkelstein's Milk Drip

Winkelstein therefore suggested that the standard Sippy diet with cream and milk hourly for 12 hours daily, alkalies and evening aspiration could not cope with nocturnal acidification. In 1932, therefore, Winkelstein (11) dripped through an indwelling Rehfuss tube 3 quarts of milk and 15 g of $NaHCO_3$/day, which he calculated would

theoretically neutralize 9 quarts of N/10 HCl. This novel alkanized milk drip did markedly decrease or even abolish free acidity at night: "To prevent psychic secretion, and this a point of considerable importance, food should not be seen nor discussed" (8). The treatment was given for 3 weeks together with atropine 3 or 4 times a day. The tube was then removed during the day while the patients had a Sippy regime, but the night alkaline milk drip was given as well for a further week. Symptomatic improvement occurred in hours with excellent sleep, and radiological healing of most ulcers (duodenal, gastric or jejunal) was achieved in 4 weeks, after which the patients could leave the hospital and it was feasible for them to resume the nightly drip at home if symptoms recurred.

Winkelstein's milk drip was widely used (and indeed by the author until the late 1950s) until effective acid inhibitors became available. Aluminum hydroxide, used as an antacid since 1922 and tested by Crohn in 1929 (6), was tried as an alternative to sodium bicarbonate so that Mount Sinai could then compare the biochemical effects (in one of its first controlled trials [12]). This scientific advance was almost certainly due to the arrival of Franklin Hollander in 1936 to direct the gastroenterology research laboratories, because the acidity measurements were now presented as pH and the results presented as mean pH, range and n (number of observations). The arithmetical mean nocturnal pH was calculated (deliberately and reasonably disregarding its logarithmic nature) to be and was 1.5, raised to satisfactory pH 4 by milk-bicarbonate, and aluminum phosphate or hydroxide with or without milk. However, calculations of the frequency distributions of individual pH values suggested that "no free acid, pH = 3.5–9.0, mEq/L < 1" was achieved in only about half of the patients on the various drips.

By 1945, Winkelsein (13) could report on 13 years' experience with the drip, which was now given through a soft latex tube rather than the semirigid Levin tube: "most of these patients are 'tube broken' having had various gastric analyses performed upon them, so that they do not find the method drastic or difficult." However, only 22 of 60 ulcer patients refractory to Sippy therapy responded to the milk drip. Nevertheless, the Mount Sinai group made a motion picture (14). The final development of the alkaline milk drip was to omit both alkali and milk and instead use a high-calorie, high-protein, high-neutralizing powder (15), which Winkelstein (16) claimed produced a favorable response on 35 of 40 private patients who were refractory to conventional ulcer therapy including anticholinergic drugs.

Winkelstein, throughout his long career, held that "the pathologic physiology of peptic ulcer is mediated through the dorsal vagi and nerves" (17) and he therefore encouraged both the addition of vagotomy to gastroenterostomy and partial gastrectomy as well as the nocturnal alkaline milk drip, while awaiting the marketing of a "medical vagotomy." That Winkelstein believed the precipitating cause of vagal hyperactivity was "an emotional psychogenic disturbance" will be discussed separately.

Anticholinergics

Winkelstein studied several of the new anticholinergics developed in the 1950s. In uncontrolled studies with methantheline bromide and despite minimal inhibition of basal and nocturnal postprandial or insulin-stimulated acidity "in an experience of 25 years with large numbers of ulcer patients, I have not encountered a drug which provides such excellent clinical results in such a large percentage of cases" (17). However, oxyphencyclimine (18) markedly inhibited the volume and acidity (by pH paper) of morning gastric juice residue 11 hours after 20 mg given at 9 PM, and similarly for juice volume three hours after 20 mg given with breakfast. All 96 patients had dry mouth but only 4 had to stop because of other side effects. Symptomatic response was good, encouraging Winkelstein for the first time to use the drug as maintenance treatment for a year or more. A third new anticholinergic, endobenzyline bromide, also gave favorable acid-reducing and clinical results (19).

Winkelstein was receptive to any novel rational therapy for peptic ulcer, such as increasing mucus secretion. Hollander had shown eugenol to be an effective mucigogue (20), so this compound was given to 14 patients, with the usual mixed response (21). Presumably because of the scientific background of Hollander, this was the only one of Winkelstein's papers on ulcer therapy which included conclusions such as "no correlation was found between clinical response and laboratory findings (x-ray and acidity curves). Because of this, and also because of the demonstrated lack of reliability of the patients' statements, we were unable to report any unequivocal beneficial effect of eugenol therapy . . ." (21). Another rational therapy which proved unsuccessful was physically induced pyrexia (22).

Enzyme Inhibitors

Hollander and Janowitz (23) categorized three mechanisms for reducing gastric acid in the treatment of peptic ulcer. The first, neutralizing acid already secreted into the lumen by antacids, had been studied at Mount Sinai (see above). The second, blockers of acetylcholine, had long been available in their natural forms of belladonna and atropine. New anticholinergics were synthesized in the 1940s and became available both for studies of animal and human gastric secretion and for treatment of peptic ulcer. Some of these drugs were tested at Mount Sinai (see above). However, homatropine, methscopolamine, methantheline, propantheline, oxyphenonium, penthienate, diphemanil, mepiperphenidol and dibutoline were not major clinical advances, because reductions of gastric acidity were slight unless dosage was so large as to cause adverse effects in other parts of the body, especially the eye, the bladder and the bowel.

Thus, a third approach was conceived (23): "The search for an ideal therapeutic agent would be to attack the machinery of the acid-producing cell itself." The compound they tested was acetazolamide, one of the potent inhibitors of carbonic anhydrase, the enzyme which catalyzes the hydration of carbon dioxide. In 1939, Davenport (24) showed that this zinc-containing enzyme was most concentrated in acid-secreting mucosa, and was correlated in cat and rat with the density of parietal cells. He suggested that it hydrated carbon dioxide to carbonic acid, which was ionized to hydrogen ions to be secreted into the lumen, and to bicarbonate ion to pass into the bloodstream.

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

Davenport therefore suggested that carbonic anhydrase might be an essential agent for acid formation, and if it was, then an inhibitor of this enzyme would inhibit gastric acid secretion. Unfortunately, the early inhibitors such as sulfanilamide failed to inhibit gastric acid, and in 1946 Davenport retracted his theory (25). However, when newer inhibitors of carbonic anhydrase became available, the Mount Sinai group tested acetazolamide first in the dog (26) and then in man (27, 28).

In dogs with Heidenhain pouches, acetazolamide given intravenously in bolus doses of 5–120 mg/kg led after 20–80 min to inhibition of histamine-stimulated acid output lasting 3–6 hours, and with doses of 20–60 mg/kg, the reduction in acid ranged from 70–97% with no obvious side effects (26). Similar studies in humans in whom acetazolamide 35–154 mg/kg was infused intravenously over 1 to 8 hours showed profound and dose-related inhibition of 4–100% of histamine-stimulated gastric acid. A dose of 100 mg/kg produced 97% inhibition of basal acid output. With doses above 114 mg/kg, some subjects became breathless and anxious, and noted tingling of the extremities (27). Given orally, acetazolamide 30 mg/kg was ineffective, and while doses of 45–79 mg/kg did profoundly inhibit gastric acid, the effect lasted only one hour (28). Thus, while these studies did show a convincing role of carbonic anhydrase in catalyzing the removal and extrusion into the bloodstream of bicarbonate released by the secretion of HCl into the lumen, the drug, given orally, produced too short an inhibition for therapeutic usefulness when taken in tolerable doses (29).

Nevertheless, Hollander, in this innovative attempt at acid-lowering ulcer healing by inhibition of a specific enzyme inside the parietal cell, was prescient in his prophecy:

> We have serious hope that, within the next few years, there will be available to clinicians some chemical substance which blocks an enzyme which is more or less specific for the parietal cell — perhaps an enzyme which operates within the wall of the intracellular canaliculus, where we believe the hydrogen ion is separated to form hydrochloric acid. When this happy day comes, I think that duodenal ulcer will, in great measure, be removed from the category of surgical disease and became one which responds very early, very simply to medical therapy. (30)

However, the new inhibitors were not to come from The Mount Sinai Hospital or even from the U.S.; they came from Britain as H2 receptor blockers (cimetidine, ranitidine) and from Sweden as H^+K^+ATPase inhibitors (omeprazole). Thus, peptic ulcer was "removed from the category of surgical disease" by powerful new acid inhibitors even before these were superseded by therapy eradicating *Helicobacter pylori.*

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The Pancreas

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Abstract

Pancreatic secretion was first studied at The Mount Sinai Hospital by Crohn in 1912, but measurements of pancreatic enzymes in duodenal aspirate or feces were found unhelpful in diagnosis. Such pancreatic tests fell into disuse because of advances in radiology of the biliary tree in the 1920s. Once extracts of secretin and cholecystokinin-pancreozymin became available from Sweden in the 1930s, it became possible for the biochemist Franklin Hollander and the surgeon David Dreiling to develop pancreatic secretion tests into practical procedures for the diagnosis of benign and malignant diseases of the pancreas and biliary tree, and produce physiological studies of the mechanisms of ion transport. With more purified hormones, it became possible to measure maximum (alkaline) bicarbonate output of the pancreas analogous to the maximal acid response of the stomach to an augmented histamine test, and to determine whether patients with duodenal ulcer had decreased neutralization of gastric acid in the duodenum. Clinical studies were also directed to the pathophysiology of acute relapsing and chronic pancreatitis and carcinoma. However, advances in imaging and endoscopy have now shifted the thrust of pancreatology. **Key Words:** Pancreatic secretion, secretin, cholecystokinin-pancreozymin, pancreatitis, pancreatic carcinoma.

AS WITH THE STOMACH, there was close collaboration between the departments of medicine and surgery at The Mount Sinai Hospital in their studies of pancreatic physiology and disease.

Pancreatic Secretion

Crohn's chief, Dr. Julius Rudisch, was a friend of Dr. Max Einhorn (1862–1953) of the German (later Lenox Hill) Hospital, an early specialist in gastroenterology (1). Einhorn was one of the first to investigate the duodenal juices, and on a visit to The Mount Sinai Hospital presented two of his inventions, a duodenal bucket on a string and the flexible duodenal rubber tube, to Dr. Rudisch, who passed them on to Crohn because, according to Crohn (2), Rudisch was interested only in diabetes and not in gastroenterology. However, Rudisch certainly was interested in hepatogastroenterology and wrote on acute yellow atrophy of the liver (3). Moreover, in Crohn's own memoirs (4), The Mount Sinai Hospital attending in the anecdote is not Rudisch but Dr. Nathan Brill (who had written on primary carcinoma of the duodenum [5]). In 1912 Crohn, with the help of Dr. Bookman, the hospital biochemist, began his secretory studies.

> In order for me to study the diseases of the pancreas, it was important first to establish the norm. To put ward patients through the test, which is uncomfortable for even healthy persons, seemed an injustice. Who was more normal and more accessible than myself? Night after night, at bedtime, I would swallow that 36-inch long rubber catheter, drink a glass of milk to stimulate pancreatic secretion and go to sleep. In the morning I would aspirate the pancreatic secretions and the bile from my duodenum. The tube constituted no great discomfort or inconvenience and on every afternoon the secretions would be tested and the normal pancreatic enzymes evaluated at the laboratory. (4)

Statistics and biometry were not then used in clinical measurements. Crohn determined the

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normal ranges for the various constituents of the duodenal aspirate from samples of aspirate obtained 2 1/2 hours after 8 ounces of milk which he drank at 6:30 AM. Samples were analyzed for amylase, lipase, and alkali protease in both duodenal aspirate and feces. Values were also obtained from patients with gallstones, pancreatitis and carcinoma, cirrhosis and diabetes (6). He was able to show the presence of normal pancreatic enzymes and the absence of bile in a 10-week-old infant in whom the bile ducts were absent (7).

Crohn tried to diagnose tumors involving the terminal bile and pancreatic ducts (8) and to distinguish between different causes of jaundice, such as cholecystitis and lithiasis, catarrhal jaundice and impacted common bile duct stones, and between benign and malignant strictures of the biliary system, pancreatitis, carcinoma of the pancreas, and liver cirrhosis (9, 10).

In this series of papers (6–10), Crohn always reviewed the literature (usually including the many tests devised by Einhorn) and disclaimed any fundamental novelty in his studies, or in his assessment of duodenal lavage with magnesium sulfate (11) or his experimental studies on gall bladder physiology at Cornell (12).

The Lyon test continued in use at The Mount Sinai Hospital at least until 1923 (13): "Since gall bladder disease, with its protean clinical manifestations, is a frequent cause of intra-abdominal symptoms (second only to disease of the appendix), this test should be included as . . . routine in the study of gastro-intestinal cases."

The Department of Physiologic Chemistry at The Mount Sinai Hospital continued to improve the assays for rennet and other pancreatic enzymes (14–16) and also performed the first quantitative measurements of the enzymes in juice draining from a pancreatic fistula (17). Pancreatic tests then fell into disuse, partly because they added little to clinical diagnosis, but mostly because of advances in radiology of the biliary tree in the 1920s.

Pancreatic Secretion Tests

Soon after Hollander came to Mount Sinai to direct the Gastroenterology Research Laboratory, Einar Hammarsten, professor of chemistry at the Karolinska Institute, Stockholm, came to give the 1938 Janeway Lecture on "The Secretin of Bayliss and Starling" (18). In it, he reviewed the work in his department to purify and crystallize this hormone and to prove that it was different from cholecystokinin and incretin. In this lecture, he referred to reports by Agren and Lagerlöf, and Agren, Lagerlöf and Berglund, and Lagerlöf, in which this secretin was used to test pancreatic secretion, using a double tube to aspirate gastric and duodenal juice separately over 60 minutes, and measuring volume, bicarbonate, diastase, trypsin and lipase.

It was this Stockholm test that Diamond (19) introduced in the United States and which Hollander's group then used extensively both in dog and man for more than 30 years. In July 1946, Dr. David Dreiling succeeded Dr. Henry Doubilet as the Dr. Ralph Colp Fellow in Experimental Surgery. At the time of Dr. Dreiling's graduation from the house staff, Dr. Colp called him in and said, "Dreiling, you can join me in my office and make a lot of money, or go into the lab and do research on biliary and pancreatic physiology. You'll get only $600 a year. Take your choice." Dr. Dreiling made his choice, and several books and 260 papers later, praised the foresight of the man who, though a brilliant clinical surgeon, understood the inadequacy of the scalpel in solving complex physiologic problems (20).

Dreiling added the secretin test "to the diagnostic armamentarium of the Hospital" after a preliminary series of 93 controls and 52 patients with disease, using different sources (Astra, Wyeth) of secretin (21). Dreiling and Hollander then expanded the control series to 172 and used proper statistical analysis to provide a normal range for 80 min volume, maximum bicarbonate concentration and amylase concentration, and calculated that data scatter (represented by coefficient of variation) would be minimized by expressing outputs on a per kilogram basis and using Lagerlof's 80 min collection rather than shortening it to 40 min (22).

In his third study, in which duodenal aspirate was also analyzed for icteric index, Dreiling (by now a George Blumenthal Jr. Fellow) found that of 98 patients with complaints after cholecystectomy, only two had abnormal pancreatic secretion (one with carcinoma and one with chronic pancreatitis). Responses in four other patients with a biliary pigment were suggestive of surgically remediable organic common duct obstruction (23). A series of papers reported studies on patients with obstructive jaundice, pancreatic insufficiency and cholecysto-enteric anastomosis (24), tumors in and about the pancreas, diabetes mellitus (25), and pancreatitis and various gastrointestinal diseases (26). The normal ranges for pancreatic secretion after Lilly secretin (> 2.0 mL/kg, HCO_3^- > 90 mEq/L, amylase > 6 U/kg) were established in 123 controls (27) and, unlike gastric secretion, were little affected by sex or age (28).

When potent injectable pancreozymin became commercially available (Boots, Vitrum) this enzyme-stimulating hormone was injected before the secretin (29). "Sporadic attempts at cytologic examination of duodenal aspirates had been made in this laboratory since 1948, when the first case of cancer of the pancreas had been diagnosed by demonstrating cancer cells on the duodenal smear, but a systematic investigation was not possible until the cooperation of a trained cytologist (H.E.N.) was available at the hospital" (30). Provocative blood tests (the serum amylase response to morphine, secretin, methacholine and bethanechol singly and in combination) were of no value in the diagnosis of pancreatic disorders (31).

Dreiling's classification of pancreatic deficiency states remained little altered for over 30 years:

- *Total insufficiency* (low volume, bicarbonate, enzyme) indicated extreme destruction, as in end-stage pancreatitis or advanced pancreatic cancer;
- *Qualitative insufficiency* (low bicarbonate concentration with normal flow) indicated chronic pancreatitis;
- *Quantitative insufficiency* (low flow with normal bicarbonate and enzyme concentrations) indicated ductal obstruction, as in pancreatic cancer;
- *Isolated enzyme deficiency* (with normal flow and bicarbonate) was seen in nutritional pancreatic fibrosis, sprue and inflammatory bowel disease;
- *Hypersecretion* indicated hypertrophy and hyperplasia of the hepatic and ductal systems, as in cirrhosis and hemochromatosis (29, 32–34).

As for the pancreozymin-secretin test (32): "The combined test was discontinued after 1000 tests because of the additional expense, more frequent reaction, the equivalence of information, and the lack of availability of CCK-PZ for clinical use in the USA."

The international reputation of The Mount Sinai Hospital for pancreatic research was recognized when the 1970 World Congress of Gastroenterology selected Dreiling to give one of the Quadrennial Reviews, initiated at this Copenhagen meeting, on "The early diagnosis of pancreatic cancer" (35). The data on 401 patients with pancreatic cancer showed 95% accuracy for carcinoma of the head of the pancreas, but decreasing accuracy for the body (83%) and the tail (81%). Cytologic accuracy was 82%, 89% and 75% for these parts of the pancreas. "Further refinements in exocrine secretory techniques, such as newer stimulants, altered protocols, and augmented secretory capacity, may complicate the testing but are not likely to provide much more significant data. Let me conclude with the prediction that accuracy and early diagnosis are most likely to result from advances in pancreatic scanning. . . ." (35), a prediction fully justified by our current ultrasound, CT, MRI, angiography and serologic tests.

Pancreatic Physiology

Although pancreatic secretion became a routinely available diagnostic test at Mount Sinai, research in gastrointestinal physiology assumed greater importance, especially after the return of Dr. Henry Janowitz in 1948 after World War II. Neither vagotomy (36), histamine, histalog (37) nor glucagon (38) had any direct effect on pancreatic secretory flow, bicarbonate concentration or enzyme output. However, the carbonic anhydrase inhibitor acetazolamide (Diamox) given intravenously to dogs led to 95% inhibition of secretin-stimulated duodenal juice volume and 60% inhibition of bicarbonate secretion (39); there were similar marked inhibitions of duodenal juice volume (40), and hepatic bile output (41) in man. Dreiling and Janowitz's studies of the secretion of electrolytes (42, 43) in the above studies and in those where various anticholinergic piperidyl drugs inhibited fluid but not bicarbonate concentration (44), led them to the following conclusions at the 1962 Ciba Symposium (45): (1) specialized cells of the pancreas secrete HCO_3^- by an active transport mechanism whose nature is unknown at present; (2) the HCO_3^- of pancreatic juice is derived in part from metabolic CO_2 and in part from the HCO_3^- of the blood; (3) carbonic anhydrase activity is required for high rates of secretion; (4) the carbonic anhydrase functions in part to maintain a critical intracellular pH-CO_2 range; and (5) probably as the HCO_3^- solution moves down the collecting system it undergoes an exchange with Cl^- of the interstitial fluid or blood (the existing concentrations favoring this).

Pancreatic Secretion in Animals

It was impossible to study pure pancreatic duct juice uncontaminated by biliary and intestinal secretions in human subjects until the introduction of endoscopic retrograde cholangio-pancreatography (ERCP); thus, the human studies described

above were of duodenal aspirate. Dogs can be equipped with a chronic duodenostomy cannula through which the papilla of the pancreatic duct can be cannulated under direct vision with a bent glass capillary tube. This Thomas and Crider technique (46) was used for many years at Mount Sinai and was described in detail by Hollander's group (46).

While enzyme secretion of the pancreas had long been known to be stimulated by the vagus nerves, the bicarbonate and water outputs were usually attributed to stimulation by secretin, so that increases in both volume and bicarbonate secretion of secretin- or histamine-stimulated pancreatic juice after supradiaphragmatic vagotomy suggested that the vagi do contain inhibitory fibers (47).

When I came to work with Dreiling and Janowitz in 1961, I suggested that the commercial availability of the more purified Jorpes-Mutt preparation of secretin from Vitrum provided an opportunity to attempt to evoke a maximum (alkaline) bicarbonate output of the dog pancreas analogous to the maximal acid response of the stomach (I had been researching this in England, by measuring peak acid output [48, 49] using Kay's novel augmented histamine test [50]). With Claude Perrier of Geneva we did achieve maximum bicarbonate output with either single intravenous injections or continuous intravenous infusions of secretin, and we were able to produce inhibition by supramaximal doses (51).

We showed that the dog pancreas could secrete about one-third as much alkali as the stomach could secrete acid (52). There was, however, no significant correlation between maximum bicarbonate output and maximum acid output (52). Nevertheless, there was a highly significant correlation between maximum bicarbonate output and weight of pancreas (52), a finding studied by Jack Hansky and Oswaldo Tiscornia (53), who concluded that the female dog pancreas could secrete 0.08 mEq bicarbonate/g, a figure identical to that found in normal female human subjects. Hansky and Tiscornia also achieved maximum amylase output with either single intravenous injections or continuous intravenous infusions of pancreozymin (Cecekin, Vitrum) (54). Moreover, a combination in a single injection of a maximal pancreozymin dose with a maximal secretin dose evoked the maximal amylase, fluid and bicarbonate secretory capacity of the pancreas (54).

The Augmented Secretin(-Pancreozymin) Test

There was no general agreement on whether the diagnostic discrimination between normal subjects and patients with chronic pancreatitis would be better with a submaximal or a maximal dose of secretin. Agren and Lagerlöf (55) injected 3 cat units kg: "We have chosen this as our standard dose since there are reasons to believe that in pathological conditions . . . a subnormal function will be easier detected after submaximal stimulation." With the demonstration of a maximum bicarbonate output of the dog pancreas, it was suggested that "the measurement of maximum secretory capacity in man may allow more quantitative assessment of secretory impairment" (51).

There have been many human studies of this augmented secretin test with the proprietary Boots preparation, the Vitrum preparation or pure G.I.H. (GastroIntestinal Hormone, Karolinska Institute) secretin given as a single injection or as a continuous intravenous infusion. Dreiling's group compared the standard with the augmented secretin test in 366 patients (56). In 130 without pancreatic disease, the mean (SD) volume response doubled from 3.2 (0.6) to 6.3 (0.9) mL/kg, with the lower limit of normal (LLN) also doubling from 2.0 to 4.5 mL/kg. The maximum bicarbonate concentration increased only slightly, from 110 (10) to 117 (12) mEq/L and its LLN from 90 to 93 mEq/L, and output from 21.6 (4.7) to 40.7 (9.1) mEq/80 min and LLN from 12.2 to 22.5. The amylase secretion increased markedly from 21.4 (7.4) to 36.7 (14.2) U/kg and its LLN from 6.6 to 8.3 U/kg. However, in patients with pancreatic insufficiency, volume flow and bicarbonate secretion did not increase to the same degree as in normal subjects, and in patients with pancreatic cancer there were no significant increases in flow or bicarbonate with the augmented dose of secretin. Thus, the augmented secretion test both corroborated and enhanced the diagnostic discrimination of the standard test.

Some studies suggested that an augmented secretin test of maximal or near maximal bicarbonate output did improve diagnostic discrimination (57, 58). In one small series, we found that peak bicarbonate output in response to either a submaximal or near-maximal dose of secretin provided absolute discrimination between 10 male control subjects and five men with chronic pancreatitis (59). In Norway, full dose-response studies in healthy volunteers and in patients with chronic pancreatitis showed that diagnostic discrimination was better with a G.I.H. dose of 0.7 clinical units/kg/hr than at lower or higher doses (60).

Interpretation of Secretin Tests

A low volume even with normal concentrations suggests a carcinoma. Low concentrations even with a normal volume indicate chronic pancreatitis. The combination of a low volume and low concentrations of bicarbonate and enzymes expresses severe exocrine insufficiency. Hypersecretion may occur in some phases of pancreatitis, hemochromatosis and cirrhosis. Diagnostic discrimination may be improved by considering volume and bicarbonate concentration together, or by calculating bicarbonate output. Wormsley has emphasized that the bicarbonate concentration should always be assessed in conjunction with the secretory rate (57). A high bicarbonate concentration denotes a normal bicarbonate secretory capacity. I found that with high rates of secretion in response to large doses of secretin, the bicarbonate concentration may decrease as the volume increases (61), so that a low bicarbonate concentration does not denote a low secretory capacity unless the volume is also low. Wormsley has also re-emphasized that a low bicarbonate output may represent a small response from a normal gland with a high threshold or low sensitivity to hormonal stimuli; only if a repeat test with a near-maximal stimulus results in a low output can the pancreas be definitely classed as abnormal.

Let Dreiling have the last word (56): "In clinical practice a standard secretion test is sufficient when normal results are obtained. If a low or borderline volume or maximum bicarbonate response is encountered, the standard test should be followed by an augmented test with the expectation that any questionable abnormality in secretion will not only be confirmed, but enhanced."

Gastric Acid and Pancreatic Alkali

It has long been appreciated that the pH in the human postbulbar duodenum normally remains neutral in spite of being exposed to several liters per day of gastric juice of pH about 1. But the relative neutralizing powers of food and antral, duodenal, jejunal, biliary and pancreatic secretions were uncertain. Once measurements of maximal secretory capacity of both the stomach (50) and the pancreas (51) become available, the hypotheses that pancreatic secretion might be correlated with, and/or neutralize gastric secretion could be tested. In the two Mount Sinai studies, maximum bicarbonate output of the dog in response to secretin alone ranged from 2.4 to 4.6 (mean 3.3) mEq/15 min (51) and to secretin and pancreozymin from 2.6 to 4.3 (mean 3.2) mEq/15 min (54). Thus, bicarbonate outputs expressed as a proportion of maximum acid output in the same dogs ranged from 19–45% (mean 30%) (52), a proportion similar to the one-third found in dogs by Preshaw and Grossman (62). Although Perrier and I (51) found no significant correlation between maximum bicarbonate and acid outputs in the dog, on my return to London I was able, with Gutierrez, to find a correlation in humans. Bicarbonate secretory capacity in patients with duodenal ulcers was normal and comparable to gastric acid secretory capacity (63). We found that the basal bicarbonate output of the duodenal aspirate in patients with duodenal ulcers was only half that of control subjects, and suggested this might lead to decreased neutralization of gastric acid in the duodenum.

Hypersecretory States

Certain patient groups showed marked hypersecretion of volume and bicarbonate output (64). In patients with Zollinger-Ellison syndrome these are doubled, presumably due to the high acid load entering the duodenum (and thus increased release of secretin), together with the pancreas-stimulating effect of the ectopic gastrin. In hemochromatosis, these outputs may be triple normal, suggesting either increased sensitivity of the ductular parenchyma to secretion or increased ductular cell mass. However, in patients with cirrhosis, part of the hypersecretion must come from increased output of bicarbonate in bile from the hepatic ductular system.

Pancreatitis

At the end of the 19th century, Manges reported a woman of 21 with an acute abdomen, found at laparotomy by Dr. Gerster to have acute pancreatitis with fat necrosis. She was only the fourth patient in the literature "in which recovery has followed operative interference in acute pancreatic disease" (65). Half a century later, Dreiling and Janowitz extended their physiological measurements of pancreatic exocrine secretion in man and dog toward the study of the etiology and pathogenesis of pancreatic inflammation. Much of this work was summarized in the 1962 Ciba symposium (45) and their 1964 monograph (66).

These studies were occasionally clinical. Thus, from 1945 to 1959, 417 patients were admitted to Mount Sinai with pancreatic cancer as well as 100 with chronic pancreatitis (51 with biliary disease and 33 with alcohol excess), of whom 24 had calcinosis: six of these 24, and none of the 76 without calcinosis, had pancreatic cancer (67). In the dog, calcium was secreted not

with the secretin-stimulated electrolyte component, but with the pancreozymin-stimulated enzyme fraction (68). The chronic effects of alcohol on the pancreas had been extensively studied elsewhere, but acute intravenous infusions of alcohol in dogs, in doses giving comparable blood levels (25–29 mg/100 mL) to those in human drinkers, produced prompt and marked inhibition of flow rate and bicarbonate concentration. This was thought to be due to an effect on the electrolyte transport systems (69). Patients with chronic pancreatitis with typical low post-secretion volume and bicarbonate concentration showed differences by etiology: those with biliary tract disease had higher volume and bicarbonate concentrations than those with alcoholic pancreatitis (64). Most interesting were alcoholics with no symptoms or signs of either hepatic or pancreatic diseases; they showed high volume with lower bicarbonate concentration, that is, pancreatic hypersecretion (64). This pancreatic hypersecretion also had been found in patients with cirrhosis and hemochromatosis (see above). It was suggested that this hypersecretion might represent an "initial reaction of the pancreas to injury, normally ductular reduplication and hypertrophy. As the inflammation and fibrosis continues, the increased flows return towards normal . . . accompanied by a marked fall in bicarbonate concentration. The final stage of low flow, low bicarbonate, and low enzyme secretion, corresponds . . . to the more advanced . . . fibrosis, atrophy and calcification" (64). Of 17 alcoholic patients who underwent secretin tests annually for 10 years, in 11 patients who continued to drink, the observed early increased flow rate returned to normal in 2–3 years and then, together with the bicarbonate concentration, continued to decrease. In the six patients who stopped drinking, these measurements increased (64, 70), suggesting pancreatic ductular cell regeneration after injury.

This problem of pancreatic regeneration was pursued in the dog, in which (as in man) obstruction of the pancreatic duct leads to atrophic degeneration. Immediate microsurgical reanastomosis of a cut pancreatic duct prevented these changes. If ductal reconstruction was satisfactorily performed, then exocrine secretion, histology and pancreatography recovered within 13 to 44 days after the duct was cut (71, 72). This exocrine functional recovery after ductal decompression, alloxan (73), and ethionine (74), led Dreiling and his colleagues to give an affirmative answer to their rhetorical question (75), "Does the pancreatic gland regenerate?"

Further dog studies tested the Janowitz and Dreiling preference for the exchange rather than the admixture model of the ionic composition of pancreatic juice (45). For the sum of Cl^- and HCO_3^- to be constant, yet Cl^- to vary inversely with HCO_3^- then the isotonic primary HCO_3^- secretion must be altered by either an exchange of luminal HCO_3^- for interstitial Cl^- in the ductular system, or an admixture with a low HCO_3^- concentration interstitial fluid. Both stop-flow (76) and duct perfusion (77) studies showed both loss of HCO_3^- and increases in Cl^- consistent with the exchange hypothesis.

Various metabolic and endocrine effects on exocrine pancreatic secretions were studied in animals and man at The Mount Sinai Hospital (78). A ten-year follow-up of a patient with type V hyperlipoproteinemia observed both recurrent attacks of abdominal pain and progressive impairment of pancreatic juice volume, bicarbonate concentration and enzyme output (79). Hypophysectomy in the dog depressed maximally stimulated pancreatic function, and this suppression could be partly reversed by administration of ACTH or corticosteroids (80), just as the decreased exocrine maximal outputs after bilateral total adrenalectomy were partly corrected by intravenous aldosterone (81).

Although the Mount Sinai researchers focused on the volume flow and bicarbonate concentration and output, amylase was also studied, as were other enzymes such as desoxyribonuclease I (82). Amylase in serum was confirmed as electrophoretically heterogeneous, with a probable hepatic component not reduced by pancreatectomy (83); moreover, the elevated amylase in acute pancreatitis could be partly due to reduction of a normally present amylase inhibitor (82). False positive diagnoses of acute pancreatitis due to macroamylasemia could be avoided by also measuring urine amylase and creatinine routinely and calculating the amylase-creatinine clearance ratio (84).

The phenomenon of hyperlipemia in acute pancreatitis, whether in patients or experimental animals, was studied by Jacques Kessler (85), who demonstrated lipoprotein lipase (LPL) activity in canine pancreas and in pancreatic juice and the juice LPL stimulated by secretin and pancreozymin administration. However, LPL activity increased with progressive dilution of the juice, suggesting the presence of an inhibitor and raising the possibility that pancreatic necrosis either releases an inhibitor which interferes with the normal clearing mechanism of plasma triglycerides or releases a source of LPL.

Comment

In the early years of this century and again from the mid-1940s to the 1970s, Mount Sinai gastroenterologists had a major interest in the pancreatic physiology and pathophysiology of acute relapsing and chronic pancreatitis and carcinoma. However, in recent years, pancreatic research elsewhere has moved to imaging and tumor markers with improvement in early diagnosis even if these did not lead to great changes in medical or surgical treatment.

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16

The History of Liver Disease at The Mount Sinai Hospital

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Abstract

Diseases of the liver and biliary tract interested the physicians of The Mount Sinai Hospital from the time the hospital started until the present. Indeed, the institution has become a well-recognized center for the study of the liver and its diseases. During the first 75 years of the hospital, there were many admissions for hepatobiliary diseases, resulting in many case reports. The evolution of the hospital into a teaching hospital brought with it a more systematic method of studying diseases, not only in Pathology under Paul Klemperer, but in Clinical Chemistry and Microbiology as well. Liver biopsy was also attempted. With the arrival of Hans Popper in 1957, the emphasis shifted to coordinated studies of both normal and abnormal liver structure and function in diseases. Soon, Liver Diseases (Hepatology) was split from Gastroenterology, with Fenton Schaffner as the first chief. Over the next 30 years, more than 1000 papers, chapters and books were published. The main areas of research were fibrosis, cholestasis (especially morphology and bile salt metabolism), toxic liver injury, metabolic transformations and carcinogenesis. Primary biliary cirrhosis and viral hepatitis were and continue to be special interests. Fellows from all over the world were trained and many moved on to leadership positions. Although he was active in the development of the liver transplant program, Popper did not live to see its start. A new generation of hepatologists maintains the interest and position of The Mount Sinai Hospital in this important field of medicine. **Key Words:** Liver disease, history, The Mount Sinai Hospital.

LIVER DISEASE had been an uncommon reason for admission to The Mount Sinai Hospital in the first one hundred years of its existence, but this has changed in the last fifty years. The Mount Sinai 100th anniversary issue of the *American Journal of Medicine*, published in November 1952 with George Baehr as guest editor, contained reprints of what were considered the most significant contributions to medicine from the hospital. None was related to the liver. Included in this issue of the *American Journal of Medicine* were an informative forward by Baehr and an article on the founding and the early days of Mount Sinai, written by Eli Moschcowitz.

The first recorded death from liver disease at Mount Sinai was in 1861 from primary hepatocellular carcinoma. The decade 1897–1907 saw a total of 67 patients with such tumors admitted to the hospital, while in 1986–1995, 183 were admitted. However, 890 patients with hepatobiliary diseases were hospitalized from 1897–1907, while in the recent last decade, 4347 were admitted. During the 19th century, contributions from Mount Sinai to the medical literature concerning liver diseases consisted of case reports of unusual conditions or unusual presentation of common diseases, mainly cysts and abscesses. Two were in the newly established *Mount Sinai Hospital Reports*, which first appeared in 1899 (1, 2). This became the *Journal of the Mount Sinai Hospital* in 1933. Between 1900 and 1904, four cases of rapidly fatal liver disease, termed acute yellow atrophy, were seen in young women (3, 4). Despite careful study and autopsy examination, no cause was found, although pregnancy may have been a factor in two. Such individual case reports of unusual cases of liver diseases have continued to appear, albeit less frequently. Series of cases were reported soon after the turn of the century (5, 6). Now very large series, natural history studies, controlled trials and experimental

George Baehr Professor of Medicine Emeritus, deceased.

data related to the liver make up the bulk of publications, in addition to books, book chapters and periodicals.

Many factors contributed to the shift in direction of the role of Mount Sinai in hepatology. The first was that the institution became a teaching hospital at the turn of the 20th century, with the start of an intern training program. Medicine, surgery and pediatrics were established as separate disciplines, with the development of the "giants" of the hospital's history, including Albert Berg in Surgery, Emanuel Libman in Medicine and Abraham Jacobi in Pediatrics, to name just a few. Chronic jaundice in those days was considered to be obstructive in nature and mainly a surgical condition (7).

Shortly after Word War I, Paul Klemperer was appointed as the first full-time chairman of the Department of Pathology. This was a second factor in the development of interest in liver diseases at Mount Sinai. Klemperer and his coworker, Sadao Otani, began to describe hitherto unrecognized conditions, first in the innovative clinical pathological conferences published in the *Journal of the Mount Sinai Hospital* or its predecessor. Collections of some of these unusual cases led to the establishment of lupus erythematosus, thrombotic thrombocytopenia, giant follicular lymphoma and regional enteritis as disease entities. Klemperer described chronic intrahepatic obliterating cholangitis but did not connect this condition with inflammatory bowel disease (8). Rare tumors of the liver like primary sarcoma were reported (9) and primary hepatocellular carcinomas were the subject of clinical pathological conferences (CPCs) reported in the *Journal of the Mount Sinai Hospital* (10). Numerous cases of parasitic diseases of the liver and abscesses also were published in *The Journal* in the form of case reports or CPCs. Jaundice in heart failure was ascribed largely to hepatic anoxia (11), but three years earlier pulmonary infarction with excess bilirubin production was blamed (12). Arthur Sohval wrote an extensive review of hepatic complications of polycythemia vera, including descriptions of hepatic and portal vein thromboses, and the appearance of cirrhosis in some cases (13). Adverse hepatic drug reactions were beginning to be recognized, especially with cinchophen (14) and arsenicals (15) and experimental production of these in laboratory animals was attempted (15, 16). Reuben Ottenberg and Rose Spiegel compiled a detailed description of jaundice due to various chemicals, which served as the standard reference on the subject for many years (17).

A third factor contributing to the establishment of hepatology at Mount Sinai was the utilization of the clinical chemistry and later, the microbiology laboratories, in a systematic fashion. This was part of the global trend of moving away from empiricism to scientific medicine. Nitrogen metabolism was studied at various stages of medical and surgical hepatobiliary diseases (18) and in the hepatorenal syndrome (19, 20). Early attempts were made to investigate bilirubin and bile salt metabolism (21). New laboratory tests for assessing liver function were evaluated (22). One interesting test detected benzoyl glucuronide after administration of hippuric acid (23). This was devised by Isidore Snapper, who arrived from China in the early years of World War II. He had previously described the test for and significance of direct and indirect bilirubin with van den Bergh in Amsterdam just before the First World War. Snapper never associated glucuronide formation with bilirubin metabolism, although he lived to see direct bilirubin discovered to be bilirubin glucuronide. Mount Sinai joined the debate about whether catarrhal jaundice was the result of inflammation of bile ducts or necrosis of liver cells (24). The role of medications such as arsphenamine (25) and cinchophen (26) in causing jaundice that resembled hepatitis was explored. Just prior to World War II, attempts were made to biopsy the liver percutaneously by Edgar Baron (27) and just after the war by punch at surgery by Edward Jemerin (28). Percutaneous needle biopsy at this time did not succeed because bleeding could not be adequately predicted or controlled. The war itself offered the opportunity for the many Mount Sinai physicians in military service to see numerous cases of hepatitis, no longer called catarrhal jaundice and recognized to be either infectious or transmitted via serum. The heightened interest in liver disease resulted in the publication of the first large American textbook on diseases of the liver by Solomon Lichtman, which appeared shortly after the war. It went through three editions and was the standard mid-century text on the subject (29). A liver clinic was started as an adjunct to the GI clinic, with Alexander Richman as chief and Albert Parets as his associate.

The Popper Era

The next important factor in the growth of interest in liver disease at Mount Sinai was the appointment in 1957 of Hans Popper as chairman of the Department of Pathology after Klemperer's retirement. A few months later, Popper brought

Fenton Schaffner to New York to provide the clinical arm for a growing liver team forming in Pathology. The aim of the group was to correlate structure and function in the various liver diseases. Popper had been investigating many clinical and pathologic aspects of liver diseases for more than 20 years, first in Europe under Hans Eppinger in Vienna and then in Chicago where he was the pathologist for the Cook County Hospital. Schaffner was first a Fellow in Pathology at Cook County under Popper and then a part-time colleague while in full-time internal medical practice. Together they had just published a new type of text on liver, *Liver: Structure and Function* (McGraw-Hill, 1957), which emphasized structure as a guide to function.

The liver team was assembled and functioning, and research grants began to be received. Areas developed included histochemistry with recruitment of Tibor Barka (who became the first editor of the *Journal of Histochemistry*), biochemistry with Edward Singer and Ferenc Hutterer, immunocytochemistry with Fiorenzo Paronetto, and electron microscopy with Schaffner, under the tutelage of the Cell Research Laboratory headed by Leonard Ornstein. The number of liver biopsies performed in the hospital increased dramatically to about 600 a year with the introduction of the Terry Needle, brought from Chicago. The biopsy specimens were processed with great care by Hendrika van der Noen, who also trained many technicians in preparing truly beautiful histologic slides that remain the mainstay of teaching and research as well as diagnosis.

The Popper years saw an explosion in description and discovery, and in the number of papers published, which amounted to more than 1000 in a period of 30 years. The main topics were hepatic fibrosis, cholestasis with special emphasis on morphology and bile salt metabolism, toxic liver injury, metabolic transformations, and carcinogenesis. The early work of the team was described in annual progress reports from 1960–1963, which appeared in volumes 27–30 of the *Journal of the Mount Sinai Hospital*. These reviews dealt mainly with our work in hepatic fibrosis and the development of chronicity of liver disease. Later reviews were published in each volume of *Progress in Liver Diseases*.

The studies of fibrosis revealed that as collagen increased, it was distributed around portal tracts, proliferating ductules, and sinusoids in the spaces of Disse (30). The perisinusoidal fibrosis was associated with the formation of a basement membrane, resulting in capillarization of the sinusoids (31). The fibrosis of schistosomiasis was found to be periductal (32) and resulted in presinusoidal portal hypertension (33). Detail of the structure of the ductule was described, including how it acted as a trellis for the deposition of collagen (34, 35). Various aspects of alcoholic (36, 37), autoimmune (38, 39), and later, viral chronic liver disease (40, 41), were explored, including clinical and chemical correlations. Drug-induced liver disease was classified as hepatic or cholestatic (42), and many publications followed, ranging from case reports to large series and reviews. Ultrastructural and histochemical aspects of Wilson's disease were detailed (43) and experimental copper intoxication was studied (44). Involvement of the liver in AIDS was investigated as the epidemic progressed (45, 46). Much attention was devoted to cholestasis (47). The morphology of the condition was examined in patients in whom a bile duct had been ligated (48, 49) and in animals to which lithocholate was administered (50), as well as in those given cholestatic drugs (51) and alpha naphthylisothiocyanate (52). The site of the initial injury in primary biliary cirrhosis (53) and the stages of the disease (54) were described. Immunologic markers of the disease were studied (55). A large series of patients with primary biliary cirrhosis was accumulated, enabling description of the natural history (56), serum bilirubin as a prognostic indicator (57), and the effects of treatment in trials including penicillamine (58), colchicine (59) and later ursodiol and methotrexate. The serum bilirubin level also proved to be a prognostic marker for sclerosing cholangitis (60). The role of the bile acids in causing cholestasis and in producing hepatocellular injury (61) was examined. The state of the art facilities assembled also permitted a search for a no-effect level of toxic substances (62) and the earliest indications of hepatic injury and malignant transformation (63). The substances examined had either military (intravenous fat emulsions [64] and space cabin atmospheres [65]) or environmental importance (pesticides [66], vinyl chloride [67]).

A steady stream of foreign fellows and visitors began arriving, beginning with Perez from Argentina, Pang from Indonesia, Scheuer from England, and many more. Giorgio Menghini visited Mount Sinai in 1958 at the time the first meeting of the International Association for the Study of the Liver was held in Washington. Popper was a founding father of this society, which was modeled after the American Association for the Study of Liver Diseases (AASLD), which Popper founded a decade earlier

in Chicago. Menghini brought his newly-invented aspiration liver biopsy needle and performed the first such biopsy at Mount Sinai. He left one of his needles and Schaffner performed the second such one-second biopsy on a young diabetic girl in ketoacidosis who suddenly developed massive hepatomegaly and ascites. This was reported as a case of excessive glycogen deposition in the liver, visualized by electron microscopy (68). Albert Parets reviewed our early experience with the needle (69), which we continue to use to this day. The team and the visitors began producing a torrent of more than 500 papers, as well as frequent presentations at national and international meeting which continued for more than 30 years. The work continued even while Popper was Dean and President of our new medical school; he was the main driving force in its foundation.

Popper and Schaffner edited a special issue of *Gastroenterology* devoted to liver diseases in November 1959. As a result of this special issue, the series, "Progress in Liver Diseases," was begun in 1961, published by Grune and Stratton. It went through nine volumes, the last published by Saunders. One volume appeared every three years, until after Popper died in 1988. Other books appearing were *Clinico-Pathological Conferences of The Mount Sinai Hospital* by Schaffner and Popper, published by Grune and Stratton in 1963; *Cirrosis Hepática* by Anibal Latuff (from Venezuela) and Schaffner, published by Editorial Científico Médico, Barcelona in 1966; and *The Liver and Its Diseases,* put together as a festschrift for Popper's 70th birthday by Schaffner, Sheila Sherlock (of London) and Carroll Leevy of (New Jersey), published by Intercontinental Medical Books in 1983. Popper and Schaffner contributed chapters to the third and fourth editions of Bockus' *Gastroenterology*, Schaffner being an associate editor in the fourth edition and a senior co-editor in the fifth. Popper was an associate editor for the first two editions of *The Liver: Biology and Pathobiology*, published by Raven Press, with Irwin Arias as senior editor. Popper also served as an associate editor for *Gastroenterology* and for *Hepatology*.

During the Popper era, a program project grant was awarded by the National Institutes of Health (NIH) to Pathology to cover much of the research activity. A training grant for liver fellows was also awarded and Alexander Gutman, the chairman of the Department of Medicine, split Liver Diseases from Gastroenterology in 1965 and created a separate division with Schaffner as the first chief. One or two liver fellows were trained each year and when the grant ended, the hospital funded the fellowship and continues to do so. Several fellows elected to stay at Mount Sinai for varying periods of time. Franklin Klion remained as a full-time clinician for several years and then went into private practice. He continues to maintain close ties to the Division of Liver Diseases and when Richman retired as chief of the Liver Clinic, Klion was his successor. He also takes a very active role in the transplant program, and wrote a book, *Guide to Liver Transplantation*, with Thomas Fabry, published by Igaku-Shoin in 1992. Popper trained many pathologists from all over the world and several have become chairmen of their own departments, including Stephen Geller, Michael Gerber and Emanuel Rubin in the United States, Peter Scheuer and Helmut Denk in Europe, Zilton Andrade in Brazil and Goruku Ohta in Japan. They have all achieved international reputations and retain an active interest in the liver. Swan Thung was also a Popper student and she inherited the job of being responsible for all the liver biopsies as well as immunologic studies involving the liver, which she is still doing. Several internists from abroad also spent time learning about liver disease in the Department of Pathology and then returned home to become chiefs of their medical departments. These included Massimo Colombo in Italy, Whan Kook Chung and, later, Boo Sung Kim from Korea, and Hiroshi Sasaki from Japan. Many specimens of liver tissue were sent to Mount Sinai for second opinions and a very large collection of slides with accompanying histories was accumulated. After Popper died, these were donated to the Armed Forces Institute of Pathology in Washington.

Popper received many honors, including several honorary doctoral degrees. One was from the University of Vienna, his alma mater, on the 600th anniversary of the founding of the institution. The school also renamed the pathology department the Hans Popper Institute of Pathology. The Hans Popper Primate Center in Orth, a suburb of Vienna, was dedicated in 1992 for the study of viral diseases, including hepatitis. He received numerous honors in the United States. The Friedenwald Medal was bestowed on him in 1971 by the American Gastroenterological Association (70). Popper was elected to the Academy of Arts and Sciences. He spent the year 1974 as a Fogarty Scholar in residence at the NIH in Bethesda after he stepped down as dean and president. During his year away, he was able to organize a meeting on nomenclature chaired by Carroll Leevy of New Jersey. The meeting resulted in a book on standardization of nomenclature, diagnostic criteria and diagnostic methodology (71).

Mount Sinai named the department of pathology the Popper and Stratton Department of Pathology, Lillian and Henry Stratton being major benefactors and close friends. Dr. Popper was awarded the Jacobi Medallion in 1973. Thomas Chalmers, Popper's successor as dean and president of the Medical Center, received the medallion in 1981, while Schaffner received it in 1992 (Fig. 1). Popper was very active in the national and international liver associations, having served as president of both the American and international societies. Chalmers (before he came to Mount Sinai), Schaffner and Paul Berk also were AASLD presidents. Berk, Schaffner and Rudi Schmid of California produced a book honoring Popper entitled *Hans Popper, a Tribute*, published by Raven Press in 1992. This was also translated into German as *Hans Popper, Freunde Erinnern Sich*, published by Schattauer. Herbert Falk, who founded the pharmaceutical firm devoted mainly to hepatological and gastrointestinal medications, paid for and distributed the book. Falk and Popper were close friends, and Popper served as an important advisor to Falk. For forty years, Falk sponsored many of Popper's symposia and other teaching activities that promoted interest in liver diseases. Falk has honored this relationship by creating the Hans Popper Prize for outstanding work in the field; it is awarded during the triennial Basal Liver Week.

Chalmers, who succeeded Popper as dean and president in 1974, was responsible for introducing the liver team to randomized, double-blind, controlled trials of therapy for liver diseases. Berk came to Mount Sinai as chief of Hematology, from NIH, where he was Chalmer's successor as chief of the liver program. He put together a team and laboratories dedicated mainly to bilirubin and membrane transport in the liver. During the Popper era, in 1980, two journals devoted to the liver were founded in the United States. AASLD gave birth to *Hepatology*, with a big push by Popper. Many of the Mount Sinai team served on the editorial board. The second journal, *Seminars in Liver Diseases*, began and still is at Mount Sinai, with Berk as editor and Chalmers, Charles Lieber, Popper and Schaffner constituting the original editorial board. Both journals continue to flourish and Berk has just completed a six-year term as editor of *Hepatology*. Lieber, who works at the Bronx Veterans Administration Hospital, has been editor of *Alcoholism*. When Schaffner became emeritus in 1991, Berk became the second chief of the division and the laboratories he established in the Division of Hematology came with him to Hepatology.

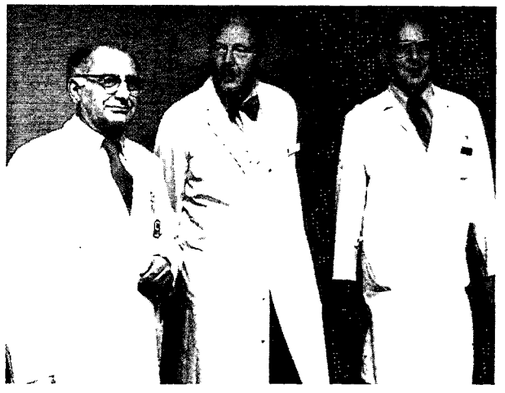

Fig. 1. Hans Popper, Thomas Chalmers, and Fenton Schaffner (l to r), together at a Mount Sinai School of Medicine conference in 1973.

The Transplantation Era

The year 1988 marked the end of the Popper era with his death at the age of 83 from pancreatic cancer. It also marked the introduction of liver transplantation at Mount Sinai. Within a few years, under Charles Miller, the institution became the third largest transplant center in the country. Both Popper and Chalmers pushed hard to have a transplant program at Mount Sinai. They did this, with the help and blessing of Arthur Aufses, Jr., the chairman of the Department of Surgery (Fig. 2). The trustees and the administration of the medical center gave their enthusiastic support for the program.

The first liver transplantation at Mount Sinai occurred on September 3, 1988, involving a patient with sclerosing cholangitis. The 1000th transplantation was done on October 9, 1995 and the 1000th patient was transplanted on September 18, 1996. As of September 1996, 2868 patients had been evaluated for transplantation and 254 were on the waiting list. The youngest surviving patient at transplant was not quite six months old and the oldest was 75 years. Several living-related and split-liver transplants have been performed. These data were obtained from the Fall 1996 issue of *Transplantation Update*, a publication of the Division of Liver Transplantation of the Department of Surgery.

After transplantation was begun, the need for more help from the Division of Liver Diseases

Fig. 2. The original Mount Sinai Liver Transplant team. First row (l to r): Fenton Schaffner, Arthur Aufses, Charles Miller, Paul Berk; Second row (l to r); Nancy Bach (medical Liver Fellow), Elizabeth Harrington, Myron Schwartz, Margaret Kadian (first coordinator), Martin Harrington (transplant Surgical Fellow) and Angelina Korsun (first administrator).

became obvious. Nancy Bach, then the liver fellow when transplantation began, was the one who set the tone for the cooperation of the division with the transplant team. Bach remains a full-time clinician with the division. Not only were more fellows needed, but more supervision and training had to be provided. To supervise the training as well as the clinical activity of the division, Henry Bodenheimer was invited to return to Mount Sinai. He had been an intern, medical resident and liver fellow at the hospital from 1975 to 1979, after which he went to Providence to finish his training in gastroenterology and then join the Brown Medical School faculty. More fellows and several full-time faculty members were recruited. During his fellowship and while he was in Rhode Island, Bodenheimer participated with Schaffner in clinical trials of therapy for primary biliary cirrhosis and conducted multi-center investigations including Mount Sinai. He participated in national trials of interferon treatment of chronic viral hepatitis, work he continues to this day.

Increasing clinical responsibilities, mainly related to the active transplant program, and a decrease in funding from government and other sources have curtailed some of the research activity. Nevertheless, studies of primary biliary cirrhosis (72, 73), chronic viral hepatitis (74, 75), nonalcoholic fatty liver (76), and acquired immunodeficiency syndrome (77) continue, as do investigation of various aspects of transplantation (78) and pathologic (79) and immunologic changes (80) in different liver diseases. An important goal of the Division of Liver Disease is making transplantation unnecessary by curing and ultimately preventing liver diseases.

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17

Alcohol and the Liver:

Metabolism of Alcohol and Its Role in Hepatic and Extrahepatic Diseases

CHARLES S. LIEBER, M.D.

Abstract

Dr. Charles S. Lieber has conducted clinical and experimental studies for more than four decades (three at Mount Sinai and the Bronx VA Medical Centers) with emphasis on liver, nutrition and GI pathophysiology. His major contributions include elucidation of the pathogenesis of alcoholic liver disease, by demonstrating the toxic role of alcohol and describing associated metabolic disorders. This was achieved through judicious clinical studies and newly developed rodent and primate models with the administration of ethanol in liquid diets. The mechanisms of various pathological and metabolic effects of ethanol were clarified, including hyperlipemia (with the rise in HDL), hyperuricemia, the role of acetaldehyde toxicity and alcohol-induced oxidative stress. The latter, including glutathione depletion, was corrected by S-adenosyl-1-methionine given to alcohol-fed baboons; the compound is now being used successfully for the treatment of patients with alcoholic liver disease in Europe. Alcoholic cirrhosis was produced for the first time in nonhuman primates and shown to be fully prevented by polyenylphosphatidylcholine, which is now being tested in a multicenter clinical trial. Lieber also discovered a new (microsomal) pathway of ethanol metabolism, responsible for the tolerance to ethanol and for several clinically important toxic interactions with other drugs (e.g., acetaminophen), anesthetics, industrial solvents, carcinogens, as well as retinol and β-carotene, with narrowing of their therapeutic window. His work defined the role of the stomach in ethanol metabolism, description of corresponding gender differences, cloning (for the first time) of the gene for sigma ADH (a newly recognized gastric alcohol dehydrogenase isozyme) with its chromosomal localization, and the discovery of the effects of commonly used medications (e.g., H_2 blockers and aspirin) on the activities of the enzyme and on blood alcohol levels in social drinkers. Lieber was among the first to use antibiotics for the elimination of gastric bacterial urease and its ammonia production in man, thereby alleviating chronic gastritis and hypoacidity, with attenuation of hepatic encephalopathy in cirrhotics. He promoted early detection and treatment of heavy drinkers before their social or medical disintegration, by defining precirrhotic lesions and markers of alcohol consumption.

Conclusions: The research of Dr. Lieber and his group has yielded a better understanding of the pathogenesis of common hepatic, gastric and nutritional disorders, with elucidation and prevention of serious toxic alcohol-drug interactions and the development of methods for early recognition and more effective approaches to prevent and treat liver and gastrointestinal diseases.
Key Words: Ethanol, liver, cirrhosis, drugs, nutrition.

A. Alcohol and Nutrition

ETHANOL IS A PSYCHOACTIVE DRUG, but, besides its pharmacologic action, it has a substantial energy value (7.1 kcal/g). In the heavy drinker, alcohol represents, on the average, 50% of the total dietary energy intake. As a consequence, alcohol displaces many normal nutrients of the diet, resulting in primary malnutrition and associated symptomatology (Fig. 1). Alcohol also impairs the activation and utilization of nutrients, and secondary malnutrition may result from either maldigestion or malabsorption caused by gastrointestinal complications associated with alcoholism. Originally, it was believed that liver disease in the alcoholic was due exclusively to malnutrition. This dogma was primarily based on the experiments of Best and Hartroft, who had observed that in rats given alcohol as part of their liquid diet, no liver damage resulted when the diet was adequate. The first stage of liver disease, namely fatty liver, only developed when the diet was deficient. From their experiments, Best et al. (1) concluded that "there is no more evidence of a specific toxic effect of pure ethyl alcohol upon

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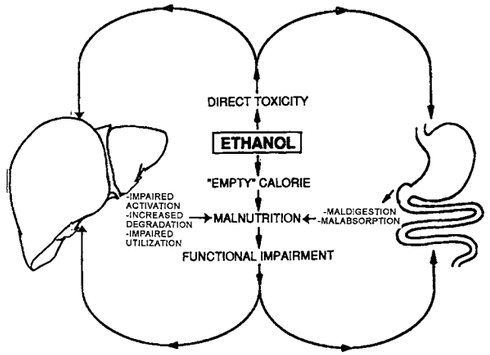

Fig. 1. Interaction of direct toxicity of ethanol on liver and gut with malnutrition secondary to dietary deficiencies, maldigestion, and malabsorption, as well as impaired hepatic activation or increased degradation of nutrients (154).

liver cells than there is for one due to sugar." Lieber et al. confirmed these experiments but added the observation that under those conditions, blood alcohol levels were negligible. Indeed, rats have a natural aversion for alcohol that was overcome by giving alcohol in totally liquid diets (2). This diet also allowed perfect pair feeding of controls and, using such a diet, it was established for the first time that alcohol, even in the absence of nutritional deficiencies, can cause the first stage of alcoholic liver disease, namely a fatty liver, a finding confirmed in human volunteers (2, 3). The question still remained of the pathogenesis of the more severe stages of alcoholic liver disease, culminating in cirrhosis, which is responsible for the high rate of mortality in the heavy drinker. This issue was addressed by extending the liquid diet technique to an experimental animal more closely related to man, namely nonhuman primates (4). The latter studies were conducted after Dr. Lieber and his team had moved from Harvard and Cornell to the Bronx Veterans Affairs (VA) Medical Center and the newly created Mount Sinai School of Medicine in 1968. There, it was shown for the first time that alcohol can cause cirrhosis of the liver, even in the absence of nutritional deficiencies (4, 5).

This realization had profound consequences on the preventive as well as therapeutic approaches to the medical disorders of alcoholism. The major therapeutic efforts shifted from the mere correction of nutritional deficiencies to the moderation of alcohol consumption and the development of new therapeutic modalities by a better understanding of the mechanism of hepatotoxicity. The latter was investigated by a systematic study of the biochemical pathways through which the body rids itself of the alcohol.

B. Alcohol Metabolism and Associated Toxicity

Alcohol is oxidized primarily in the liver and the main pathway involves alcohol dehydrogenase.

1. *Metabolic Disorders Associated with Alcohol Oxidation by Alcohol Dehydrogenase*

a. Hepatic effects

The oxidation of ethanol via the alcohol dehydrogenase pathway results in the production of acetaldehyde with loss of H. Nicotinamide adenine dinucleotide (NAD) is reduced to NADH. The large amounts of reducing equivalents generated overwhelm the hepatocyte's ability to maintain redox homeostasis, and it was shown that a number of metabolic disorders ensue (Fig. 2), including hyperuricemia (6) and hyperlipemia (2), with a rise in HDL (7) popularized more recently in conjunction with some apparently beneficial effects of moderate drinking on coronary arteries. It was also found that the increased NADH opposes lipid oxidation and promotes fatty acid synthesis with, as a net result, hepatic fat accumulation (8). The perivenular exaggeration of this redox change (because of the relative perivenular hypoxia) was found to be responsible for the exacerbation of the alcohol-induced injury (including steatosis) in the perivenular zone of the hepatic lobule (9). The respective roles of the amount of dietary fat (10) and dietary deficiencies (11) were elucidated. An associated metabolic disorder, namely ketoacidosis, was discovered and defined (12). In addition to the raised NADH, microsomal induction (*vide infra*) was incriminated through increased activity of enzymes involved in lipogenesis (13, 14) which was found to be associated with enhanced production of low and very low density lipoproteins (LDL and VLDL) (15). LDL and VLDL, in addition to alterations in cholesterol turnover (16), were shown to play a role in the alcohol-induced hyperlipemia (17–19). The latter was observed to involve the high density lipoproteins (HDL). Their increase was described by Baraona and Lieber (7), and has gained much attention in recent years. Ethanol was also found to affect the lipids, the microviscosity (20) and the structure of plasma membranes, as demonstrated by scanning electron microscopy (21). Thus, the hypothesis that the NADH generated by alcohol dehydrogenase (ADH)-mediated ethanol oxidation may play a major role in alcohol-induced disorders (22) was shown indeed to explain a vast array of associated metabolic abnormalities, including the steatosis (Fig. 2).

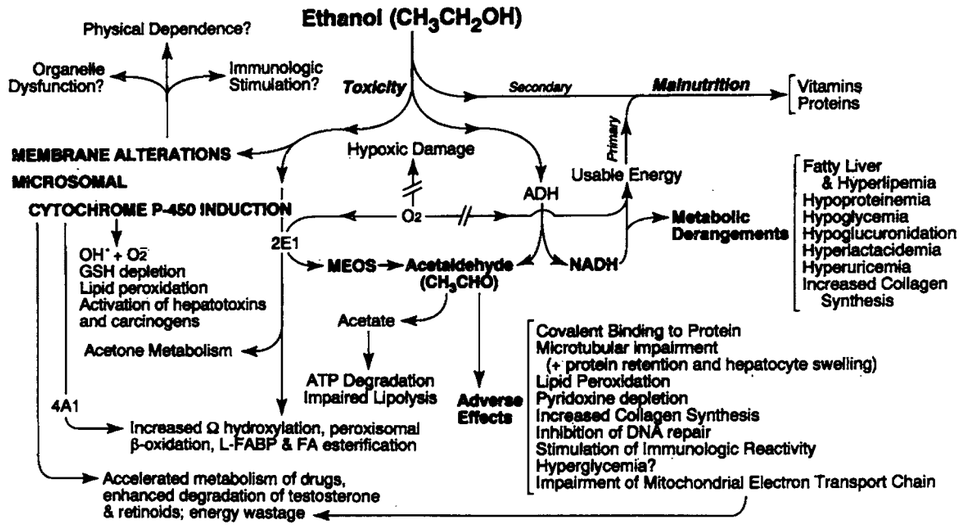

Fig. 2. Hepatic, nutritional and metabolic abnormalities after ethanol abuse. Malnutrition, whether primary or secondary, can be differentiated from metabolic changes or direct toxicity, resulting partly from redox changes, or effects secondary to microsomal induction, including increased acetaldehyde production (155).

b. Gastric effects

1. Gastric ethanol metabolism and interactions with other drugs

Chronic ethanol consumption was found to produce a significant decrease in gastric alcohol dehydrogenase (ADH) activities (23), associated with greater bioavailability (lesser first pass metabolism) of ethanol (23, 24). Significant ethanol metabolism was also observed in cultured rat (25) and human (26) gastric cells. Women were found to have a lower gastric ethanol metabolism than men, which explains, at least in part, their greater susceptibility to the effects of ethanol (27). Commonly used drugs, e.g., aspirin (28) and H_2 receptor antagonists, e.g., cimetidine (29), were discovered to inhibit gastric ADH activity and to enhance the bioavailability of ethanol, with a resulting increase in blood ethanol levels (30). This effect was shown to be particularly important for social drinkers who commonly take several small drinks, with a cumulative effect on blood alcohol levels, strikingly exaggerated by various drugs (Fig. 3), either because of an inhibition of gastric ADH (*vide supra*) and/or an acceleration of gastric emptying (31).

At least three different forms of ADH were observed in the human stomach, with either high or low K_m's for ethanol (32), including a newly recognized gastric isozyme, now called class IV or sigma ADH. A deficiency of this gastric ADH was uncovered in Asians (33), and the lower

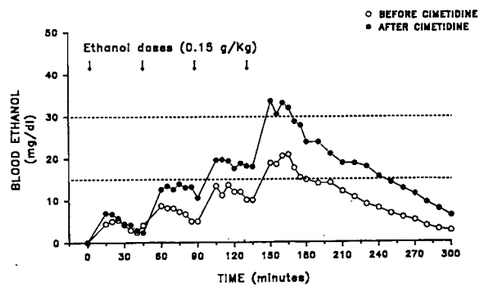

Fig. 3. Effects of cimetidine (400 mg twice a day for 7 days) on average blood levels after oral consumption of ethanol in nine subjects. Four small doses of ethanol (150 mg/kg) were imbibed at 45-min intervals, before and after administration of cimetidine. The effect of cimetidine on repeated drinking was significant ($p < 0.01$ by two-way analysis of variance for repeated measures). (Modified from ref. 156).

ADH activity was found to be associated with a lesser first pass metabolism of ethanol (34), in keeping with a predominant role for ADH in human first pass metabolism. The full length cDNA of sigma ADH was determined and the complete amino acid sequence deduced (35). The corresponding ADH_7 gene in Caucasian and Japanese subjects was compared (36), including the upstream structure and the organ distribution of its expression (37) with, for the first time, molecular cloning and chromosomal localization of the gene (38). These studies not only established

the role of gastric ADH in ethanol metabolism, but they also delineated corresponding differences at a molecular level and opened a new approach to explain differences in the handling of ethanol and possibly of other dietary xenobiotics, such as gastric carcinogens.

2. Gastritis in the alcoholic

The product of ethanol metabolism is acetaldehyde, a toxic compound (*vide infra*) which may contribute to the chronic gastritis which is common in the alcoholic. An additional pathogenic factor is *Helicobacter pylori* infection (HP). Indeed it was found that this chronic gastritis generally resolves with the eradication of the microbe (39). The role of the gastric microbial flora in converting urea into NH_3 was first recognized by the successful elimination of gastric NH_3 using antibiotics in man (40, 41). These studies were completed at Mount Sinai (42). Adverse effects of NH_3 included hypoacidity and gastritis, especially in the alcoholic (41). Gastric NH_3 was shown to correlate with the severity of gastritis (39), and its measurement is now the basis for an accurate, yet simple, method for the detection of HP (43). The infection has its most striking impact in patients with uremia (40, 41) and in those with cirrhosis whose encephalopathy was improved with the antibiotic therapy (44).

Other gastrointestinal effects of ethanol that were elucidated comprised significant intestinal lesions in the rat (45), confirmed in man (46). These alterations included B_{12} malabsorption (47) and decrease of intestinal lactase (46).

2. *Microsomal Ethanol Oxidizing System (MEOS)*

a. Ethanol metabolism

A toxicological breakthrough was achieved with the discovery of a microsomal ethanol oxidizing system and its interactions with xenobiotics (48, 49). This second pathway for alcohol metabolism was separate from that of alcohol dehydrogenase and catalase (49, 50) and characterized (51) and reconstituted by a semi-purified preparation of cytochrome P-450 (52). The role of the microsomes in ethanol metabolism and its increase after chronic ethanol consumption was demonstrated in rats (53), nonhuman primates (54, 55), acatalasemic mice (56), and deermice lacking alcohol dehydrogenase (57–62). It was quantitated using, in part, deuterium isotope effects (61). An ethanol-inducible form of cytochrome P-450 was discovered (52) and was subsequently purified by various groups from the livers of different species, including rats (63) and humans (64); it is now called 2E1. Unlike ADH, MEOS was found to be strikingly inducible by chronic ethanol consumption, with its key component, namely 2E1, increased 4- to 10-fold in liver biopsies of recently drinking subjects (65), with a corresponding rise in mRNA in hamsters (66), rats (67) and man (68). P4502E1 induction was demonstrated with normal, as well as low-fat diets (69). It was shown in hepatocytes and in nonparenchymal cells of the liver (70), and also in extrahepatic tissues (71).

b. Other microsomal effects

Microsomal induction was found to have an impact on sex hormones in normal men (72), and to enhance fatty acid ω-oxidation (73). Induction of 2E1 contributes to the tolerance that develops to ethanol in the alcoholic and other drugs that are microsomal substrates. The tolerance of the alcoholic to various psychoactive drugs had generally been attributed to central nervous system adaptation, but metabolic adaptation now had to be considered, because the clearance rate of many drugs from the blood was found to be enhanced in alcoholics (74). Indeed, controlled studies have shown that chronic administration of pure ethanol with nondeficient diets either to rats or man (under metabolic ward conditions) results in a striking increase in the rate of blood clearance of ethanol (75), meprobamate and pentobarbital (74) as well as other drugs.

Contrasting the effect of chronic ethanol consumption, which results in microsomal induction and tolerance to a number of drugs, the presence of ethanol may slow down disposition of some drugs and enhance their pharmacologic effects by competing for some common component(s) of the microsomal degradation process. This was shown for meprobamate (76), acetaminophen (77, 78) as well as methadone (79).

c. Activation of hepatotoxins

One of the most important consequences of the discovery of this new microsomal pathway of ethanol metabolism was the realization that the ethanol-inducible cytochrome P4502E1 not only catalyzes ethanol oxidation, but is also capable of activating various other compounds to highly toxic metabolites. This pertains to analgesics, such as acetaminophen (80), anesthetics (81), hepatotoxins (82), industrial solvents (83), as well as carcinogens (e.g., nitrosodimethylamine [NDMA]) (84). Activation of the latter was achieved at concentrations significantly lower than those required after the administration of other inducers (84), in part because the ethanol-inducible P4502E1, including the human variety (64), has a high affinity for NDMA. Increased activation of carcinogens was also demonstrated

in the alimentary tract and the lungs (85). Thus, this inducible microsomal ethanol oxidizing system explains not only the metabolic tolerance to ethanol that develops in the heavy drinker, but also the concomitant increased vulnerability to ubiquitous xenobiotics. Furthermore, the proliferation of the endoplasmic reticulum (86) associated with P4502E1 induction is also accompanied by enhanced activity of other cytochrome P-450s, resulting in accelerated metabolism and tolerance to other drugs, as well as increased degradation of retinol and its hepatic depletion.

d. Interactions with retinoids and carotenoids

Liver microsomes were also found to harbor hitherto unrecognized pathways for retinol metabolism (87, 88) which were found to play a role in the homeostatic control of hepatic vitamin A levels (89). Using purified cytochrome P-450 isozymes, including the human P4502C8 (90), retinol (87, 90) and retinoic acid (90, 91), metabolizing systems were reconstituted; chronic ethanol or drug administration was shown to result in increased microsomal degradation of retinoic acid (92) and retinol (93). This provided a possible mechanism for the striking hepatic vitamin A depletion which was discovered to result from chronic ethanol consumption in rats (94), nonhuman primates (94), and man (95) (Fig. 4). This hepatic vitamin A depletion was associated with striking lysosomal lesions (96). Potentiation of the deleterious effects of vitamin A depletion by ethanol was also found in other tissues, including a profound loss of the ciliated epithelium in the lining of the respiratory tract and the exacerbation of squamous metaplasia, a precancerous lesion (97). Hepatic depletion of vitamin A was also demonstrated after administration of other drugs (98); the combination of ethanol with drugs or food additives (such as butylated hydroxytoluene) resulted in a striking potentiation of the depletion, with almost all of the vitamin A disappearing from the liver (99).

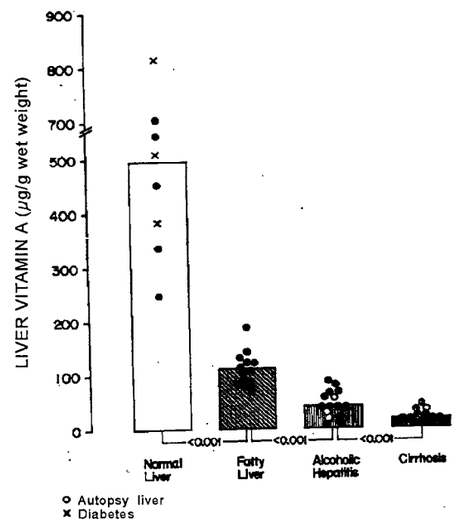

Fig. 4. Hepatic vitamin A levels in subjects with normal livers and various stages of alcoholic liver injury. Figures below the graph denote P values (95).

Thus, vitamin A requirements had to be revised for the large segment of our population that chronically abuses ethanol and/or other drugs. The practical limits of vitamin A supplementation, however, were delineated by the demonstration that vitamin A toxicity can be markedly exacerbated by chronic ethanol consumption, with development of mitochondrial injury (100), necrosis and fibrosis (101). Indeed, amounts of ethanol and vitamin A which, by themselves, did not produce fibrosis, when combined, resulted in necrosis and fibrosis in the liver (101), with development of severe mitochondrial injury (100). Furthermore, it was discovered that alcohol interferes with the clearance of β-carotene, possibly by impairing its conversion to vitamin A, resulting in enhanced hepatic and blood levels in baboons (102) and also in man (103), with associated potentiation of hepatotoxicity (102) possibly due, in part, to the beadlets used as carrier for β-carotene (104). In addition, carotenoids were found to undergo significant biliary excretion in man (105) and are therefore affected by liver pathology. The recognition of a narrowed therapeutic window for vitamin A and β-carotene in the alcoholic has prompted a redefinition of the optimal conditions for their use in nutritional repletion and therapy.

C. Acetaldehyde Toxicity and Mitochondrial Impairment

Ethanol oxidation, whether by the ADH or the microsomal pathway, results in acetaldehyde, which may cause ubiquitous damage, including in the mitochondria. Indeed, the ethanol-induced ultrastructural lesions of the mitochondria (86) were found to be associated with functional abnormalities, including decreased oxidation of fatty acids (106) and acetaldehyde (107, 108). The latter, together with the increased production by the induced microsomes (109), explains the elevated blood level of acetaldehyde observed in alcoholics (110). Using improved analytical methods (111), the high acetaldehyde levels were found to be reversible upon alcohol withdrawal

(112), and exaggerated by pregnancy and lactation (113). The human placenta was shown to be capable both of transferring acetaldehyde from the mother to the fetus and of converting ethanol to acetaldehyde (114), which may thus play a role in the pathogenesis of the fetal alcohol syndrome, the most common preventable cause of congenital abnormalities.

Administration of ethanol, particularly at high levels and in animals fed alcohol chronically, was accompanied by a 10-fold increase in splanchnic acetaldehyde release in the hepatic vein (115), associated with a striking leakage of the mitochondrial enzyme glutamic dehydrogenase into the hepatic venous blood. There was also an inappropriately low oxygen utilization by the liver. The flow-independent O_2 extraction (VO_2) was measured by reflectance spectroscopy with a probe placed on the liver surface through a peritoneoscope: VO_2 significantly decreased after the high ethanol dose in the alcohol-treated baboons (115). This impaired O_2 utilization was associated with a marked shift in the mitochondrial redox level (measured by the β-hydroxybutyrate / acetoacetate ratio). A "vicious cycle" was thus recognized, with chronic ethanol consumption inducing increased acetaldehyde formation leading to mitochondrial toxicity, including an associated decreased capacity of the mitochondria to oxidize acetaldehyde. As a consequence, acetaldehyde rises even further, and perpetuates and aggravates the toxicity.

The morphologic (116) and functional (117) impairment of the mitochondria after chronic ethanol consumption was accompanied by a significant decrease in cytochrome oxidase activity associated with the depletion of mitochondrial phosphatidylcholine, whereas restoration of cytochrome oxidative activity was achieved by replenishment of the phosphatidylcholine *in vitro* (117). This observation was one of the factors that led to the supplementation of phosphatidylcholine *in vivo* (using delinoleoylphosphatidylcholine), which resulted in the discovery of its spectacular beneficial effects, including the prevention of liver fibrosis and cirrhosis (*vide infra*). The uncoupling of oxidation with phosphorylation associated with mitochondrial impairment, together with the net loss of chemical energy that accompanies the operation of the induced microsomes explained, at least in part, the startling observation that "alcohol calories do not fully count" and why many alcoholics do not maintain an adequate body weight despite a large caloric intake (118).

One mechanism for the hepatotoxicity of acetaldehyde is its high chemical reactivity and formation of adducts with various proteins. Indeed, it was discovered that acetaldehyde binds to microsomal proteins (119) and forms adducts *in vivo* with P4502E1 (120), collagen (121–122), as well as VLDL and LDL (123). Acetaldehyde adducts also elicit an immune response with increased circulating antibodies in alcoholics (124). The appearance of antibodies against acetaldehyde-protein adducts was found to reflect the severity of liver disease, both in alcoholics and non-alcoholics (125). Furthermore, even in non-alcoholic liver disease, hepatic acetaldehyde was found to be increased to a potentially toxic level (126). Moreover, acetaldehyde toxicity was shown to interfere with the repair of alkylated nucleo-proteins; human and rat O6 methylguanine transferase was inhibited *in vitro* by minute concentrations of acetaldehyde (as low as 0.01μM) (127). Acetaldehyde binding was also shown to impair microtubule polymerization and hepatic protein secretion (128, 129) which, together with an increase in constituent proteins (130), resulted in protein accumulation and hepatocyte swelling, thereby explaining the ballooning of the hepatocyte and the hepatomegaly, two characteristic features of alcohol-induced liver injury.

Acetaldehyde also contributes to depletion of glutathione and its potentiation of lipid peroxidation (131), verified in human liver biopsies (132). These effects were found to be attenuated by S-adenosyl-L-methionine (133), which has now been introduced in Europe for the treatment of liver disease. The oxidative stress was exacerbated by a low vitamin E diet, and ethanol was found to aggravate hepatic vitamin E depletion, in part by promoting conversion of α tocopherol to α tocopheryl-quinone (134), probably by free radical reaction. Allopurinol partially prevented the ethanol-induced lipid peroxidation (135), most likely through inhibition of purine degradation (enhanced by ethanol) and the associated free radical generation.

D. Fibrosis and Cirrhosis of the Liver: Pathogenesis and Prevention

Traditionally, fibrosis and cirrhosis were viewed as a "scarring" response to the necrosis and inflammation associated with liver injury, most clearly demonstrated in alcoholic hepatitis. However, the observation that chronic alcohol administration (under controlled dietary conditions) stimulated fibrogenesis (136) and produced cirrhosis in the baboon (4) without an obvious stage of alcoholic hepatitis (137) but with evidence for increased collagen production, including enhanced type I procollagen mRNA (138),

raised the hypothesis of a more direct effect of alcohol on fibrogenesis. Indeed, in baboons fed alcohol (139) as well as in man (140), perivenular fibrosis was identified as a precirrhotic lesion and shown to be useful for the early detection of subjects prone to rapidly develop cirrhosis, even in the absence of alcoholic hepatitis (141) (Fig. 5). Scanning electron microscopy also revealed significant changes of the endothelial fenestrations of the liver sinusoids (142), a finding of obvious implications for the exchange of nutrients and metabolites between the hepatocytes and the blood. Efforts were then directed to define the cell(s) involved. Myofibroblasts were identified in normal liver (139) and were discovered to proliferate after chronic alcohol consumption (139, 140). Furthermore, stellate cells (also called lipocytes or fat-storing cells) were found to be transformed or activated to "transitional" myofibroblast-like cells (143), associated with active fibrogenesis. Lipocytes and myofibroblasts were isolated from the liver and cultured, and acetaldehyde was shown to stimulate collagen production *in vitro* (144, 145), with an associated increase in mRNA for collagen (146). The acetaldehyde-induced increase in collagen accumulation was prevented by polyunsaturated phosphatidylcholine (PPC) extracted from soybeans (147) and by its main phosphatidylcholine species, namely dilinoleophosphatidylcholine (DLPC) (148), selected because of its high bioavailability. Several modes of action were elucidated: increased collagen breakdown (148), a significant decrease in the number of lipocytes activated to myofibroblast-like cells (148, 149), correction of the ethanol-induced depletion in phosphatidylcholine (148), as well as an attenuation of some of the associated enzyme deficiencies, including that of phosphatidylethanolamine methyltransferase (150). More recently, PPC was also found to prevent alcohol-induced steatosis and hyperlipemia (151) and to exert an unexpected but potent antioxidant effect (152) of possible relevance to the fibrosis, since the latter is known to be stimulated by products of lipid peroxidation. Furthermore, PPC prevented or attenuated non-alcoholic cirrhosis produced by either CCl_4 or heterologous albumin in the rat and accelerated the regression of preexisting cirrhosis (153). PPC is now being tested in man.

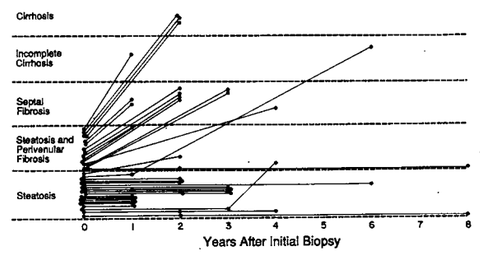

Fig. 5. Progression of fibrosis in alcoholics without hepatitis followed up to eight years after initial biopsy. The presence of perivenular fibrosis on the initial biopsy specimen was found to be a harbinger of rapid development of fibrosis to more severe stages, including cirrhosis (141).

Acknowledgments

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18

Inflammatory Bowel Disease up to 1932

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Abstract

Inflammatory bowel diseases have been a major interest of generations of Mount Sinai Hospital gastroenterologists. Although clinical descriptions of diarrhea with or without blood go back thousands of years, clear distinctions between enteritis and ulcerative colitis were possible only in the 19th century. At that time, many case reports were published of, in retrospect, classical regional enteritis. The term "ulcerative colitis" dates from 1888; the introduction of the electric sigmoidoscope soon after made it possible to make proper diagnosis of ulcerative colitis and distinguish it from infective dysentery, membranous mucous or catarrhal colitis, and nervous diarrhea. Doctors at The Mount Sinai Hospital adopted this diagnostic approach in the 1870s and 1880s, and were particularly interested in patients with tuberculosis-like ileocecal disease without tubercle bacilli. Articles were written by Weiner in 1914, Moschcowitz and Wilensky in 1923 and 1927, and Goldfarb and Suissman in 1931. Dr. A.A. Berg, in 1925, encouraged his assistant Leon Ginzburg to conduct a study of the inflammatory granulomatous diseases of the bowel, when Ginzburg and Gordon Oppenheimer were working in Dr. Paul Klemperer's laboratory. Initial reports came in 1927 and 1928, but Ginzburg and Oppenheimer "in conjunction with Dr. Burrill B. Crohn" presented a definitive paper, "Non-specific Granulomata of the Intestine," on May 2, 1932, to the American Gastro-Enterological Association. On May 13, 1932, Dr. Crohn presented a paper on "Terminal Ileitis" to the American Medical Association; this was published later that year with the title "Regional Ileitis: A Pathologic and Chronic Entity," under the authorship of Crohn, Ginzburg and Oppenheimer. **Key Words:** Inflammatory bowel disease, ulcerative colitis, regional enteritis, Crohn's disease, history.

INFLAMMATORY BOWEL DISEASES are the Mount Sinai gastrointestinal specialty par excellence, because of their high incidence among Jews, and because of the contributions of generations of Mount Sinai gastroenterologists to their diagnosis and treatment. The history of these diseases has often been reviewed (1–10), but their etiology and pathology are unclear, their management remains empirical, and the origins of their description are still controversial.

It is particularly useful to determine when particular diseases first appeared in human history, because the circumstances of their emergence may provide clues to their pathogenesis. This process is easier for bone or tooth disease, which may be traced in skeletons over thousands of years, but for internal disorders one needs more contemporary evidence from autopsies, laparotomies, and histologic and microbiologic examinations.

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Enteritis in Europe

Clinical descriptions of acute and chronic diarrhea with or without blood go back thousands of years. Most of these symptoms may have been due to acute bacterial infections, whether self-limited, progressive, or fatal. However, autopsies were unusual before the 16th century, only becoming common in the 18th and routine (in certain hospitals) in the 19th century (11). Histology became available early, and microbiology later, in that century.

The hospital of S. Maria Nuova in Florence allowed dissections not only by Leonardo da Vinci (for his anatomical studies) but also by Antonio Beniviene (1443–1502), for comparison

with the clinical course of his deceased patients. Of his 15 autopsies published posthumously (12), a nun with chronic intestinal obstruction ("XXXIV") had "intestines contracted by a thick callus" (possibly carcinoma rather than enteritis). "XLV" was a kinswoman with chronic recurrent flux of the bowels; the condition was cured "instantly" by a Dominican friar and showed no recurrence in a three-year follow-up [irritable bowel syndrome?]. "XCV" had "gripes in the intestines, called by the Greeks *dysenteria* . . . apt to ulcerate the lining of the intestines and thus the excrement comes down bloodstained and mucous." Both he and "XCVI," with similar symptoms, and in addition wasting and fatality with "entrails . . . internally eroded," may have had chronic dysentery or ulcerative colitis.

Autopsies were performed on the eminent, particularly royalty, in whom acute illness and death often raised suspicions of poisoning. Moreover, the previous medical events of monarchs were recorded, sometimes daily, and some of these records have survived. Thus, Louis XIII is known to have been prone to attacks of diarrhea for decades, with fever and a rectal abscess that discharged spontaneously. In 1642, he had bloody diarrhea, fever, abdominal pain and a perianal abscess or fistula; he died the following year, at age 42. Autopsy showed ulcerated small and large bowel, with abscesses and fistulas compatible with ileocecal tuberculosis or regional enteritis (13).

In 1761, Morgagni (14) reported a similar history in a man of 20 who had "mesenteric lymphadenopathy, . . . erosions, ulceration and perforation of the extremity of the ileum and the nearest point of the colon to the extent of two hands breadth." Again, retrospective precise diagnosis is impossible. Matthew Baillie's 1793 *Morbid Anatomy* (15) describes intestinal inflammation, more common in the large intestine, with thickened mucosa, ulcerated, sometimes tattered to shreds with perforation, penetration or fistula, all to be distinguished from cancer, with thick-walled, ulcerated mucosa, narrowed lumen, and dilated bowel cephalad. Some of these patients may have had regional enteritis rather than tuberculosis or cancer. Recently it has been suggested that Sir William Johnson (1715–1774), superintendent of Indian Affairs for the Six Nations, had inflammatory bowel disease with sclerosing cholangitis, arthritis and uveitis rather than alcoholic cirrhosis (16).

More convincing is Combe's Mr. Georges, in whom "The lower part of the ileum as far as the colon was contracted, for the space of three feet, to the size of a turkey's quill. The colon had three constrictions, one about three inches long at the distance of seven inches from the cecum, a second about one inch long at the distance of four inches from the former, and a third not quite half an inch long at the distance of three inches from the last" (17).

Crohn (2) recalled that as a medical student in 1907 he was asked to "skip the chapter on diseases of the small intestine in the *Osler Textbook of Medicine*, since only tuberculosis of the small bowel was recognized." Crohn's recollection is not confirmed; while Crohn may have been told to skip that chapter, the relevant section of the 6th edition (London and New York, 1905) discussed not only tuberculosis but also catarrhal enteritis, the celiac affection, sprue, diphtheritic or croupous enteritis, phlegmonous and ulcerative enteritis, intestinal ulcers and syphilis.

As early as 1828, Abercrombie (18) had devoted six sections of his book to mucosal diseases of the intestine: active, chronic, symptomatic ulceration, treatment, in infants, and incidental to other diseases. Abercrombie also distinguished between diseases of the rectum and colon (whole or part) and those of the ileum. Perhaps twenty of his case reports in this and subsequent editions would today be diagnosed as regional enteritis. One girl of 13 had ileocecal inflammatory thickening with skip lesions. Other patients had involvement of various parts of the small intestine, especially the terminal ileum, as well as various parts of the colon; some lesions had perforated. Some of the illustrations in Cruveilher's *Anatomie Pathologique* may represent regional enteritis (19); the strictured skip lesions from pylorus to rectum in Lever's patient at Guy's Hospital (20) may indicate the same condition. Bristowe (21) reported ulceration from the lower jejunum to the colon, with an ileal stricture, a perforation and an ileo-ileal fistula.

Wilks performed thousands of autopsies at Guy's hospital in London, and it is possible to trace, in successive editions of his *Lectures* (22–24), the evolution of his classification of inflammation of the bowel. In the first edition, in 1859 (22), he distinguished between enteritis, tuberculosis, caecitis, typhlitis, colitis and epidemic dysentery. In the same year, his forensic autopsy (25) suggested that a woman had not in fact been poisoned by her bigamist doctor husband, since the inflammation of the last 3 feet of ileum and ulceration of the whole large intestine to the rectum were more likely to have been primary, acute, non-epidemic dysentery, of which Wilks had seen only two other such cases in his

3000 autopsies. Was this regional enteritis (26) or even some drug-induced ileocolitis (27)? In his second edition (23), however, Wilks expanded the section on colitis and described local acute ileitis with inflammation of the whole wall, and at last, with microscopy available, the whole tissue charged with "pyoid corpuscles" (granulomas). These sections were not changed in the final edition (24). As microscopy became more routine, strictures at the ileocecal valve could be declared neither tuberculous nor carcinomatous, but merely chronically inflamed (28). In 1889, Fenwick (29) devoted the whole of his second lecture to non-malignant stricture of the ileocecal valve, but no microscopy was reported.

Probably the most scholarly attempt at documenting the existence and frequency of regional enteritis before 1900 was made by Fielding in a doctorate thesis for Cork in 1970, "An Enquiry into Certain Aspects of Regional Enteritis" (30). He searched the *Transactions of the Pathological Society of London* for 1850–1899 and tabulated 31 cases he considered probable regional enteritis; 4 had small intestine disease, 15 large bowel involvement, and 12 had both small bowel and colon affected (31). He even identified 25 possible additional cases (one ileal, 17 large colonic, 7 ileocolonic). Fielding then repeated this sampling for Dublin over the same 50 years, reviewing the *Dublin Quarterly Journal of Medical Science, Proceedings of the Pathological Society of Dublin* and the *Dublin Hospital Gazette* (32). He found 29 cases (including five from the 1840s), with 6 involving small bowel, 8 large intestine, and 14 both, fully supporting his conclusion that regional enteritis was not exclusively a 20th century disease (33).

Fielding was careful to point out that these retrospective diagnoses were his own. I would certainly accept his analysis of the probable diagnosis for Abraham Colles's "Organic Stricture of the Rectum" (34), in view of the perianal inflammation and fistulas, the rectovaginal and rectovesical fistulas, and the autopsy reports of non-ulcerated thickening of all coats of the intestine except the peritoneal tunic. In another case, described by Redmond (35), I agree with Fielding's interpretation that the painful swelling in the extremities was not due to acromegaly, in view of the normal face and skull. While the painful swelling in the extremities is more likely due to hypertrophic osteoarthropathy, I would still be reluctant to attribute the affliction to inflammatory bowel disease, because it preceded the diarrhea by 10 months, which (though possible) is unusual.

Some of Mayo Robson's (36) seven cases of chronic intestinal tuberculosis (photographs of specimens are provided for the first time in the 1902 article) were probably non-tuberculous giant cell granulomas. Six years later, in 1908, Robson reported patients with self-resolving abdominal tumors simulating malignant disease; some of them probably had diverticular disease and others "chronic infiltrating colitis" (37). Other accounts of idiopathic chronic inflammatory disease of the large or small intestine were reported from: England (38–40), France (41–43), Germany (44–51), Hungary (52), Italy (53), Japan (54), the Netherlands (55), Poland (56), Russia (57), and Scotland (30, 58). Some of these cases of intestinal inflammation were probably not idiopathic but pericolitis (59), diverticulitis (60) or post-appendectomy abscess (61). By 1939, Shapiro was able to give 289 citations on regional ileitis (1).

Enteritis in the U.S.

The first American contribution to the study of chronic inflammatory bowel disease was in 1901 by Lartigau, who described chronic hyperplastic tuberculosis of the intestines (62). By then, microscopy was able to identify the hidden bacilli in his and similar cases, but Lartigau raised the possibility of non-tuberculous causes of granulomas.

A steady stream of similar publications came from many parts of the U.S. in the 1920s. Jones and Eisenberg (63) from Cleveland removed a hard ileocolic mass which turned out to be simple inflammation and not carcinoma. Coffen (64) from Portland, Oregon, treated a young man who in nine years needed three operations for granulomatous tumors causing intestinal obstruction. Horsley (65) reported three patients from Richmond, VA whose resected specimens showed granulomas which he thought were tuberculous until that diagnosis was rejected by A.C. Broders of the Mayo Clinic. In 1926, the Cabots (66) reported a case from Boston. In 1930, Bargen and Weber (67) reported 23 cases of regional, segmental, localized or migratory ulcerative colitis seen over a period of 18 months at the Mayo Clinic; in the absence of histology it is not possible to be sure whether they were true ulcerative colitis or regional enteritis. In 1931, Mock (68) from Chicago described six cases: "Infective granulomata are far more frequent than the literature on this subject would lead one to believe," and he chose his complex subtitle "Non-specific chronic tumor-like productive inflammations of the gastrointestinal tract," after consulting eight pathologists and seven surgeons. Golob (69) from Sydenham Hospital, New York, resected the cecum for a hypertrophied ileocecal valve; granulomas and giant cell infiltration were found on histology by D.C. Balfour of the Mayo Clinic, who used a fourfold classification for such operative specimens: tuberculosis, diverticulitis, pyogenic, nonspecific granulomas.

Colitis

Throughout the 19th century, there was increasing recognition that there were non- infective causes of colonic ulceration. When Allchin, in 1885, reported a typical clinical and autopsy case of "follicular ulceration of the colon," he pleaded that "the term dysentery . . . should not at once be applied in an adjective form to any diarrhea depending upon ulceration of the colon, when the factors for the production of the specific disease are, so far as we can recognize, wanting" (70). Wilks (22) had referred to a ragged ulcerative surface in colitis, but the term "ulcerative colitis" was coined in 1888 by Hale-White (71), who later (72) distinguished (without sigmoidoscopy) 60 cases of "membranous colitis" or "mucomembranous entero-colitis," terms he preferred to mucous colic, glairy enteritis, glutinous diarrhea, tubular diarrhea, mucus affection of the intestine or intestinal croup. Hale-White's patients passed membrane or mucus or (rarely) blood and were all constipated; many had constant or acute pains, symptoms we should probably label today as irritable bowel syndrome. The 60 were mostly nervous, neurasthenic, hypochondriacal or hysterical.

Clarity came in the early 1900s from a surgeon, Lockhart-Mummery, at St. Mark's (the London rectal hospital). He stated quite simply, "The most important advance in our knowledge of these cases has been due to the invention of the electric sigmoidoscope" (73). Among his 36 patients Lockhart-Mummery saw definite inflammation in 24 and found a tumor in 7. In 4, he saw excess gelatinous mucus on a thick edematous, but still shiny, mucosa; he called the condition "chronic hypertrophic catarrh" (74). His sigmoidoscopic distinction between this chronic hypertrophic catarrh and true colitis led him to emphasize that colitis was not a neurosis but a disease with visible structural lesions. In 1907, he used the term "sigmoiditis" to indicate that with a sigmoidoscope he could be sure only that the colitis involved the rectosigmoid, and he could not know whether the whole colon was involved (75).

Two long meetings at the Royal Society of Medicine in 1909, taking up almost one hundred pages in the *Proceedings* (76), analyzed 333 patients with colitis over a twenty-year period from nine of the great voluntary hospitals in London, and again Lockhart-Mummery rightly complained that the internal medicine specialists did not use sigmoidoscopes. One of the chairmen, Sir Patrick Manson, still regarded ulcerative colitis as merely a dysentery, a position still proposed by Sandwith as late as 1914 (77).

The Mount Sinai Hospital

The annual reports of The Mount Sinai Hospital from 1857 tabulate the diagnoses assigned to diarrheal illnesses, such as Ascaris (1860) and Taenia (1864) and, in 1864, catarrh of the intestine, or gastrointestinal catarrh. These diagnoses, together with dysentery (1868) or (gastro-)enteritis (1869), remained the most common for digestive diseases after gastric catarrh.

Colitis first appears in these reports in 1876. In 1879, dysentery is divided into acute and chronic, and enteritis into acute, chronic and follicular. Colitis was further classified as membranous (1887), acute and chronic catarrhal (1888), acute and chronic ulcerative colitis and acute proctitis (1890), subacute (1892) and hemorrhagic (1897). Tuberculous enteritis was reported in 1888. By 1898, mucous colitis with neurasthenia was recognized, and in the following year membranous/croupous and necrotic colitis were described, as well as enterocolitis. In 1901, Lilienthal reported a total colectomy for "hyperplastic colitis" with ileorectal anastomosis (78).

There are occasional references in *The Mount Sinai Hospital Reports* to patients who in retrospect may have had regional enteritis. For example, in 1904 (2nd Surgical Service, p. 234), there was a patient with "Chronic Intestinal Obstruction and Stricture of Ileum" who was operated upon and survived. In 1905 (1st Surgical Service), there was a patient with a "Stricture of Ileocecal Valve (Polypoid Colitis)" who died, but no details are available. In 1906 (2nd Surgical Service), there was a patient with a tumor of ileocecal junction who died without an operation having been performed.

Tuberculosis or Granulomatous Disease of the Intestine

Mount Sinai's first published contribution to the study of ileocecal inflammation came in 1914. During a 13-year period, Weiner (79) collected 10 cases of ulcerative enteroperitoneal and hypertrophic ileocecal tumors, all of which were attrib-

uted to tuberculosis. However, pathological details were minimal and no tubercle bacilli were found, either in the resected bowel or in sputum, so that some or all of these patients may have had regional enteritis. Definite tuberculomas of the cecum with tubercle bacilli in the tissue sections, however, were still being found at Mount Sinai in the 1920s (80).

The landmark publication from Mount Sinai was in 1923 by Moschcowitz and Wilensky (81), who labored, however, under the impression that the disease had not been reported before 1908 or outside Europe. Their first patient had strictures initially of the cecum and later of the ileum. Detailed histology by O.B. Hunter showed giant cell granulomas, which were also found in the resected masses of the other three cases (in ascending colon, splenic flexure, ascending colon). Moschcowitz and Wilensky too were convinced that most patients diagnosed with hyperplastic tuberculosis of the intestine simply had granulomatous disease. They emphasized the increasing number of cases being published, "so that it is safe to say the malady is not at all a rare one." Three years later Wilensky and Moschcowitz reported another case (82). A young man of 18 presented first with a right iliac fossa abscess following a perforated appendix; the right hemicolectomy specimen showed inflammation only in the ascending colon. He was well for five years, until he had a recurrent right iliac fossa mass of thickened, coiled small intestine. The resected mass showed that only the terminal ileum was inflamed, with the now typical granulomatous inflammation. The Mount Sinai authors were satisfied that granulomatous disease of the intestine (small and/or large) was the undoubted cause of "many if not a majority of the cases of so-called 'hyperplastic tuberculosis of the colon,'" but this paper seems to have made little impact and was rarely if ever cited before 1932, even by Mount Sinai investigators in this field.

As late as 1931, tuberculosis of the intestines was still being diagnosed radiologically at The Mount Sinai Hospital. Goldfarb and Sussman (83) were well aware of work at Mount Sinai (81, 82, 84) indicating "that chronic, non-specific, infectious granuloma of the colon can resemble very closely chronic, hyperplastic tuberculosis, clinically, roentgenologically and pathologically." Two of their cases had pulmonary tuberculosis, and both laparotomy and histology of the resected colon were reported as tuberculosis. However, their third case of "tuberculosis of the colon," with narrowing of the terminal ileum and skip lesions in the colon, had a normal chest X-ray, and final diagnosis was uncertain in the absence of laparotomy.

Only one of 4,800 autopsies at The Mount Sinai Hospital between 1926 and 1938 revealed primary intestinal tuberculosis, and this case had progressed to the miliary stage (85). In the same 12-year period, seven other cases were "substantiated" as tuberculous in surgical resection specimens (although only two showed acid-fast bacilli), while 130 specimens were diagnosed as nonspecific granulomatous regional ileitis and segmental colitis. Presumably, one of the specimens re-examined by Crohn and Yarnis in 1940 was a resected ascending colon stricture reported by Klein in 1936 (86) and confidently diagnosed as hyperplastic ileocecal tuberculosis, even though no tubercle bacilli could be found. Crohn and Yarnis concluded:

> The relative scarcity of intestinal tuberculosis, as of today, in comparison with the nonspecific forms, may be explained on several grounds. The primary reason consists in the fact that all these nonspecific forms, like ileitis, were previously regarded as tuberculosis, though the scientific proof was carelessly lacking or was rarely sought for. By eliminating the nonspecific forms from all right lower quadrant granulomata, we find, on analysis, that very little remains as true tuberculosis. In the second instance, primary intestine tuberculosis, if ever a frequent disease, seems now definitely on the wane . . . bovine herd infestation by tuberculosis has been almost completely eliminated. (85)

Yet intestinal tuberculosis (proven by acid-fast bacilli in the resected specimens) was still occasionally a surprising finding at laparotomy from the 1930s to the 1950s at Mount Sinai, disproving preoperative diagnoses of granulomatous ileitis, cecal carcinoma, retroperitoneal sarcoma, pancreatic carcinoma, granulomatous jejunoileitis, acute appendicitis and metastatic carcinoma (87). Moreover, by the 1950s effective antituberculosis chemotherapy was available to arrest the tuberculosis (87).

The Two Mount Sinai Presentations of May 1932

In May 1932, there were two relevant presentations by Mount Sinai staff at national meetings in the U.S.; both presentations were sponsored by Crohn. On December 11, 1931, Crohn had written to the American Gastro-Enterological Association:

> I have an important scientific contribution I would like to present before the American Gastrological Association next May. I have discovered, I believe, a new intestinal disease, which we have named Terminal Ileitis. I should like to present the facts before the Association in connection with the general subject of Benign Granulomata of the Intestinal Tract. I am submitting the abstract on a separate sheet. My very kind regards.
>
> P.S. I should like the name of Dr. Leon Ginzburg associated with mine, by invitation, at the reading of the article. B.B.C. (88)

The first of the two presentations was read by Ginzburg at Atlantic City on May 2–3, 1932, to the American Gastro-Enterological Association. This presentation was ultimately published "in conjunction with Dr. Burrill B. Crohn" in the 1932 *AGA Transactions* (84), and subsequently in the *Annals of Surgery* (89) in expanded form in 1933. The second presentation was given by Crohn on May 13, at New Orleans, to the Section on Gastro-Enterology and Proctology of the American Medical Association. In due course, it was published in *JAMA* as by Crohn, Ginzburg and Oppenheimer (90) (see Fig.); however, the Section Program in *JAMA* April 9, 1932 states "Terminal Ileitis: Its clinical manifestations (Lantern Demonstration). BURRILL B. Crohn, New York. Discussion to be opened by JOHN E. JENNINGS, Brooklyn." (91)

Page 152 of the Program given to those at the 1932 AMA meeting included the following:

> Terminal Ileitis: Its Clinical Manifestations (Lantern Demonstration). Burrill B. Crohn, New York.
>
> **Abst.** — Report of fifteen [Editor's note: 14, in the published papers] cases of a disease hitherto undescribed in the literature, except for sporadic references to incompleted observations. The disease constitutes a clinical entity and is characterized by a chronic and progressive course, a necrosing and cicatrizing inflammatory lesion of the terminal 8 to 12 inches of the ileum, and diarrhea. Another pathognomonic feature is fistula formation; such fistulas lead usually from the ileum to various parts of the colon and occasionally to the anterior abdominal wall. The patients have all been operated on; death from peritonitis resulted in two cases, the remaining patients all being alive and well. No etiologic factor has been found as a cause of the disease. It is definitely not neoplastic nor bacterial; it may be a disease of the vascular supply of the mesentery.
>
> Discussion to be opened by W.C. Chaney, Memphis, Tenn., and John E. Jennings, Brooklyn.

The Section Minutes (92) state that "Dr. Burrill B. Crohn, New York, read a paper on 'Terminal Ileitis, its clinical manifestations' which was discussed by. . . ."

The AGA Paper

Ginzburg was A.A. Berg's house surgeon in 1925, and for the next five years his adjunct and his assistant in private practice (93). During these years, at Berg's suggestion (94), Ginzburg made a specific study of the inflammatory granulomatous diseases of the bowel. In 1927, he and Beller (95) reported 12 cases of non-metallic perforating intestinal foreign bodies (6 fish bones, 5 chicken bones, 1 wooden toothpick) inciting an inflammatory granulomatous reaction with multinuclear giant cells. Three patients had presented with intra-abdominal tumors, but in each the mucosa and submucosa were normal, as distinguished from the cases of Tietze (50) in Germany and those of Wilensky and Moschcowitz at Mount Sinai (81, 82). In 1928, Ginzburg, with Eugene Klein (96), described five cases of late fibrotic intestinal stenosis following strangulated hernia, producing tubular or annular strictures, presumably ischemic, in which the submucosa was thickened and the mucosa often ulcerated.

Ginzburg and Oppenheimer then searched back to 1920 for excised inflammatory masses of the large or small intestines (excluding sigmoid diverticulitis) and found 52 such cases. Together with Drs. Gross, Klemperer, Otani and Antopol, they restudied the pathology. They described six groups with detailed case histories in the 1932 paper (84) but with no radiographs, pathological photographs or references; these parts of the case reports appear in their December 1933 paper (89), but without the case histories or the discussion. The six groups were as follows.

1. Extra- or peri-intestinal granulomata secondary to sealed-off perforations of the bowel. These ten cases were akin to those in their 1927 paper (95).

2. Granulomata secondary to known vascular disturbances of the gut. These five were probably not those in their 1928 paper (96).

3. Localized hypertrophic ulcerative stenosis of the terminal ileum. Of these 14 patients, 12 had been studied by Ginzburg and Oppenheimer, and two added by Crohn (93). There were four modes of presentation:

   a. simulating acute appendicitis, but with the terminal ileum abnormal and the appendix normal;

   b. symptoms of ulcerative enteritis, low grade diarrhea, weight loss, colic, anemia;

   c. symptoms of chronic incomplete small intestinal obstruction;

   d. chronic intractable fistulae.

   Tuberculosis was excluded by all available tests, and indeed only six cases of localized hypertrophic tuberculosis had been resected at Mount Sinai in the previous ten years, as opposed to 18 of the non-specific variety.

4. Localized hypertrophic colitis with or without low-grade generalized colitis (cecum/ascending 5, rectosigmoid 3, midsigmoid 1, sigmoid/descending 3). Some cases also had ileal and perianal diseases.

5. Simple penetrating ulcers of the colon.

6. Lesions secondary to inflammation of the appendages of the bowel, such as appendicitis, diverticulitis, typhlitis.

The discussants of the Ginzburg and Oppenheimer paper at the AGA were all internists (84). Bockus thought these lesions rare, and wondered "whether in some individuals with undue ptosis the factor of disturbed circulation might be a contributing factor in the production of terminal ileitis by twisting the (ileo-colic) artery or by undue stasis in the vein (terminal branch)." Alvarez, however, thought otherwise: "I have long felt that there must be such a thing as terminal ileitis. I think it is a fairly common disease." Crohn re-emphasized this point:

> One may mistakenly think that we are demonstrating a very rare lesion. Now that we are aware of the clinical condition, we are seeing at Mount Sinai at least three, four or five cases a year. We had one case two months ago and I have now a case which will be operated upon on our return. At a session of the New York Surgical Society about four weeks ago, one of the members of that association presented a case of granuloma of the terminal ileum; to my surprise he was showing this same condition. The chairman asked for general discussion; six surgeons of large experience with abdominal conditions discussed the subject. Several men recounted having seen a case six years ago or twelve years ago, upon which he had operated with good result. These were surgeons with wide experience; several of these surgeons in the course of a lifetime had seen such lesions, but had apparently not been able to recognize or identify the underlying pathological process. (84)

The Ginzburg and Oppenheimer AGA 1932 presentation is referred to by Ginzburg himself (97), in the 1933 *Annals of Surgery* publication (89). However, I can find no previous account, even by Ginzburg or Oppenheimer, that they were aware that Ginzburg's presentation in Atlantic City to the AGA was published in the annual *Transactions of the American Gastro-Enterological Association* for 1932 (84).

The AMA Paper

Fifty-five years after the event, Ginzburg related the following account (97):

> In the summer of 1931, Dr. Crohn spoke to me about 2 patients of his, upon whom Dr. Berg had operated for unusual lesions in the terminal ileum. He told me that he had been to the Path Lab to inquire about the nature of these lesions. There he was told that Ginzburg and Oppenheimer had already studied and described a similar series of cases. He told me that he had spoken to Dr. Berg, who wanted me to turn over to him (Dr. Crohn) the studies and the already written article for his (Dr. Crohn's) perusal. I gave him the already written article and that was the last I saw of it, until the actual publication appeared in the fall of 1932. By that time the original short, descriptive article, limited to the actual definition of the apparently new entity, had been almost submerged under the sections that had been added by Dr. Crohn. Its volume had more than doubled!

In the spring of 1932, some members of the Mt Sinai Medical Staff noticed that on the program of the forthcoming annual meeting of the AMA, Dr. Crohn had listed an article on regional enteritis. It was also noted that the names of Leon Ginzburg (L.G.) and Gordon D. Oppenheimer (G.D.O.) who were known to be studying this same condition, were absent. A considerable to-do developed and rumors spread about this omission. Eventually, a group was informally chosen to investigate the situation. I am not personally privy to what actually went on, except that as a "subpoenaed material witness" I was pretty roughly handled by Dr. Berg, who chaired and dominated the committee. In any event, the eventual decision was that the names of Leon Ginzburg and Gordon D. Oppenheimer were either to be added and/or restored, as coauthors in the published article.

Ginzburg did concede:

> There is no doubt that Dr. Crohn "put regional enteritis on the map," so to speak. He popularized, publicized and spent much time, effort and travel on lecturing and spreading knowledge about it. His extensive collection of statistics gathered from his own practice helped clarify matters in the early days. (97)

Crohn's communication to the AMA had the title "Terminal Ileitis" (91, 92, 97) and was limited to the 14 patients of A.A. Berg, of whom 12 had been studied originally by Ginzburg and Oppenheimer's group (95) and 2 patients seen by Crohn and categorized as a distinct group which they called "localized hypertrophic ulcerative stenosis of the terminal ileum" (84, 89). The discussion was enthusiastic, with similar cases reported by Friedenwald (Baltimore), Hirschman (Detroit) and Bargen (Mayo Clinic): "This presentation would seem timely, for, with improved roentgen technique and more intensive study of intestinal disease, the condition may prove to be less [*sic*] common than it is now supposed to be. . . . I am wondering whether the designation 'terminal' is adequately descriptive. To some it has conveyed the meaning of agonal. Perhaps the modifying adjective 'regional' or some other word suggesting its localized nature, instead of the end, would be more suitable." The paper, as published in *JAMA* on October 15, 1932, was therefore entitled *Regional Ileitis* (90). Hirschmann questioned the statement that it was uncommon for a patient to have both ulcerative colitis and granulomatous ileitis, since he had "just such a case." In closing, Crohn did not address this especially important point.

Conclusion

The entity now termed "Crohn's disease" clearly has been reported in the medical literature for many centuries. However, I conclude that the Ginzburg and Oppenheimer AGA presentation in 1932 and subsequent papers (84, 85) were the definitive clinicopathological studies which established the entity of regional enteritis in both small and large intestine. Yet the earliest presentation made little impact, probably because it was delivered to a small, select audience at the AGA, could be read in 1932 only by the 100 members of the AGA in their *Transactions* (84), and did not appear in a journal of wider circulation until 1933 (89). Moreover, neither paper, i.e., the *AGA Transactions* or the one in the *Annals of Surgery*, was complete in itself, and both would have had to be read together and collated, which to my knowledge has never been done before. In both of these papers by Ginzburg and Oppenheimer (84, 89), there is a footnote: "The section on Localized Ileitis represents a joint study with Dr. Burrill B. Crohn." By contrast, the paper Crohn delivered at the AMA was to a wider audience, and ultimately appeared in print in the *Journal of the American Medical Association* (90) earlier than the previously mentioned papers.

My conclusion is based on an examination of all 3 papers, Crohn's 1932 statement (98), interviews (99, 100), and memoirs (101), Ginzburg's interview (102) and historical perspective (97), as well as Winkelstein's interview (103), all of which (except the first) were written decades after the events of 1931–1932 (see Appendix).

Epilogue

In 1933, a paper appeared with the eponymous title ". . . Regional Ileitis (Crohn). . ." (104) and another Mount Sinai eponym was born. Seventy years later, it is probably more widely used than other Mount Sinai eponyms, such as Koplik spots, the Hollander and Schick tests, or Buerger's or Tay-Sachs diseases.

Appendix

Statement by Dr. Burrill B Crohn, 1932 (98):

Following is a statement aiming to explain the relationship between Dr. Leon Ginzburg and myself on the subject of "Terminal Ileitis":

During 1929–1930 I was interested in three private cases of intestinal disease. These cases were operated upon by Dr. Berg in 1930–1931. They were all three instances of unusual pathological processes which led for the first time in our experience to the recognition of what we later named "Terminal Ileitis." Shortly thereafter Dr. Berg operated upon two more cases, confirming the fact that we had run across an interesting clinical entity. I proposed to Dr. Berg a joint publication on the subject. He preferred that I should associate with myself a younger man.

For several years previous to our clinical findings, Dr. Ginzburg and Dr. Gordon Oppenheimer had been studying benign granulomata of the intestinal tract. These were pathological studies and included a collection of general benign inflammatory processes of the intestine. Dr. Ginzburg was therefore the logical man to associate with me. The proposition to study and to write, from me to Dr. Ginzburg, was accepted by him, and a completely harmonious relationship has existed from that day until this week.

Among Dr. Ginzburg's general collection of specimens of intestinal granulomata was one which corresponded very definitely with the pathological picture of Ileitis. This specimen had been described in detail in a paper written by Dr. Ginzburg on intestinal granulomata, which unpublished paper and specimen I was privileged to see. The work progressed smoothly; fourteen clinical cases were collected, seven of these being old cases and old pathological specimens which had been unclassified, but which now in the light of our new grouping, took definite form and were now clearly recognized as examples of this same disease.

Publications

It was suggested by Dr. Ginzburg in November or December 1931 that we write a joint preliminary paper and publish it quickly in the *Annals of Surgery*. This was suggested because I had been free in showing the specimens to prominent medical men, visiting the hospital, all of whom had stated that they had never seen a like process in clinical medicine. I invited Dr. Ginzburg to my home for dinner and to write the paper. We divided the work, he to write the pathology and the surgical treatment of the disease, and I to write the clinical description. I finished my share within three days and then waited so long for Dr. Ginzburg's contribution, that it finally became evident that it would be too late for any publication before the annual meetings. We decided that the subject was of a sufficient importance to warrant fairly wide notice. I therefore reserved space on the program of the Gastrointestinal Section of the AMA Meeting in New Orleans. I personally was to go, at my own expense, and read that joint paper. I also arranged to have Dr. Ginzburg present the entire subject of benign granulomata of the intestinal tract before the American Gastro-Enterological Association, lending my name, so that be might be included "by invitation." This paper was to be a general paper on granulomata, but to deal prominently with ileitis. This was to be the first reading of that original paper by Doctors Ginzburg and Oppenheimer. I did not ask to be co-author in this paper. These were the two important national presentations. The Academy of Medicine Meeting of the Medical Section was an afterthought suggested by Dr. Baehr. Both names were to appear on the program, I as the member of the Section necessarily to read the paper. There were three local hospital presentations, two were in the course of Friday afternoon rounds, one by Dr. Ginzburg, one by myself; there was one presentation at the February Clinical Conference. This presentation was by Dr. Ginzburg with my knowledge and agreement, in fact, on my suggestion.

All these arrangements were apparently harmoniously made, and as far as I knew, harmoniously carried out. There were however, two possible slip-ups; one, the arrangements with Dr. Andresen, Secretary to the Section of the A.M.A., were made by telephone to Brooklyn. Apparently in the course of these several telephone messages, Dr. Ginzburg's name slipped by, at least as far as the preliminary program published in the April number of the A.M.A. Dr. Andresen assures me that the permanent program will only appear at the New Orleans session, and he cannot re-call whether Dr. Ginzburg's name is or is not on that program. The second slip was made by Dr. Pardee at the Academy of Medicine, which unfortunate occurrence was corrected by Dr. Pardee publicly at the meeting, and due apology made. The final manuscript bears the names of myself and Dr. Ginzburg, and in addition as a courtesy to the unfortunate Dr. Oppenheimer, his name has been included as co-author, though I have never seen nor spoken to Dr. Oppenheimer on this subject.

I should like to further state that very little question of priority, or of precedence or of privilege has ever arisen between Dr. Ginzburg and myself. I am convinced that any bad feeling arose from poor advice from some of his more radical friends. In submitting to the Committee

the documentary evidence confirming my statements, I wish to say that I am perfectly satisfied with my own conduct in the matter. I feel that I never was under any compulsion to include Leon Ginzburg in this study, as I feel convinced that the identification and recognition of this not unusual clinical condition had been missed until I pointed it out. And I make this statement with the full knowledge that Dr. Ginzburg had described one specimen of ileitis in his paper on granulomata, that Eli Moschcowitz had seen a somewhat similar but not identified pathological condition in 1927, and that several surgeons of wide experience had at least operated upon one, or at most two cases, without having recognized or understood the nature of the pathological process. I invited Dr. Ginzburg to cooperate as a matter of harmony and courtesy, and to establish a harmonious link with the Pathological Laboratory, thus accelerating all processes.

I do not regret today that invitation, and feel, that I could continue to work harmoniously with Dr. Ginzburg if the subterranean and unknown faction that refuses to be named and refuses to come out in the open, would cease insinuating to him that someone is trying to wrong him.

In final proof of my spirit in the past under similar conditions, I submit reprints of the last several years. In nearly all my publications I have included younger men. In many of them I have put my name last. In one, the name of a medical student, Lionel Auster, who worked with me five to six years ago; in another publication from my clinic, from my own material, Sylvan Manheim appears as sole author, though I wrote the paper; and in many other similar conditions, I have always cooperated with younger men. (B.B. Crohn)

In 1965 Dr. Crohn recalled (99):

When I was a medical student at P and S, College of Physicians and Surgeons, Professor Evan Evans, Professor of Medicine, said when we came to the chapter on the small intestine in the textbook of medicine, "Gentlemen, we will skip the next chapter, since there are no recognized diseases of the small intestine, except tuberculosis."

In the laboratory at Mount Sinai, during the autopsies, Dr. Libman always insisted that the small intestine, not even to bother to open it and look into it. *[Perhaps Crohn meant to say that the small intestine should always be opened.]* In spite of that, we saw no diseases of the small intestine. We assumed that everything was intestinal tuberculosis.

I had a private case with a mass, with fever, with diarrhea and abdominal pain, but at this time we had new laboratory tests which the past generations didn't have. We had the Von Pirquet test for tuberculosis. We had the intradermal tubercular test. And now we had X-rays of the chest.

In this boy, all the tests for tuberculosis were negative. I said to Dr. Berg, "There is only one way to cure this boy, and that's to operate upon him." Whereupon Dr. Berg said, "I will not operate for intestinal tuberculosis. I was persuaded by Dr. Trudeau at Saranac to operate on five of this [type of] case for intestinal tuberculosis. Three of them died, and the other two I never heard from and I never want to."

So it took a great deal of persuasion on my part to talk Dr. Berg into resecting this case, into operating and resecting it. He did resect the case. When we opened it, we saw that it was something new, a granuloma. We went through every exhaustive test in the laboratory, including guinea pig inoculations, rabbit inoculation, watching over it for months, exhausting ourselves to try to find tubercle bacilli or the evidence of tuberculosis. And finally we said this was a non-specific disease.

At this time also Drs. Leon Ginzburg and Gordon D. Oppenheimer had been engaged independently in a study of granulomas of the body, of the abdominal cavity, intestines, liver, spleen, and anything else. They were doing pathological work, not clinical work. When we . . . I . . . had corralled fourteen cases using my private cases . . . the first three were private cases, using also ward cases . . . we found fourteen cases on which to publish the paper. And I suggested to Dr. Berg that he be the co-author with me, because he and I had done all the clinical work. He, in the graciousness of his personality said, "I think you should take Ginzburg and Oppenheimer as your partners. You can leave me out."

Ginzburg and Oppenheimer therefore became co-authors with me. The paper was read at New Orleans in the spring of 1932. It was immediately acclaimed. Strange that no one questioned the fact that a new clinical entity had been described. The Mayo people went home to Rochester, Minnesota. Shortly, I heard from them that they'd taken out and reviewed all the X-ray films of the past couple of years, and shortly they published, on the basis of old films which they had ignored and overlooked, their very large experience with ileitis.

John Cantor came home, got his film out, saw that he too had overlooked the X-ray picture of ileitis, and he said, "It looks like a string to me, a spasm in a string." It was on the basis of his remark, his published remark, that the demonstra-

tion of ileitis was called "a string sign." (B.B. Crohn)

In 1968 Crohn recalled (100):

Here is the case history of the first case of ileitis: The patient was admitted in 1929. A young man, 17 years old, with fever, abdominal mass and diarrhea. And I put down the diagnosis as "Tuberculosis" because it was the only etiologic agent that could cause this. The patient was readmitted in 1930. This time I left the diagnosis out because I couldn't determine it. He was readmitted the 3rd time in 1930; again the diagnosis: "Tuberculosis of the Colon, Hyperplastic Ileocecal Type," given oxygen intraperitoneal insufflation with improvement. Admitted the 4th time in 1931, he was operated upon. Now the old diagnosis of tuberculosis was out and the diagnosis became: "Terminal Ileitis, with resection of terminal ileum, cecum, ascending colon and of the transverse colon." And that was case number one of regional ileitis. And then, as I said in my book, we began to look for granulomas of the intestinal wall, because Dr. Leon Ginzburg and Dr. Eli Moschcowitz had studied granulomas in the laboratory as pathological specimens but without any clinical collaboration or correlation between the laboratory findings and clinical aspects of the cases; they were doing pure pathology research. It was my opportunity to combine pathology and clinical medicine, having had training in both disciplines. Dr. A.A. Berg and I then re-examined all the obscure cases of diarrhea with abdominal mass and with fistulas; very shortly we had the data on the first 14 cases. (B.B. Crohn)

In 1965 Ginzburg recalled (102):

This was in the mid-Twenties. From there, I suggested to Dr. Gordon Oppenheimer, who at that time was working in surgical pathology at the old laboratory, that we ought to keep an eye on these granuloma[s] of the bowels, and that we were interested in inflammatory tumors and strictures of the bowel. At that time we were interested in them mainly in so far as it would be possible to distinguish them from neoplastic diseases of the bowel.

I was an Assistant for Dr. Berg and on his service. We collected a series of these cases. Then we started to encounter something that we'd never seen before, and we couldn't make head or tail of it. It was a disease involving the distal ileum. Those cases all seemed to stop short right at the ileocecal valve. Most of them, in those days prior to radiological study of the small bowel, which was very primitive then, had been diagnosed as lymphosarcoma or carcinoma, and as a matter of fact there were a couple of cases that had sigmoidal ileofistulas. The deformity in the sigmoid was interpreted as evidence of carcinoma of the sigmoid and that's what patients were operated upon for.

In any event, we had a few of these specimens. And at the same time, we were very much interested in some chronic intractable fistulae that occurred after appendectomy, after what was supposed to be an operation for bad appendicitis. A great many of these patients had had local closures attempted, which were all failures, and some had had an ileocolostomy with exclusion, where they healed up, but we hadn't had any specimens.

Then one day a patient who had had intractable fistulae following appendectomy and drainage of an abscess, a resection of a segment of bowel was undertaken, again by Dr. Berg. And incidentally, Dr. Berg is the unsung hero of ileitis, because he resected every specimen on which the studies were made. In this case, he again resected the terminal ileum, and we were all aflutter, because when that specimen was opened, it looked just like the specimens that had previously been resected for what appeared to be tumors and obstructions in the bowel.

See, the original cases were operated on mostly for obstruction. That's what brought them to operation. These people had all had histories of diarrhea, etc. But this was the first case where a link was shown between the basic underlying pathology of these so-called post-appendicular fistulae, which we found not to be due to the appendix, since the appendix stump was quite healed over. It was in this case that we saw that these lesions had perforated in between the leaves of the mesentery, and that an abscess had formed intermesenterally first which had perforated secondarily.

So we hooked up these different types, and we defined four different types at that time: one, where patients presented themselves with signs of obstruction; then with signs of what you might call an enteritis; thirdly, those who had appeared as acute appendicitis or appendix abscesses; and finally, the ones that appeared as intractable fecal fistulae and intra-abdominal inflammation. And although now we just take it for granted, after all there was quite a bit of clinical diversity between an appendix, or an intra-abdominal inflammatory mass which drained interminably, and a patient who had an obstruction without any evidence of intra-abdominal inflammation, who had simply had symptoms of severe enteritis without any evidence either of obstruction or intra-abdominal inflammation.

About this time, Dr. Crohn had a couple of cases. We had, I think, six or seven different types of inflammatory diseases. We had excluded diverticulitis, because by that time it had been pretty well studied, but aside from that we had the ones due to foreign bodies, we had the strictures and so forth due to vascular impairment, we had this regional enteritis, which we had originally called segmental granulomatous disease of the bowel. Incidentally, although we didn't hook up the two, we also found cases of localized (. . . we called them hypertrophic) colitis, which is the same as the granulomatous colitis, but we didn't hook them up with the granulomatous diseases of the bowel. We thought that was something quite different. We also called attention in that paper to the fact that in some of these patients with the granulomatous localized hypertrophic localized colitis, this was also evidence of a diffuse colitis. This, too, had been brought out, I think at the Mayo Clinic, where they had some time ago reported the segmental hypertrophic colitises.

But the one thing that we called to the attention, struck the attention, was this regional enteritis, and Dr. Crohn saw a couple of cases of this type which had been operated on by Dr. Berg. Since his mind hadn't been to some extent beclouded by the other types of inflammatory diseases of the bowel, he picked this out, took it out of the ordinary group and described it by itself. We were originally going to describe it as one of the groups of inflammatory diseases of the bowel producing tumors or strictures. We didn't know the etiology then any more than we knew the etiology of colitis.

The paper first appeared; it was read by Dr. Crohn. The paper was written in different parts. The paper was written actually by Dr. Crohn and myself absolutely independently.

I don't think that one has to be a literary Sherlock Holmes to tell by reading the paper who wrote what. I mean, the styles are entirely different. One of them is a rather clipped, succinct style, and the other is a rather florid and — well, call it poetic if you wish, or hyperbolic or something — but at any rate, a diffuse style. And anyone who wants to, who is interested in literary Sherlock Holmesism, can find out just who wrote what by reading the article.

I wrote the pathology. Actually the study of the pathology was done mainly by Dr. Klemperer, Dr. Otani, and Dr. Oppenheimer. He [Oppenheimer] followed these things up in the lab, and he looked these things over, and they were again gone over by Dr. Klemperer and Dr. Otani, and some animal inoculations were made from titrated glands, etc. to see whether tuberculosis was present or not. And a considerable study was made to see whether we could ever find any evidence of caseation. We never found any evidence of caseation, although from many other standpoints, both in the local specimens and in the glands, there were things that looked very much like tubercles. But never in any instance was the tubercle bacillus found in smear or culture, and caseation was never demonstrated.

Getting Dr. Berg to participate in the paper was quite a job. There was one thing about Dr. Berg. He had a peculiar type of integrity about these things, and he would never permit his name on a paper if he didn't actually do the writing. I mean, it's a far cry from what we have today, where thousands at the bidding of the chief, post over land and ocean without cease, to get various arbeits [Editor's note: German for "jobs"] under way and to write them up, and then to have the chief's name, like Abu Ben Adam's, leading all the rest. But Dr. Berg, being an old-fashioned gentleman, brought up in the Victorian code of morals which we all rather snicker at nowadays, nevertheless would never permit his name to be put on any paper that he hadn't written. He just wouldn't have his name on it. We kept after him time and time again. And as a matter of fact, whenever I've ever had anything to say about the paper, I've always brought out the fact that actually, if it wasn't for Dr. Berg, who had the intestinal fortitude — and it took some in those days, in the 1920s, to do the massive resections that he did — certainly regional enteritis would not have come from this institution. (L. Ginzburg)

Footnote by Dr. Janowitz (1997):

Ginzburg told me that Dr. Berg insisted both that his own name should not be on the paper and that the three authors' names should be in alphabetical order.

In 1965 Dr. Winkelstein recalled (103):

I think that I know at first hand exactly what took place at the time of this so-called discovery of regional ileitis or regional enteritis.

What happened was this. Dr. Berg, A.A. Berg, was very interested in the findings, in his surgical material . . . which, as you know, was vast . . . something like six to eight operations a day, year in year out . . . finding inflammatory tumors in various parts of the gastrointestinal tract: stomach, small bowel, and in the colon. Dr. Berg was a very busy man, in private practice and surgically, operating all the time, and couldn't make these studies himself. So he assigned all these cases to two young men who at the time were adjuncts and attending surgeons in the

Hospital, Drs. Leon Ginzburg and Gordon Oppenheimer. And for a certain number of years, they collected these cases. They collected quite a few cases and they put them together in a paper. This paper was entitled "Non-Specific Granuloma of the Gastrointestinal Tract."

There were various headings for the different types of granulomas or inflammatory lesions of the gastrointestinal tract in this paper. This paper was written for presentation before the American Gastroenterological Association, I say this with all honesty and sincerity and clear recollection of what happened . . . before Dr. Crohn, Burrill Crohn, had ever heard of the disease called terminal ileitis. In this paper, I believe that Drs. Ginzburg and Oppenheimer had either fourteen or sixteen cases, [in] which they described both the clinical and the pathological characteristics of the disease, very correctly.

Some time after this paper was written, but before it was presented to the American Gastroenterological Association, a patient consulted me in my office. This patient had a bloody diarrhea, and he said, "It's due to hemorrhoids," and he wanted me to treat him. I said I refused to treat him unless I examined, with sigmoidoscopy and barium enemas and GI X-rays and so on. . . .

He went to Dr. Crohn's office. Dr. Crohn at once diagnosed tuberculosis of the intestine, and he sent him to Florida to bask in the sun. While there, he suddenly developed an intestinal obstruction and was rushed back to New York, and Dr. A.A. Berg operated on him. Dr. Berg believed in resection of the terminal ileum for terminal ileitis, as it was called then, or regional ileitis or enteritis, as we call it now. So he resected the involved area, and did either an ileotransverse colostomy or an ileosigmoid colostomy, I don't remember which.

Dr. Crohn's name was not on that paper, with one exception, which I'll tell you in a moment. Dr. Crohn came running to the pathology laboratory. At that time I was a volunteer assistant in pathology, and I had this specimen. I was studying it. Dr. Crohn was unable to come to the operation, but he wanted to see this specimen, since this boy had been his patient. I opened the specimen and showed it to him. He said, "What is this?" I said, "This is terminal ileitis." "What is terminal ileitis?" he said to me. "I never heard of it." So I explained to him: Drs. Ginzburg and Oppenheimer had sixteen cases from Dr. Berg's service. We know all about it . . . it's an inflammatory lesion, it's not tuberculosis, it's not a tumor, it's not a malignancy. And we didn't know the etiology, but it belonged in this group of the gastrointestinal tract.

So, as luck would have it, a few weeks later Dr. Crohn ran into a patient. He was the examining physician for some fraternal organization, and he sent in a patient to the ward that had the same lesions. To his credit, I must say that he got quite excited about this . . . not knowing anything about the disease before. It seems that he and Dr. Berg for a long time had been enemies. He had worked with Dr. Wilensky, and they both published some papers, or they rubbed Dr. Berg the wrong way, and he disliked both of them exceedingly. . . .

So Crohn went to Berg, and he told him he was very interested in this subject. Berg didn't care about Ginzburg and Oppenheimer, two young adjunct attending surgeons, and he gave them orders to turn over that part of the study to Dr. Crohn from that point on. They resisted this very strongly. And the Hospital . . . whether it was the board of directors or the Superintendent of the Hospital or the medical staff . . . appointed a committee to look into this. The committee reported that Dr. Berg and Dr. Crohn were 100 percent wrong, and that the disease belonged to Ginzburg and Oppenheimer, but in view of the fact that if this was brought out outside of the Hospital it would cause a lot of scandal, they decided to drop the whole matter, and let things take their natural course.

The course they took was that Dr. Berg threatened to get Dr. Ginzburg and Dr. Oppenheimer out of the Hospital if they didn't fall in with his wishes and turn that part of the study over to Dr. Crohn. And Dr. Crohn took it over from that point on, published the big paper with the other two in 1931 [1932]. Their paper had been written a couple of years before that, I believe. Dr. Crohn is a wonderful publicist, as a speaker and as a writer, and he quickly put this on the map, to the extent that it is now known as "Crohn's Disease," which is absolutely unfair. In the first place, it's not a new disease. In the second place, he was not the first to describe it, and he has never anywhere, publicly or in writing, said that the credit belongs originally to Dr. Berg, for separating this material, and after that to Ginzburg and Oppenheimer, who wrote the first description and collected the cases. (A. Winkelstein)

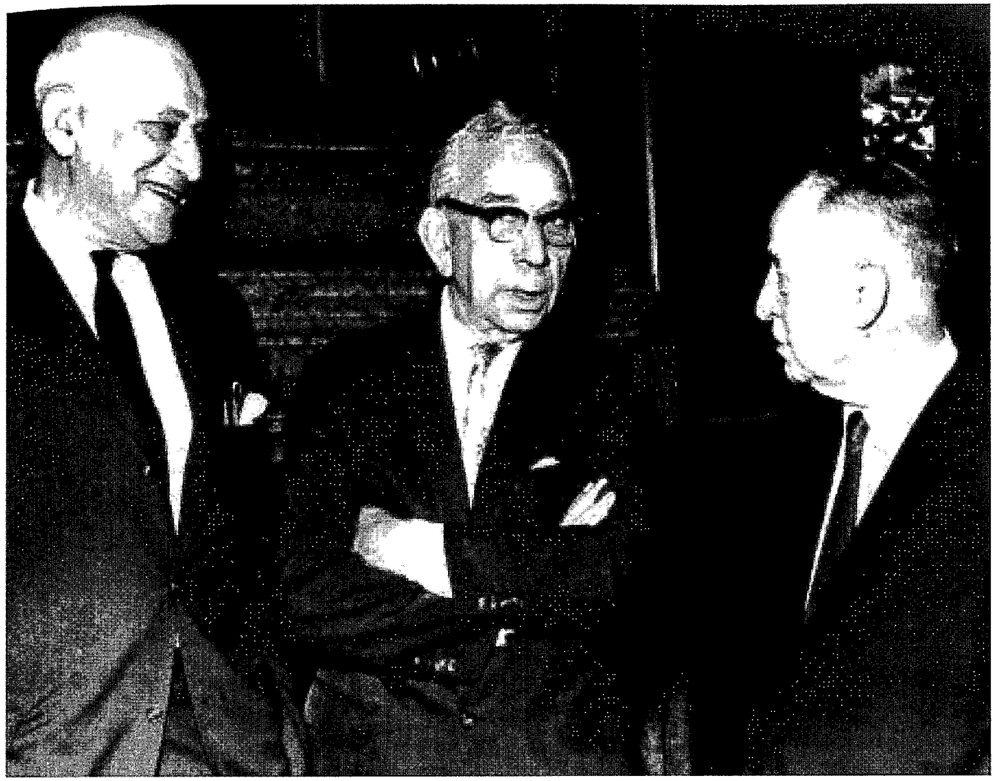

Fig. Drs. Oppenheimer, Crohn and Ginzburg

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19

Inflammatory Bowel Disease after 1932

HENRY D. JANOWITZ, M.D.

Abstract

The clinical diseases of ulcerative colitis (UC) and Crohn's disease (CD) were defined by 1932–1933. After that, the major conceptual developments were the recognition that regional enteritis could clearly involve the colon, and that cancer and toxic megacolon could occur in both CD and UC. In the last half of the 20th century the main thrust of gastroenterology at The Mount Sinai Hospital has been in inflammatory bowel disease (IBD), with contributions to extra-intestinal manifestations, measurement of clinical activity in CD, the natural history of the placebo arm of controlled trials, complications and therapy with corticosteroids, 5-ASA, 6-mercaptopurine, immunomodulators and cyclosporine. Actuarial life tables were introduced for postoperative recurrence and re-operation rates, as well as for quality of life analysis. Two forms of CD were defined, perforating and non-perforating, and the role of the fecal stream was explored in light of the higher risk of recurrence after operations with anastomosis as compared with ileocolostomy. **Key Words:** Inflammatory bowel disease, regional enteritis, ulcerative colitis, Crohn's disease.

THE STUDY OF INFLAMMATORY BOWEL DISEASE (IBD) has a long history at The Mount Sinai Hospital. The preceding section by Hugh Baron documented the path that led to the discovery of the disease we now call Crohn's disease (CD). By 1932–1933, the papers of Ginzburg and Oppenheimer (presented before the American Gastroenterological Association), Crohn, Ginzburg and Oppenheimer (before the American Medical Association), and by Ginzburg and Oppenheimer (before the American Surgical Society) had described the entity not only in the ileum, but in the colon as well. With the subsequent description of cecal involvement (1) and the recognition of perineal disease (2), the basic clinical and pathologic features of this still enigmatic, serious, chronic and lifelong disorder were in place.

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The 1930s to the 1950s

One would have expected an explosion of interest and study at the institution where it was discovered. Crohn continued to collect his series of cases, and with John Garlock, his surgeon, reported the results of resection (3, 4). In 1939, Ginzburg and his colleagues noted the surprising effects of bypassing the ileal lesion by diversion of the intestinal fecal stream (5). However, gastroenterologists at The Mount Sinai Hospital did not focus intensely on CD. This was especially so in the question of colonic involvement. Bargen and Weber (6) and Crohn and Berg (7), in the 1930s, called attention to "right-sided colitis," and several years later, in 1952, Wells (8) recognized "segmental colitis" as a variety of CD, separating it from ulcerative colitis (UC). Indeed, most American gastroenterologists remained indifferent as to this important feature of CD. This held true not only for Crohn himself but for the other gastroenterologists at Mount Sinai, except for Richard Marshak, the radiologist, who firmly maintained and lectured on the fact that regional enteritis could clearly involve the colon (9).

Two factors were probably important in causing this delayed recognition of Crohn's colitis. First, the focus of clinicians such as Asher Winkelstein, and radiologists such as Bernard Wolf, was directed to peptic ulcer disease and hiatal hernia. The Gastrointestinal Research Laboratory, directed by Franklin Hollander and sponsored by the surgical departments at The Mount Sinai Hospital, especially that headed by Ralph Colp, was centered on ulcer disease, acid secretion, vagotomy, and the mucus barrier of the stomach (see chapters 5–10). Additionally, David Dreiling had started his work on the pancreas in this laboratory (see chapter 15).

Perhaps more important was the strong stand that the pathologist, Sadao Otani, had taken. He had insisted that the ileocecal valve separated regional ileitis from ulcerative colitis. It was the publication by Lockhart-Mummery and Morson (10) and the worldwide acceptance of their concept of CD of the colon that really opened the floodgate at this institution.

Some indication of the climate of opinion at Mount Sinai during this interval may be seen in the fact that, when I arrived as an intern in November 1939, seven years following the seminal papers, the general clinical attitude was tinged with slightly skeptical amusement at Crohn's interest in regional enteritis. When I returned again in 1950, after World War II and a period of research elsewhere, the climate had changed. Senior clinicians, and especially radiologists, were intensely interested in IBD. Marshak meticulously described the evolution of regional enteritis as it appeared in serial x-ray films during the life of a patient (11).

Interest too was centered on ulcerative colitis, focused, in particular, on toxic dilation of the colon. R.H. Marshak, L.J. Lester, and A.I. Friedman (12) had described the megacolon of ulcerative colitis and coined the term "toxic megacolon" and Greenstein et al. (13) followed up with a study of the outcome of toxic dilation of the colon in UC and CD. Even the problem of cancer in inflammatory bowel disease had been recognized. Crohn had described the first case of cancer of the colon in UC in 1925 (14). In 1956, Ginzburg et al. (15), described the first case of carcinoma (of the jejunum) in regional enteritis.

From the 1960s

The formal organization of gastroenterology at The Mount Sinai Hospital in 1958, with the founding of the first separate division within the Department of Medicine, marked the beginning of more intense interest in many aspects of inflammatory bowel disease. Contributions by those in Surgery, Radiology and Immunology are detailed in this issue, by Aufses, Maklansky and Mayer. By the end of the 1960s, an informal group of clinical investigators was slowly forming. Present, Korelitz, and myself, from the Division of Gastroenterology, were later joined by Sachar and Meyers. The combined cooperation of the surgeons Aufses, Gelernt, and Greenstein played an important part. Greenstein had begun to assemble a database of all patients with IBD (UC and CD) seen at the hospital, making an especially important contribution. The return of Lloyd Mayer to The Mount Sinai Hospital, after a brilliant stint at the Rockefeller Institute in the laboratory of Henry Kunkel, further strengthened the collaborative team in immunology, while a younger generation of graduating fellows who became involved with this group included Lichtiger and Kornbluth. These contributions are now reviewed.

The Natural History and Complications of IBD

The first American paper on Crohn's colitis in the post-Lockhart-Mummery and Morson era appeared in *The New England Journal of Medicine* in 1963, a joint paper of Lindner (a fellow in Gastroenterology), Marshak, Wolf (Radiology), and myself (16). Articles on "granulomatous colitis," the term we used at The Mount Sinai Hospital to avoid offending Leon Ginzburg, appeared in *JAMA* in 1965 (17). Others were then published in rapid succession in the *Annual Review of Medicine* of 1966 on ileocolitis (18) and in *Gut* in 1966, with Marshak as a co-author (19).

Extra-intestinal Manifestations of IBD

The long-standing interest in these manifestations culminated in 1976 in the paper most frequently cited in the literature, which was from this division (20). It offered for the first time a classification into the categories of "colitis associated," "results of small bowel pathology," and "an immunological group." This classification helped sort out the protean manifestations associated with inflammatory disease activity (especially in the colon) from those unrelated to disease activity.

Measurement of Clinical Activity in CD

The measurement and quantification of disease activity in CD represent a continuing problem. A wide range of laboratory tests, including

labeled colonic or fecal leukocytes, are widely used by different clinical investigators. Following the report of Thomas et al. (21) on the use of random stool specimen concentrations of fecal α-1-antitrypsin in children with CD, we reported that this technique was a useful measure of clinical activity of CD in ileum and colon in adults (22) and the effects of therapy and anatomical extremes in this disorder (23). Other studies indicated that the erythrocyte sedimentation rate (ESR) was also a useful indicator of disease activity, but primarily in extensive colonic disease as opposed to small bowel involvement (24, 25).

Natural History of Inflammatory Bowel Disease

More recently, our interest in the natural history of IBD led to the novel suggestion that we look at the "placebo arm" of published trials. Since almost all patients described in the literature with these diseases have been treated with a variety of drugs, we used the placebo arm of controlled trials as a measure of the natural history of CD and UC. This approach, focused on the placebo response in IBD both in Crohn's disease (26) and ulcerative colitis (27), has markedly affected evaluations of results of current therapeutic trends.

Complications of Inflammatory Bowel Disease

The complications of IBD have been explored with an avid and active interest on the part of the division of gastroenterology.

Cancer in IBD

Cancer in IBD is fully discussed by Adrian Greenstein (see chapter 24). Here we call attention to the early recognition of cancer risk in Crohn's disease, not only in bypassed loops (28, 29), but also in long-standing Crohn's disease of unoperated small bowel and colon (30–33).

Toxic Dilation of the Colon

An early interest in toxic dilation of the colon was sparked by Marshak (34), and again in 1985, in a paper by Greenstein, Sachar and others (13), devoted to the outcome of toxic dilation in patients with these diseases. In 1980, pneumomediastinum was described as a perforating complication of toxic dilation (35) and in 1988 Present reported on his therapeutic use of "rolling" of the patients with toxic megacolon (36).

Obstructing Hydronephrosis

The discussion of renal disease in IBD began at The Mount Sinai Hospital with the report by Deren, Porush, Levitt and Khilnani on the study of kidney stones as a complication of UC and CD (37). The important and, up to then, frequently unrecognized obstructive hydronephrosis complication of Crohn's disease was detailed by Present, Rabinowitz, Banks and Janowitz (38).

Suppurative pylephlebitis with liver abscess was recorded early in 1962 (39).

Blood Disorders

Autoimmune hemolytic anemia was described in some detail along with an analysis and evaluation of its current therapy in 1979 (40). Cryoglobulinemia with skin involvement, including gangrene of fingers and toes, was described early in 1979 and in 1981 (41, 42). The association of acute myelogenous leukemia with ulcerative colitis was first correlated by Fabry, Janowitz and Sachar with the considerable amount of previous x-ray exposure in these patients (43). Additional reports from other institutions then followed.

Pyoderma Gangrenosum

Pyoderma and trauma to the upper extremities were reported in 1981 as being associated with IBD, their existence having been known to dermatologists but apparently not recognized by gastroenterologists (44). An important study of the outcome in patients with pyoderma treated by colectomy appeared in 1983 (45). It showed that patients with active colitis healed promptly, while patients with less active disease required up to one year to heal, although all did heal eventually.

Amyloid

Amyloidosis, especially renal amyloidosis, has been of continued interest to the division. One of the earliest series (five cases of amyloidosis) in regional enteritis was published in 1960 (46) and the 50-year experience with 25 patients was recently brought up to date in *Medicine* (47) in 1992. The first cases of renal amyloidosis with severe proteinuria associated with inflammatory disease treated successfully with colchicine were reported by Meyers, Janowitz, Gumaste and other colleagues (48).

"Metastatic" CD

Along with cutaneous manifestations of CD patients, an early interest in "metastatic" CD was reported from the gastroenterology division and the Department of Dermatology in 1984 (49).

Pancreatitis

A very early report by Meyers and colleagues from the division stressed the curious association of acute pancreatitis with active Crohn's disease (50). This may be related to the recent report of elevated titers of pancreatic tissue antibodies in Crohn's disease (51).

Central Nervous System Involvement

Early on, Silverstein and Present called attention to the tragic situation of central nervous system catastrophes, in the form of cerebrovascular occlusion, in some young patients with CD (52).

Pregnancy and IBD

Mount Sinai gastroenterologists have had a very long and active interest in the effects of pregnancy on the course of IBD patients and on the outcome of the fetus, beginning with the early paper of Crohn, Yarnis and Korelitz (53). Korelitz has continued to review his and his colleagues' experiences in this area, reporting his data from time to time. His review on the effects of sulfasalazine and steroids on pregnancy and the fetus has given important reassurance to gastroenterologists worldwide of these drugs' safety (54). Present and co-workers will soon report on the largest series of pregnant women who have conceived successfully while on 6-mercaptopurine; this will help resolve the question of its safety.

Therapeutic Contributions

The division has made important contributions to the medical therapy in IBD in several areas.

ACTH versus Hydrocortisone

The introduction of steroid therapy in 1954 by Truelove and Witts (55) focused clinical attention for a long time on the intravenous administration of ACTH and the use of steroids and the routes by which they were administered. The publication by Meyers, Sachar, Goldberg and Janowitz (56), comparing the clinical responses to intravenous ACTH and hydrocortisone of patients sick with ulcerative colitis, showed that the response depended on patients' recent experiences with steroids. ACTH was superior to hydrocortisone for patients who had no recent exposure to prednisone. Resisted at first, the concept seems now generally accepted for ulcerative colitis.

Mesalamine

An early paper by Meyers, Sachar and Janowitz, joined by Present (57), showed the efficacy of olsalazine (Dipentum) in ulcerative colitis in a prospective, randomized, double-blind, dose-ranging, placebo-controlled trial. This study helped to establish this variant of 5-ASA for patients allergic to or intolerant of sulphasalazine (Azulfidine).

Immunomodulators

Although azathioprine had been used since 1964 for the treatment of UC, fear of malignancy and "cure" by colectomy, with a reasonably normal lifestyle with the Brooke ileostomy had led to its disappearance from the therapeutic armamentarium for chronic ulcerative colitis. There can be no doubt that the introduction of 6-mercaptopurine by Present, Korelitz, Wisch, Glass, Sachar, and Pasternack for the treatment of Crohn's disease in a long-term, randomized, double-blind study (58) marked an important turning point in the history of treatment for CD. The detailed story of the slow reception, published controversy and ultimate acceptance of this form of therapy (59) is given by Korelitz and Present (see chapter 23). Its triumphant story is to be attributed to the persistence and determination of the investigators, and their careful follow-up study on toxicity and malignant potential. Its worldwide acceptance is a feather in the cap of this division.

Cyclosporine

Although cyclosporine has not proved to be very effective in CD, its introduction for severe ulcerative colitis refractory to steroid therapy by Lichtiger, Present, Kornbluth and co-workers in 1994 signaled another important new modality for these seriously ill patients facing urgent colectomy (60). Careful follow-up studies of Kornbluth and others on toxicity and quality of the long-term results have already furnished us with valuable information on its long-term benefits and risks (61, 62).

Omega 3 Fatty Acids

Although the real place of fish oil omega 3 fatty acids as an anti-inflammatory agent and as a treatment in UC and CD is yet to be defined, interest in this modality was shown by a very early open trial for UC in this division (63).

Mount Sinai Gastroenterology and Its Interaction with Patients

At present, with our intense interest in the effects of IBD and its therapy on the lives of our patients, it is important to remember Mount Sinai's contributions which go back a long time. One of the earliest papers on the "quality of life" with IBD was a publication on the study of the quality of life after surgery for CD in the form of psychosocial assessment, published twenty years ago (64). More recently, direct comparisons are being made between medical and surgical treatment, for their quality of life outcomes (65).

The formation of the National Foundation for Ileitis and Colitis (NFIC), now known as the Crohn's and Colitis Foundation of America (CCFA), at The Mount Sinai Hospital, was an important step in organizing the partnership of the scientific community with the lay public, especially the families of patients with IBD 33 years ago. Present was its first Research Fellow, and was succeeded by Sachar. Its National Scientific Advisory Committee was chaired first by Janowitz (1969–1979) and later by a Mount Sinai alumnus, Lenox Hill's Korelitz (1981–1984). This partnership now raises millions of dollars for research, patient information books (edited by Present and colleagues) and physician education, an amount far greater than the NIH budget for IBD.

The Ileostomy Society, organized at Mount Sinai by Dr. Albert Lyons, was really the first self-help organization for the sufferers of IBD.

Conceptual Contributions

There are four areas in which gastroenterology at Mount Sinai has made significant contributions to conceptual advances in IBD. The first was the use of actuarial life tables for postoperative recurrence and re-operation rates in IBD. The paper by Greenstein, Sachar, Pasternack and Janowitz (66), which compared crude and cumulative rates, was among the first such uses of the life tables as a statistical method in IBD. No publication on the long-term follow-up in this field can now be accepted without the use of this method of presentation.

Second, since studies of the natural history of untreated IBD patients have not been done, and cannot be done, the use of the placebo arm of controlled trials as introduced by Meyer and Janowitz, when applied to Crohn's disease (26) and UC (27), revived interest in the placebo effect in IBD.

Third, based on Greenstein and Sachar's concept, the recognition of two clinical forms of CD, a perforating and a non-perforating one, and their indications for repeated operation as published in *Gut* (67), has attracted considerable attention and recent confirmation. This concept has proved central to current classifications of patients with Crohn's disease (68).

Fourth, workers in the division have recently questioned how effective our current drugs are in the treatment of CD (69), UC (70) and severe Crohn's and ulcerative colitis (71). The first two papers used the method of meta-analysis, and the third was an analytic review of selected clinical trials. The thrust of these papers is to point out the relatively limited effectiveness of our traditional and current drug therapies.

The Role of the Fecal Stream in Crohn's Disease

Leon Ginzburg and his colleagues, Ralph Colp and Marcy Sussman (5), noted that in patients with CD, diversion of the intestinal stream led often to such clinical improvement of the primary lesion in the cecum and/or ileum that the intended 2nd stage resecting the central lesion could be "indefinitely postponed." The important observation stimulated a long-standing interest in the division on the role of the fecal stream on the pathogenesis of localized CD.

Further evidence slowly has accumulated that surgery with anastomosis is associated with a higher risk of recurrence than ileocolostomy. Emphasized by De Dombal, Goligher and colleagues (72, 73), similar findings were also pointed out by Sachar and his colleagues at The Mount Sinai Hospital (74, 75). We have confirmed this again in a new study of end ileostomy in CD (76).

As a result of these lines of evidence, we (Janowitz, Croen, Sachar) have prepared a comprehensive historical and analytic review of all the clinical and laboratory evidence in this area (77). Many, but not all, of the accepted clinical features of CD are consistent with the contributory role for the intestinal stream concept, and fit in with recent animal studies on the role of luminal bacteria in inducing ileal and colonic inflammatory changes in some spontaneous, or transgenic, or "knock-out species."

Interaction with the Official World of IBD Activity

Gastroenterologists at The Mount Sinai Hospital have played important roles as presidents of the American Gastroenterological Association (Crohn 1935, Janowitz 1972); as the chairman of the International Organization for the Study of IBD (Sachar 1989–1992); and in founding the new series, the *American Journal of Digestive Diseases* (Janowitz, 1968–1978). Sachar launched the AGA's clinical teaching project with its first unit on IBD (78), and has contributed a number of influential and lively editorials to *Annals of Internal Medicine, Digestive Diseases and Sciences, Gastroenterology, Gut, Journal of Clinical Gastroenterology,* and *The New England Journal of Medicine.*

Monographs from the division include those of Waye on endoscopy (79), Janowitz on a clinical approach to IBD (80), and G.E. Friedman on therapeutic pharmacology in gastroenterology (81), a book by Marshak and Lindner (82), and patient information books by Present and colleagues (83, 84). The place of The Mount Sinai Hospital in the clinical world of management of IBD was advanced significantly by the endoscopic techniques used by Jerome Waye. He was the first to perform colonic endoscopy without radiographic control, and has published, lectured and edited books on gastroenterological endoscopy. Members of the original gastroenterological group in IBD played a significant role in the evolving status of the American College of Gastroenterology. The following have been among its presidents: David Dreiling, Jerome Waye, Burton Korelitz, Arthur Aufses, and Lawrence Brandt.

Appendix

The Contribution of the Division of Gastroenterology to Academia: Former Fellows and Members of the GI Division since 1958

Name	Position
J. Hugh Baron	Former President, British Society of Gastroenterology; Consultant at Hammersmith and St. Mary's Hospitals, Imperial College School of Medicine, London
Alvin Gelb	Chief of Gastroenterology Division, Beth Israel Hospital, New York
Peter Banks	Clinical Director of Gastroenterology, Brigham and Women's Hospital, Boston, MA
Fred Saibil	Head of Gastroenterology, Sunny Brook Health Science Center, Toronto
Lawrence Brandt	Chief of Gastroenterology, Montefiore Medical Center, The Bronx
Jane Geders	Chief of Gastroenterology and Hepatology, Methodist Hospital, Brooklyn
Mark Korsten	Gastroenterology Fellowship Program Director and Associate Chief of Medicine, Bronx VA Medical Center
Vivek Gumaste	Chief of Gastroenterology, The Mount Sinai Service of the City Hospital Center at Elmhurst, Queens

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The History of Surgery for Crohn's Disease at The Mount Sinai Hospital

ARTHUR H. AUFSES, JR., M.D.

Abstract

Almost certainly, the physicians and surgeons of The Mount Sinai Hospital cared for patients with inflammatory bowel disease prior to 1932. However, the accepted beginning of the surgery of granulomatous inflammatory bowel disease (IBD) and Crohn's disease (CD) at our institution occurred when the landmark paper by Crohn, Ginzburg, and Oppenheimer was published in 1932.

As a major referral center for patients with both medical and surgical complications of IBD, the surgical service has had a long and abiding interest in the disease. This review highlights the major contributions of our staff to the management of this illness over the past 67 years.

Despite major innovations in both medical and surgical management of patients with Crohn's disease, individuals suffering from this condition are ideally managed by a multidisciplinary team. **Key Words:** Crohn's disease, surgery.

June 8, 1855 — THE DOORS of The Jews Hospital opened to admit patients. Patient No. 1 was Mr. L.S., a forty-two-year-old white male with a fistula-in-ano. He was operated on by Dr. Israel Moses, one of the three attending surgeons on the staff at that time. The operation was successful and the patient was discharged on June 14th (1). Seventy-seven years later, Crohn, Ginzburg, and Oppenheimer (2) noted that the disease they were reporting was "associated with the formation of multiple fistulas," and in 1934, Bissel (3) provided the first report of a perianal fistula in association with ileitis.

Did Mr. L.S. have Crohn's disease?

April 17, 1866 — The name of our institution was changed to The Mount Sinai Hospital.

April 14, 1889 — Dr. John Wyeth, who joined the surgical staff in 1880, operated on a 12-year-old male with abdominal pain of four days' duration and drained a large abscess. Postoperatively the patient developed an enterovesical fistula which closed slowly (4). Although this young patient had had no prior history, and the history of the present illness was most suggestive of appendicitis, the development of an enterovesical fistula was certainly not in keeping with the diagnosis of appendicitis, but is a significant complication of Crohn's disease.

Did this patient have Crohn's disease?

December 30, 1899 — Dr. Howard Lilienthal (5) operated on a 21-year-old female who "had for years suffered from diarrhea, accompanied by hemorrhages and the passage of foul mucus, and finally become so weak and anemic that a left inguinal colostomy had to be performed to give rest to the lower portion of the colon and rectum. The surgeon who opened the colon at this time saw that the walls of the viscus were covered with polypoid growths which bled easily even on gentle manipulation. The patient was very much benefitted by the operation, the hemorrhages finally ceasing so that it was thought best to close the opening. No sooner had she left the hospital, however, than her old trouble returned in all its severity. . . . Dr. Lilienthal first performed a cecostomy for irrigation of the colon, then on March 6, 1900 performed an ileo-sigmoid anastomosis (using a Murphy button to perform the anastomosis) with exclusion of the terminal ileum and the remaining colon. Three months later, the excluded bowel was removed. After two more procedures, the patient did well and on January 14, 1901 was presented to the New York Surgical Society as a case of 'hyperplastic colitis.' At that time the patient was 'in excellent general health and has 2 movements a day. . . .'" (6)

Did this patient have Crohn's disease?

February 18, 1919 — Dr. A.O. Wilensky (7) operated on a twenty-three-year-old male with a right lower quadrant mass. The past history included diarrhea of about two years' duration, weight loss and anemia, and an attack of acute suppurative appendicitis treated by appendectomy. Six months after the procedure, he developed pain in the right lower quadrant and a mass appeared. The mass was in the cecum and was resected with anastomosis. Although a postoperative fecal fistula necessitated another operation, the patient did well save for episodic diarrhea, until December 1920, when an episode of acute intestinal obstruction required a resection of about twelve inches of the ileum. He again did well for about two years, when he developed an episode of peritonitis, for which no cause was found at laparotomy. Following drainage, he recovered. Pathological study revealed a granulomatous lesion of the cecum with multiple giant cells, usually present within clumps of lymphocytes. "The entire thickness of the gut appears densely infiltrated. . . . A rather strange finding is the presence of giant cells in what seems an apparently normal lymph follicle in a portion of the contiguous colon that is otherwise entirely normal." Examination of the small bowel revealed that "the gut is extremely thickened and enlarged. The peritoneal surface is much congested and is covered with fresh fibrin. Cross-section shows an immense thickening of all the coats of the gut so that the lumen is merely a bare slit. The infiltration involves the adjacent mesentery which averages 1 cm. In thickness . . . fresh fibrin covers the surface of the mucosa. Removal of the fibrin reveals numerous superficial ulcerations." Microscopic examination was similar to the colon, but there were far more giant cells, the majority of which contained an unrecognizable foreign body.

Did this patient have Crohn's disease?

May 13, 1932 — Dr. Burrill B. Crohn, as the sole author, presented a paper entitled "Terminal Ileitis" at the annual meeting of the American Medical Association in New Orleans. In the discussion that followed, Bargen stated that "several cases of this type have come to operation annually at the Mayo Clinic." He felt that the term "terminal ileitis" was inappropriate because the disease was not a "terminal illness," and he also prophesied that the disease would be described elsewhere in the intestinal tract. Crohn's manuscript was published in the *Journal of the American Medical Association* (2) in October 1932, and the name of the syndrome was changed to "regional ileitis." Also, the names of Drs. Leon Ginzburg and Gordon S. Oppenheimer were added as co-authors, since they had accumulated a large series of cases, not otherwise categorized, of unusual conditions of the terminal ileum, which included the cases presented by Crohn. Their work was presented (also in May 1932) at the meeting of the American Gastroenterological Association and finally published in the *Annals of Surgery* (8) in January 1933. At the time, Dr. Oppenheimer, who subsequently became the Chief of Urology at The Mount Sinai Hospital, was working in the pathology laboratory and Dr. Ginzburg was the assistant to Dr. A.A. Berg, the surgeon who had operated on the 14 patients in the original series.

Although the patients described earlier may or may not have had Crohn's disease, there is little doubt that the disease had existed prior to 1932. But was it a new disease? Janowitz (9) speculated that "one cannot escape the conviction that this really is a new disease, which emerged in the early part of the century, for it is difficult to believe that the great European pathologists of the 19th century who did such careful autopsies would have missed the striking pathologic entity or confused it with tuberculosis, whose appearance they knew so well." On the other hand, cases reported more than one hundred years earlier are most suggestive, and the cases reported by Dalziel (10) in 1913 almost certainly had granulomatous disease of the bowel, affecting both small and large intestine. Six of nine were successfully operated on.

The accepted beginning of the surgery of granulomatous inflammatory bowel disease (IBD) and Crohn's disease (CD) at The Mount Sinai Hospital occurred when the landmark paper by Crohn, Ginzburg, and Oppenheimer was published in 1933 (2). The fourteen patients who made up this series of cases were all operated on by Dr. A.A. Berg, one of the leading surgeons of his day and a chief of service at The Mount Sinai Hospital. Dr. Ginzburg stated (11): "Dr. Berg was an extraordinary individual. The extent of his surgical practice was almost incredible in its day, and it would be difficult for one to believe at pre-

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sent. He operated both morning and afternoon six days a week, and not infrequently on Sunday as well." Berg, as the surgeon for all of the patients, was given the opportunity to be a co-author. However, he declined (12), since it was his policy not to put his name on a paper unless he had personally written a significant portion of the manuscript. Had he accepted, and since the authors were listed alphabetically, we might now be talking about "Berg's disease" (see chapter 18).

In 1934, the first report of a patient with ileitis crossing the ileocecal valve to involve the cecum and ascending colon was reported by Dr. Ralph Colp (13). Dr. Colp was a graduate of the College of Physicians and Surgeons of Columbia University, trained at the Presbyterian Hospital, and was a senior surgeon at the Beekman-Downtown Hospital before he joined the staff of the Department of Surgery of The Mount Sinai Hospital in 1923. The patient, a twenty-two-year-old medical student, had been operated on at the Beth Israel Hospital where Dr. Colp was a consultant. Dr. Colp noted that "the microscopical pathology of both the ileum and the cecum were similar, that of a nonspecific granuloma." He went on to say that "nonspecific granulomas of the terminal ileum, the ileocecal region and the colon are probably one and the same disease." Although Hirschman of Detroit, in his discussion of Crohn's presentation, had cited the case of an 18-year-old male with "chronic ulcerative colitis" of 9 years' duration, who at operation was found to have a "large doughy thickened ileum" of about 12 inches in length, Colp's report is the first documented and published case of granulomatous ileocolitis.

The years between 1932 and 1960 were punctuated by tremendous advances in our understanding of this newly described entity. Numerous reports documented that granulomatous inflammatory bowel disease was truly panenteric, and the distinction between granulomatous and ulcerative colitis was firmly established by Lockhart-Mummery and Morson (14) in 1960. Until that time (and even after, in some quarters), granulomatous colitis had been considered to be a variant of ulcerative colitis. What in retrospect was clearly granulomatous ileocolitis had then been considered by most gastroenterologists and surgeons to be ulcerative colitis or a variant thereof, in association with regional or granulomatous disease of the small bowel.

It must be remembered that, in the years that these early patients were operated on (1925–1935), antibiotics were nonexistent, fluid and electrolyte management was in its infancy, and blood transfusions were a tour de force. As a result, one-stage ileocolic resection, the preferred operation today and the operation performed by Berg and others of his day, then had a significant mortality rate, as high as 25%. As a consequence, many surgeons performed the procedure in two stages. In the first procedure, the ileum proximal to the diseased segment was divided, the distal end closed and the neoterminal ileum anastomosed to either the transverse or sigmoid colon. At a later date, the excluded segment was resected.

Two years after Colp's 1934 report, Berg (15), who had performed primary resections on all of the early cases, reported on "an operative procedure for right-sided ulcerative colitis." This was an ileo-sigmoidostomy with exclusion of the most distal ileum. In addition, however, the sigmoid proximal to the ileal anastomosis was divided, and the distal end closed. A stoma was created with the proximal end. This effectively isolated the colon, and allowed for drainage of colonic mucus and for irrigation of the colon via the stoma. Not all of these patients did well and several, therefore, had resection of the excluded bowel. The article (15) contains an artist's rendition of the specimens. One of them depicts a terminal ileum and colon with deep punched-out ulcers and significant thickening of the affected areas, almost certainly granulomatous disease rather than ulcerative colitis.

In 1938, Richard Lewisohn (16), best known as the individual responsible for the development of citrate solution for blood preservation, summarized the then current thinking of The Mount Sinai Hospital surgical staff. His conclusions are worth noting, as many are still relevant today:

> 1) Segmental or regional enteritis is not a rare disease. 2) Opinions differ widely not only as to the pathogenesis of these interesting lesions, but also as to the best method of surgical treatment. 3) The lesion is encountered most frequently in the terminal ileum. However, it may occur in any part of the gastro-intestinal tract. 4) It is doubtful whether segmental colitis and ileocolitis are clinical entities. They may represent an attenuated form of acute ulcerative colitis and ileitis. 5) Perianal fistulas are frequently encountered. 6) Ileocolostomy with division of the ileum may effect a complete cure. 7) In the presence of fistulous communications with other parts of the intestinal tract primary resection becomes mandatory.

Ileotransverse colostomy with exclusion became the procedure of choice at Mount Sinai, and in 1939 Ginzburg, Colp, and Sussman (17) presented 32 cases of "ileostomy with exclusion," at the meeting of the American Surgical Association. Nineteen of the procedures were performed as definitive surgery for inflammatory disease, and in 13 patients the operation was performed as a first-stage procedure in the management of carcinoma of the right or transverse colon. The development of this procedure was later eloquently described by Ginzburg in 1955 (18):

> Originally, localized ileitis was treated by ileocolic resection. Before the present era of antibiotics, blood banks, intestinal intubation and improved anesthesia, this procedure was accompanied by a mortality rate rarely under twenty per cent and at times considerably greater. In order to reduce the mortality, recourse was had to a two stage operation, the primary one consisting of an ileocolostomy with exclusion. Secondary operation revealed that recession of the active inflammatory process was present in the excluded loop in almost all cases. The routine second stage procedure was therefore abandoned and performed only on those few occasions where there was evidence that healing had not taken place in the excluded loop. The results following ileocolostomy with exclusion proved to be as good as that obtained following resection and were achieved with a negligible mortality.

This operation became known as "The Mount Sinai Operation." That it was a wise decision at the time was evident in the 1945 report by Garlock and Crohn (19) reporting the series of patients personally operated on by Dr. Garlock. For these 145 patients, the mortality rate was 16% for a one-stage resection (9/55), 12% (3/25) for a two-stage resection, and 0% in 65 patients treated with ileotransverse colostomy with exclusion. In 1980, 35 years later, we were able to report 100 consecutive ileocolic resections for CD without mortality (20). Today almost all major medical centers report large series of one-stage resection with minimal mortality. Unquestionably, the advances noted by Ginzburg have had a great impact on the improved results.

Ileotransverse colostomy with exclusion as a definitive procedure fell into disfavor when it became apparent that the procedure had deficiencies. The inflammatory process in the excluded loop did not always subside, and the right colon was unnecessarily sacrificed, thereby losing its water-absorbing capacity. The report of Greenstein and his colleagues (21), showing that the excluded loop was a major risk for the development of small bowel cancer, was probably the final nail in the coffin for this procedure. On the other hand, there will always be a role for this procedure in the rare instance of massive inflammatory reaction, where the surgeon feels that resection may prove fatal. In this situation, ileocolostomy with exclusion as the preliminary step in a staged procedure may prove to be lifesaving.

In the 66 years (1932–1998) since the first description of Crohn's disease, the surgeons and surgical specialists of the staff of Mount Sinai have contributed significantly to present-day understanding of the state of the art management of the disease and its complications. As The Mount Sinai Hospital has been a major referral center for IBD, its surgeons have amassed a broad experience in the management of the surgical issues confronting this group of patients and have shared their experiences via literally hundreds of papers. In the past thirty years, approximately 5000 patients with Crohn's disease and ulcerative colitis have been treated. In 1968, Dr. Allan Kark, the then chairman of the Department of Surgery, recruited Dr. Adrian Greenstein to the staff. Dr. Greenstein became the "keeper of the records"of our inflammatory bowel disease population. His publications on the extraintestinal manifestations of IBD (22) and the nature and magnitude of reoperation and recurrence (23), written in collaboration with our colleagues in Gastroenterology, are classics. His bibliography of more than 135 papers, 30 book chapters and innumerable abstracts has catalogued the gamut of IBD.

For more than twenty years, the Department of Surgery has encouraged medical students to participate in research. There have also been a number of outstanding fellows. Many of the surgical faculty have an uncanny knack of stimulating and encouraging the students and fellows to be academically productive. Utilizing electron microscopic techniques, Michael Marin, then a student and now a member of the faculty in vascular surgery, made significant contributions to our understanding of the earliest pathological abnormalities in CD (24–26). Anthony Pucillo did yeoman work on the papers relating to the development of cancer in bypassed loops (21) and was a co-author of papers on cancer in ulcerative colitis (27, 28). Among the fellows, Yamazaki and Ribeiro deserve special recognition for their contributions to the papers dealing with carci-

noma of the small bowel in CD (29), the management of intra-abdominal abscess in CD (30), and a review of colorectal strictures in CD (31). One of Adrian Greenstein's many contributions related to the concept of two types of CD, i.e., obstructive and fistulizing (32). Originally criticized by many in the field, this concept is now generally accepted. Recent laboratory work by Dr. Robert Greenstein and colleagues (33) may provide the molecular basis underlying the concept.

Almost all of the abdominal surgeons in the department have contributed their knowledge and specific expertise in papers, monographs, book chapters, and reviews. Dr. Tomas Heimann has focused his efforts on the immunological aspects of CD, and their effect on the postoperative course and recurrence (34–40). His paper on the factors responsible for early symptomatic recurrence (41) was presented at the 1993 meeting of the American Surgical Association. Dr. Paul Tartter, one of the first to document the effects of blood transfusion on the immune system, has studied the effects of transfusion in CD patients undergoing surgery (42, 43). Dr. Isidore Kreel has had extensive surgical experience in the management of CD. In association with Dr. Arthur Aufses and then Dr. Gary Slater, he was one of the first to point out the value of ileostomy in CD (44, 45). Slater and Aufses have also been major contributors to what has been an important cooperative venture on the part of all of the surgeons of the department. A partial listing of other papers appears in the reference list (20, 46–66).

Mount Sinai Medical Center was one of the first academic medical centers to create a separate division of endoscopic surgery (1992) to promote the use of these new surgical techniques. The experiences of these laparoscopists with respect to resection for CD were reported shortly thereafter (67–69).

In conclusion, starting from the first description of the disease now known throughout the world as Crohn's disease, the surgeons of The Mount Sinai Medical Center have worked in close collaboration with colleagues in gastroenterology to the benefit of many grateful patients. This collaboration will continue to promote not only superior patient care, but also the future training of physicians and other health care workers in the ever-changing aspects of the treatment of Crohn's disease.

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Pioneer Gastroenterological Radiology Studies

DANIEL MAKLANSKY, M.D.

Abstract

In the middle third of the 20th century, Mount Sinai radiologists were able to describe and establish specific radiologic criteria for the diagnosis of many gastrointestinal diseases. They then delineated specific radiologic patterns to diagnose such diverse conditions as inflammatory bowel disease of the small bowel and colon, protein-losing disorders, vascular disease of the small bowel, benign and malignant tumors, metastases and lymphoma of the gastrointestinal tract. Richard H. Marshak, Bernard S. Wolf, and Mansho T. Khilnani were the leaders in these radiologic investigations which established criteria that enabled generations of subsequent radiologists to arrive at definitive diagnoses.

Key Words: Small bowel radiology, regional enteritis, Crohn's colitis, inflammatory bowel disease, diverticulitis, esophagus.

Introduction

STIMULATED BY THE ABUNDANCE of clinical material provided by the gastroenterologists on the staff of The Mount Sinai Hospital from the 1930s through the 1960s, Mount Sinai radiologists were able to collect, catalog, correlate and establish specific radiologic criteria for the diagnoses of a number of gastroenterological diseases and conditions, so as to enable generations of subsequent radiologists and gastroenterologists to arrive at definitive diagnoses.

Regional Enteritis

Once "regional enteritis" (Crohn's disease) had been described by Crohn, Ginzburg and Oppenheimer (1) and was generally accepted as a disease, many patients came to Mount Sinai's GI Clinic for treatment. And many came specifically to see Dr. Crohn himself, at his private office. In 1944, Dr. Richard H. Marshak joined Dr. Crohn's practice as his radiologist, at 1075 Park Avenue, New York, and had the opportunity to perform appropriate barium examinations on many patients with ileitis and other gastroenterological diseases. Within a few years, in collaboration with Dr. Bernard Wolf, Director of Radiology at The Mount Sinai Hospital, and Dr. Mansho Khilnani, Dr. Marshak was able to use this abundant material to identify the radiologic features of regional enteritis and present these findings in a logical and sequential fashion. Using this radiographic material, Dr. Crohn wrote a seminal monograph in 1949 (2), illustrated by Dr. Marshak's small bowel barium studies (Figs. 1–3), describing the pattern of radiologic changes in regional enteritis.

In 1953, Marshak and Wolf (3, 4) studied 71 cases of chronic ulcerative granulomatous jejunitis and explained the sequence from the nonstenotic to the stenotic phase. Furthermore, they demonstrated the diffuse nature of jejunoileitis which sometimes could involve the entire small bowel. They presented criteria to distinguish the marked thickening and nodularity of the folds associated with Crohn's disease from similar findings in other entities, such as lymphoma.

Subsequently, Drs. Marshak, Wolf and Khilnani transformed radiology of the small bowel from the nonspecific diagnosis of "disordered motor pattern," so commonly offered in the 1940s and early 1950s, into a coherent understanding of the radiologic manifestations of a variety of small bowel diseases, including not only inflammatory bowel disease but also such entities as sprue (5) (Figs. 4 and 5), malabsorption (6), protein-losing disorders of the gastrointestinal tract (7), parasitic infestation of the small bowel (8), immunoglobulin deficiency disease (9), vascular disease of the small bowel, including vasculitis (10, 11), benign and malignant tumors of the small bowel (12), small bowel metastases (13) and lymphoma (14). Marshak and Lindner (15) assembled and published, in 1970, the material previously reported. *Radiology of the Small Intestine* became the first standard text of small bowel radiology.

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Footnote: Figures 1–6 are illustrations of the original radiographs from the files and film library of the late Dr. Richard H. Marshak.

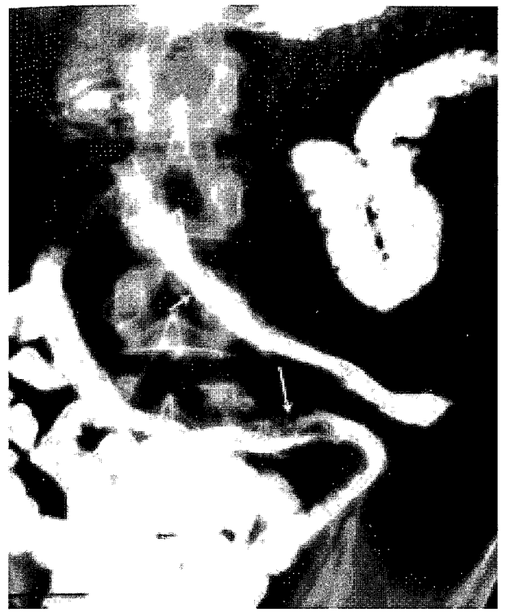

Fig. 1. Non-stenotic type of ileojejunitis. The loops are rigid and markedly separated. The mucosal pattern is cast-like (short arrow). Several pseudopolyps are also identified (long arrow).

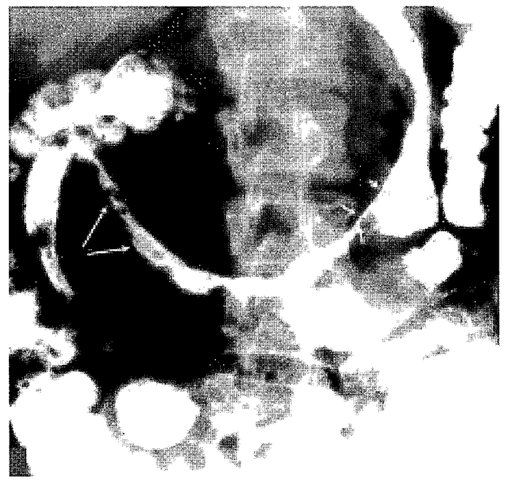

Fig. 2. Stenotic phase of ileojejunitis. The distal jejunum and proximal two-thirds of ileum are involved with alternating areas of narrowing and dilatation (short arrows) with superficial ulceration (long arrows) and separation of the loops.

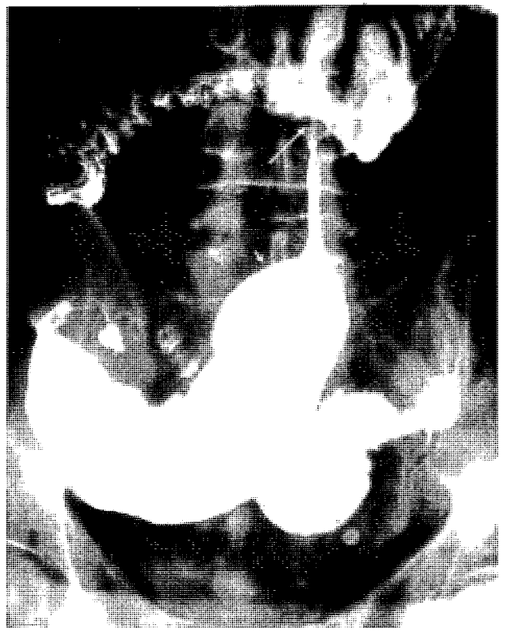

Fig. 3. Recurrent ileitis with marked stenosis and proximal dilatation (short arrows). The patient is status post ileo-transverse colostomy (anastomosis — long arrow).

Inflammatory Bowel Disease of the Colon

The Mount Sinai radiologists and gastroenterologists also investigated and described the radiologic changes in inflammatory bowel disease of the colon. Marshak, Wolf and Eliasoph had published "Non-specific Ileocolitis" (16) in 1956 and "Segmental Colitis" (17) in 1959, before the landmark publication of Lockhart-Mummery and Morson's, "Crohn's Disease (Regional Enteritis) of the Large Intestine and Its Distinction from Ulcerative Colitis" in 1960 (18). In these papers, the authors referred to granulomatous disease of the colon and were able to identify the radiologic features which distinguish it from ulcerative colitis.

Early descriptions of other radiologic manifestations of inflammatory bowel disease included a 1950 description of megacolon by Marshak and Lester, reporting a transition from a normal-sized

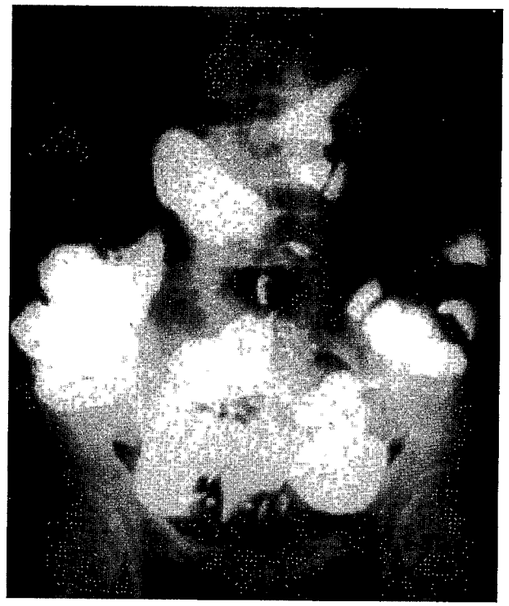

Fig. 4. Sprue. Marked segmentation in association with the moulage sign. Additionally, there is moderate dilatation and hypersecretion.

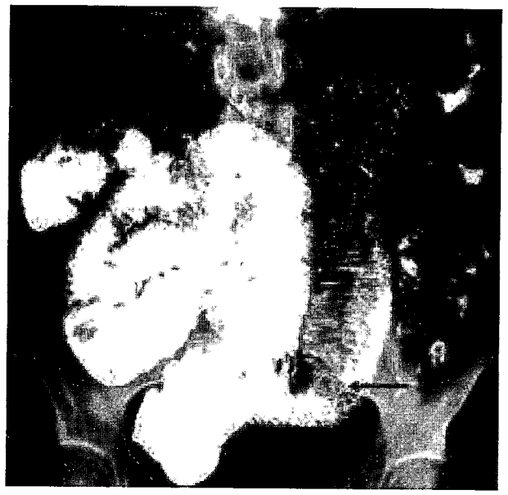

Fig. 5. Sprue. Marked dilatation, flaccidity, flocculation and non-obstructive intussusception (arrow).

bowel in a patient with ulcerative colitis, to subsequent development of toxic megacolon (Fig. 6) (19, 20). The radiologic features of strictures of the colon associated with ulcerative and granulomatous colitis were also presented by Mount Sinai radiologists in 1962. Further studies of inflammatory bowel disease of the colon by Wolf and Marshak in 1962 (21, 22) and by Marshak,

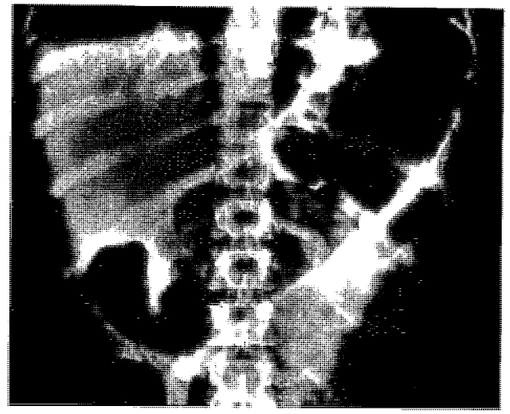

Fig. 6. Megacolon, a complication of ulcerative colitis. There is marked dilatation of the transverse colon with effacement of the haustral pattern and nodularity of the contour.

Linder and Wolf in 1966 (23) clearly distinguished Crohn's colitis from ulcerative colitis on the basis of their specific radiologic findings.

Other Colonic Disorders

Other disorders of the colon were described by Mount Sinai radiologists, including radiologic findings in diverticulitis with abscess formation and vaginal fistula (1948) (24), diverticulitis and diverticulosis (1957) (25), diverticulitis of the cecum and right colon (1958) (26), lipoma of the colon (1954) (27), scirrhous carcinoma of the colon (1963) (28) and familial polyposis with special emphasis on the differential diagnosis and radiologic features of metastases to the colon, by Khilnani, Marshak, Eliasoph and Janowitz (29) in 1966.

Esophagus

Additionally, Dr. Bernard Wolf was particularly interested in the x-ray demonstration of esophageal disease, beginning with an early description of peptic esophagitis (30), followed by a series of papers, many with Marshak and Khilnani, on the roentgen diagnosis of hiatal hernia (31), contraction ring associated with gross hiatal herniation (32), peptic ulcer of the esophagus and esophagitis with gastric-lined esophagus (33), as well as a description of the gastroesophageal vestibule and its differentiation from the phrenic ampulla and minimal hiatal herniation (34). Wolf's initial description of "use of a one-half inch barium tablet to detect minimal esophageal strictures" (35) presented an objective method for measurement of esophageal strictures (36).

Conclusion

The papers and text described above were important, classical contributions to the understanding of the x-ray findings in diseases of the gastrointestinal tract. In many cases, these primary descriptions acted as a guide to subsequent authors and clinicians during the next three to four decades.

On a personal note, I was privileged to know and work with several of these radiologists who were pioneers in gastrointestinal radiology, including Bernard Wolf, Mansho Khilnani and, most significantly, Richard H. Marshak. Initially, they were my mentors and, later, my colleagues. Although they had different personalities, they all shared a passion for excellence, a remarkable dedication to their work, and intellectual and mental energy to allow them to pursue their goals relentlessly until achieved. Richard Marshak, in particular, was instrumental in advancing small bowel radiology by deciphering the complexities of the follow-through small bowel barium study. In the decades that Dr. Jerold Kurzban and I spent working with Dr. Marshak in his office, we were exposed to an extraordinary spectrum of gastrointestinal radiology, an experience which helped us to maintain the high standards set by our predecessors.

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IBD:

Immunologic Research at The Mount Sinai Hospital

LLOYD MAYER, M.D.

Abstract

An evolution in our understanding of the inflammatory bowel diseases (IBD), ulcerative colitis and Crohn's disease, correlates with increased knowledge of the function of the mucosal immune system. In the early 1960s and 1970s, IBD was considered to be an autoimmune disease in which there was a directed attack by humoral and cellular elements of the immune system against intestinal tissues. These studies did not withstand the test of time, and from the 1970s through the 1990s there was a growing appreciation that defects in cellular immunity, not auto-reactive in nature, played a larger role in disease pathogenesis. Research at Mount Sinai focused in on these cellular T cell defects and helped pave the way for the current model of disease pathogenesis. **Key Words:** IBD, Crohn's disease, ulcerative colitis, immunology, epithelial cells, T lymphocytes.

Introduction

CROHN'S DISEASE, as described by Dr. Burrill Crohn and colleagues at The Mount Sinai Hospital in 1932 (1), was initially thought to be an infectious disease, comparable to mycobacterial infections of the intestine, described in the past. The description of Crohn's disease came at a time when there was a limited understanding of the immune system and when genetic diseases were only recognized if they were autosomal dominant or recessive. The concept of a distinct mucosal immune system was decades away, and complex genetic disorders could not even be explored. Still, Crohn and his colleagues were not too far off. As is the case for mycobacterial diseases, the expression of disease relates to the host's response, which is genetically regulated and immunologically mediated. Tools to analyze these latter components of the host response only started to become available in the 1970s as lymphocytes, monoclonal antibodies and cytokines were described. It is only recently that we have had the ability to characterize specific genes, with high throughput technology to map genetic loci.

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The end result of these advances is a new hypothesis relating to the pathogenesis of inflammatory bowel disease (IBD). It encompasses many of the components of host response which had previously evoked passionate arguments concerning their validity or regarding the roles of such areas as genetics, environment, immune system, specific pathogens, psychogenic causes, allergies, etc. The current consensus takes many of these factors into account and is built upon an interactive concept. Simply stated, the hypothesis is that in a genetically predisposed host, there is an abnormal immune response to both pathogens and nonpathogens in the gut. IBD is one of many chronic inflammatory diseases known to be multigenic.

Genome-wide screening analyses have identified loci which are IBD generic as well as ulcerative colitis (UC) and Crohn's disease (CD) specific (2–11). It may be that CD and UC involve 5–8 distinct genes and that the nature of the gene defect not only dictates the type of disease but also the subcategory of the disease (e.g., fistulizing vs. inflammatory CD, left sided vs. pancolitis, ileitis vs. segmental colitis). It is plausible that one or more of these genes codes for defects in host defense, as for example, abnormalities in barrier function or defects in mucosal immunoregulation. IBD can be viewed as two events: the trigger or initiating event, and the perpetuation of the immune/inflammatory

response. Genetic abnormalities may account for one or both of these events.

In early descriptions of CD and UC, emphasis was placed on infectious etiologies. This was plausible, since as alluded to earlier, CD looked like intestinal tuberculosis and UC looked like many infectious types of colitis. However, attempts to define transmissible agents were fraught with poor reproducibility and misinterpreted data. Many of the studies, using stool filtrates from IBD patients to transmit disease into various animal models, reported the ability of an agent in IBD stool to induce colonic inflammation or foot pad granulomas in mice. These were largely the result of reactions to foreign bodies and not a true IBD picture (12, 13). Furthermore, there was the clinical observation that some patients developed IBD following different documented intestinal infections (e.g., post-turista, Salmonella, viral gastroenteritis, etc.). These observations suggested that there may not be a specific infectious cause of IBD, but rather that any infection (in a genetically predisposed host) may result in the initial inflammatory reaction in IBD. Either the persistence of the organism, or defects in regulating the inflammatory response, would result in the perpetuation of the disease. This scenario has recently been validated with studies in a variety of new animal models of IBD, where either barrier function or immune regulation has been altered (see below) (14–29). If these animals are reared in a germ-free environment, they fail to develop colitis (still exposed to dietary antigens — proteins, carbohydrates and lipids) (14, 16, 19, 22, 30–36). If their gut flora is replete with nonpathogenic normal flora (particularly anaerobic flora (*Bacteroides vulgatus*), the disease is expressed. This has been shown to be true in every animal model tested to date, suggesting a uniform role for normal flora in IBD. In fact, one German group has documented a loss of the normal tolerance for autologous flora in patients with IBD (16). These findings suggest that both the initiation and perpetuation of inflammation in IBD relate to an aberrant reaction to the normal constituents in the gut. It places the defect squarely on the shoulders of the host immune/inflammatory response.

Immunologic Research in IBD at Mount Sinai

Role of Cell-Mediated Immunity

How did Mount Sinai contribute to the current paradigm described above? Early studies at Mount Sinai helped switch the focus away from autoimmunity and the role of antibody, to the current focus on cellular or T cell-mediated immune responses. These studies assessed the integrity of T cells in the systemic immune system. The concept at that time was that cells in the peripheral bloodstream might mirror what was actually happening in the intestine. Thus, Sachar and his colleagues (37, 38) assessed skin test reactivity (delayed type hypersensitivity) in patients with UC and CD. They found an increased incidence of anergy (i.e., limited or no skin test reactivity) in these patients, regardless of the site or extent of disease. These studies did not take into account the fact that many of these patients were taking immunosuppressive steroids and/or that their nutritional status (i.e., hypoalbuminemia) might alter the ability of their T cells to function. These questions were addressed in subsequent studies. Meyers et al. (39) asked whether the anergy seen related only to memory responses or whether the T cell defect was more proximal, i.e., the initial T cell response. Using dinitrochlorobenzene (DNCB), a contact skin-sensitizing agent which classically elicits a T cell-mediated delayed-type hypersensitivity reaction, they studied patients and their first-degree relatives for the integrity of their T cell response. As suggested from Sachar's studies, T cell reactivity to DNCB was significantly depressed in patients with both CD (87% reduction) and UC (53% reduction). However, follow-up studies in family members supported the absence of a genetic component. More important, a restoration of T cell reactivity after surgery to remove the affected bowel (although this was more evident in UC patients than in CD) was described. These findings suggested that the defects in T cell reactivity reported by several groups was likely to be secondary to factors reversible by surgery (i.e., reduction in medication, restoration of nutritional status, elimination of inflammation) (40). Other studies by Heimann et al. (41) and Gelernt et al. (42) supported the concept that some restoration of immunological defects in peripheral blood could be achieved following surgical intervention. These studies helped to underscore the need to develop technology to assess immune function in the affected organ, the small bowel and colon.

The Role of the Intestinal Epithelium in Mucosal Immunoregulation

Moving into the gut meant that the normal mechanisms of mucosal immunoregulation needed to be defined. Several groups had already reported that the lymphoid populations in the gut

were quite different from those of the systemic immune system. It was also clear that the stimulus for an immune response (antigen [Ag]) was going to be distinct from Ag given intramuscularly or subcutaneously, given the fact that antigens in the gut lumen were subject to extremes of pH, proteolytic enzymes, etc. In addition, sites of Ag uptake in the gut were clearly distinct from those in lymph nodes and spleen. With this as a background, Mayer and Shlien (43) first described a novel role for human intestinal epithelial cells (IEC), that of antigen-presenting cells (APC) which could process and present Ag to T lymphocytes. However, unlike conventional APC (macrophages/dendritic cells/B cells), T cells proliferating in response to Ag presented by isolated IEC were found to be $CD8^+$ Ag-nonspecific suppressor T cells. This discrepancy was quite unusual, given the fact that IEC express restriction elements (major histocompatibility complex [MHC] class II molecules) which typically interact with and activate $CD4^+$ T cells. Over the past decade, the mechanisms involved in this selective activation have been defined. IEC express nonclassical class I molecules such as CD1d, which are capable of activating suppressor T cells (44). However, CD1d, cannot perform this function alone. Yio and Mayer (45) described an epithelial surface glycoprotein, gp180, which is expressed on normal IEC, binds to CD8 and promotes the activation of $CD8^+$ T cells. gp 180 binds to CD8 at sites which are distinct from those used by classical class I molecules (human leukocyte antigen [HLA] — A, B, C) and, therefore, does not interfere with the function of $CD8^+$ cytolytic T cells. This glycoprotein is, however, a critical component in the activation of $CD8^+$ suppressor T cells. While an *in vivo* model supporting this role for IEC has not been clearly defined, there are a large number of *in vivo* and *ex vivo* studies which support such a role for IEC. The activation of $CD8^+$ T cells locally could explain the local, controlled, physiologic inflammation seen in the gut. Thus, Ag sampled via the IEC would result in a suppression of local responses.

Defects in IEC Function in IBD

How does this relate to IBD? In 1990, Mayer and Eisenhardt (46), using the IEC co-culture system, reported that IEC derived from patients with UC and CD failed to activate $CD8^+$ suppressor T cells. Importantly, this defect was noted regardless of where the tissue used to isolate the IEC was derived (i.e., both inflamed and noninflamed tissue). This suggested that the defect in $CD8^+$ T cell activation might be more generic. In 1997, Toy et al. (47) provided an explanation for these *in vivo* studies. Using an antibody against gp180, derived in the laboratory, they noted that defects in the expression of this molecule existed for both CD and UC. However, the defects were different. In UC there was an alteration in the form of gp180 expressed (apical and not basolateral), and in CD there was a marked decrease in total expression. The end result would be the same. If there was no interaction of gp180 with T cells, no $CD8^+$ suppressor T cells would become activated. In fact, the enhanced class II Ag expression on the cells, described by Mayer et al. (48) and others, helped to promote proliferation of $CD4^+$ T cells in these co-cultures. The failure of suppressor mechanisms in IBD is not a new concept. Several groups have suggested this from studies in peripheral blood, including Godin et al. (49), who documented an increase in the percentage of $CD4^+$ T cells in the peripheral blood. Without regulation, $CD4^+$ T cell activation by luminal antigen might continue to go on unabated, with perpetuation of inflammation.

The aberrant activation of $CD4^+$ T cells can have several consequences, the first being increased cytokine production. Mount Sinai has approached this prospect in two ways: direct measurement of cytokine in diseased tissue and the use of therapies which alter cytokine production or function. In the first case, Salomon et al. (50) measured γ-interferon (γ-IFN) production by lamina propria lymphocytes from normal patients and disease controls. In both UC and CD, there was a marked increase in γ-IFN production. Given the marked inflammatory nature of this cytokine, its presence clearly helped to explain many of the reported phenomena, including macrophage activation, enhanced class II expression on IEC, etc. (48). Therapies directed against cytokines are also a useful tool to define mechanisms. Lichtiger et al. (51) published the results of a trial of IV cyclosporin in patients with presurgical UC. The initial results were outstandingly successful, eliminating the need for colectomies in more than 80% of patients. Cyclosporin is a potent inhibitor of cytokine synthesis, particularly IL-2. The prototype anti-cytokine therapy is the newly approved anti-tumor necrosis factor (TNF) mAb (infliximab). TNF, produced by activated macrophages and T cells, may also explain several of the histopathologic features of CD. Neutralization of TNF or alteration in the cells producing TNF can have prolonged salient effects on these patients (52–54). Thus, targeting the effects of aberrantly activated T cells may be quite effective in modulating the disease. The identification of these cells may be one way of accomplishing this therapeutic effect. In a series of studies by Shalon et al. (55) and Posnett et al. (56), it became clear that the population of $CD4^+$ T cells present in the gastrointestinal tract of patients with CD was clearly altered compared to normal controls. While the function of these expanded populations was not addressed, it was postulated that these may represent the aberrantly activated T cells described above. Studies to define the true nature of these populations are in progress.

Cytokines produced by these activated T cells may also alter the function of other cells in the mucosal environment. Focusing on the effects of cytokines on the epithelium, Panja et al. (57) defined receptors for inflammatory cytokines expressed by IEC derived from normal controls as well as from patients with IBD. While there is an increase in the number of these cytokines in the mucosa, there is no increase in receptor expression. This suggests that the epithelium in IBD patients is not more sensitive to inflammatory cytokines but may be reacting to the altered cytokine environment. The effects of the increased concentration of cytokines are evident. mRNA for a variety of growth factor receptors was reduced in IEC derived from IBD patients (EGF-R, IGFI-R, CSF1-R, and PDGF-R-beta) (58), and the steady-state levels of transcripts of H-ras and five nuclear proto-oncogenes (c-myc, c-fos, c-jun, junB, and N-myc — involved in cell cycle) were lower in epithelial cells from involved or uninvolved IBD samples than in normal epithelial cells from patients with either sporadic colon cancer or diverticulitis (59). These findings might be of significance with regard to the increased incidence of adenocarcinomas reported in both CD and UC. These inflammatory cytokines may also play a role in inducing or suppressing other mediators important for mucosal integrity. Sperber et al. (60, 61) described a novel mucin secretagogue, MMS-68, which stimulates mucin secretion by intestinal and airway epithelial cells. When studying patients with IBD, they found that there was a decrease in the level of expression of MMS-68 in their tissues. Altered mucin production has been described in IBD and may be an important contributor to the defects in barrier function described in these diseases. Such a defect could result in the enhanced transmigration of bacteria from the lumen into the mucosa-associated lymphoid tissue, allowing for persistent inflammation.

When viewed in composite, the studies from Mount Sinai have suggested defects in the initial activation of important regulatory cells following antigen challenge. These defects are then magnified by the establishment of a cytokine environment which promotes further inflammation and tissue destruction. The IEC may be a focal point for many of these pathways. Correcting these defects and/or reducing their effects on the epithelium may be a viable approach to novel therapies.

Summary

The concept that IBD represents an aberrantly stimulated or poorly regulated $CD4^+$ T cell response is growing in strength. *In vivo* and *in vitro* data attest to its validity. Animal models of either T cell dysregulation or altered barrier function develop IBD. Those with B cell defects or defects in nonregulatory T cell subpopulations do not. The *in vitro* and *in vivo* data are starting to coalesce. What is likely to emerge is that adaptive immune, nonimmune and innate immune responses play a role in concert in the development of IBD. These types of studies are ongoing.

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A History of Immunosuppressive Drugs in the Treatment of Inflammatory Bowel Disease:

Origins at The Mount Sinai Hospital

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Abstract

Much of what we know about the role of immunopathologic mechanisms in causing Crohn's disease and ulcerative colitis originated from research at The Mount Sinai Hospital. The authors were privileged to have been able to share in this undertaking, along with many others, including Moschcowitz, Klemperer, Otani, Crohn, Ginzburg, Oppenheimer, Garlock, Lyons, Marshak, Janowitz, Aufses, Waye, Greenstein, Sachar, Meyers, Gelernt, Mayer, Lichtiger and Kornbluth.

In medical history, elucidation of disease processes is often serendipitous. Transplant surgery was successful because of the discovery by Hitchings and Elion of 6-mercaptopurine (6-MP) and azathioprine, which inhibited rejection. And the concept of immunosuppression slowly evolved into possible treatment of any disease thought to be caused by autoimmunity. This includes those diseases of the bowel seen so frequently at The Mount Sinai Hospital: ileitis, granulomatous colitis, ileocolitis, and ulcerative colitis.

This paper depicts the progressive role of immunosuppressive drugs, from corticosteroids to 6-mercaptopurine, cyclosporine and anti-tumor necrosis factor, in both the treatment and understanding of the pathogenesis of Crohn's disease and ulcerative colitis. Major contributions to these treatments have come from physicians and surgeons with roots at The Mount Sinai Hospital. **Key Words:** Immunosuppressive drugs, 6-MP, cyclosporine, anti-tumor necrosis factors, IBD.

WHEN WE ARRIVED AT MOUNT SINAI, several decades had already passed since the landmark publication on regional ileitis by Crohn, Ginzburg, and Oppenheimer (1). Management remained primarily in the hands of the surgeons. Drug therapy had been limited to a variety of sulfonamides, and gastroenterologists were slow to acknowledge that one (sulfasalazine) differed from all the others, and should be favored. Even so, sulfasalazine did not work as well in ileitis as it did in ulcerative colitis. The morbidity and surgical incidence for both diseases remained high and the mortality rate, particularly for children with ulcerative colitis, was unacceptable (2).

In 1949, the first edition of Dr. Crohn's book (83) included data on the course, complications, and treatment of ileitis. Corticosteroids, which became available soon thereafter, were not mentioned at all. Yet, never before had such dramatic improvements been seen as those that followed treatment with corticosteroids and corticotropin. The outcome was influenced so favorably that surgery could now be postponed and performed electively. The gastroenterologist inherited the primary responsibility for patient management and clinical observation (3).

In retrospect, this period was one of relative complacency, particularly with regard to the search for new drugs. The initial euphoria, although warranted by the success of the steroids in eliminating the inflammatory process, yielded to the sober realization that the effect was transient (4) and that the inflammation returned not only with discontinuation of the drug but even with dose reduction. Also, the inflammation responded less dramatically with subsequent courses of treatment; finally, corticosteroids were shown to be no more effective than placebos in

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maintaining remission (5). They also had the potential for major toxicity.

In the 1960s, the following factors rekindled an effort to provide new treatment for inflammatory bowel disease (IBD):

1. The causes remained unknown.
2. The concept of autoimmune diseases began to be appreciated (6, 7).
3. The question was frequently raised as to whether Crohn's disease and ulcerative colitis could be autoimmune diseases.
4. Studies demonstrating auto-antibodies in ulcerative colitis were being reported (8).
5. Azathioprine was shown to inhibit rejection of the donor's transplanted kidney (9).
6. Toxicity due to corticosteroids was reported (10).
7. Winkelman and Brown (11) reported a favorable experience with nitrogen mustard in the treatment of both ulcerative colitis and regional enteritis.
8. Bean had successfully treated an ulcerative colitis patient with 6-mercaptopurine (12), a metabolic product of azathioprine, and was pursuing this early success (13).
9. Brooke et al. (14, 15) reported previously unheard-of reversals of advanced Crohn's disease, including those with complex fistulas, when patients were treated with azathioprine after all surgical efforts had failed.

Although later epidemiologic data showed that the incidence of Crohn's disease was on the rise whereas the incidence of ulcerative colitis was stable, this was not yet apparent in the 1960s. One of us (BIK) had seen many ulcerative colitis patients with Banks and Zetzel at the Beth Israel Hospital in Boston (16). At Mount Sinai, he was disturbed by the large number of children with ulcerative colitis in whom corticosteroid therapy had failed, who were physically and emotionally traumatized by the toxicity of these drugs, and who required colectomy and ileostomy (with high mortality) (3, 17). In view of this experience, in January 1967 it was decided to add 6-mercaptopurine (6-MP) to the treatment of ulcerative colitis patients who had not responded favorably to corticosteroids and sulfasalazine treatment, and who did not have an absolute indication for surgical intervention (18).

The co-worker in this study (18) was Nathaniel Wisch, a hematologist, who favored 6-MP over azathioprine (azathioprine is converted to 6-MP *in vivo)* only because he had had experience with its use in treating childhood leukemia. Furthermore, the Food and Drug Administration had approved 6-MP for use in the treatment of that disease. At the conclusion of this study, it was clear that 6-MP had no dramatic short-term influence on the course of the disease; moreover, transient nausea and vomiting occurred frequently. Apparently, 6-MP had no role in the treatment of fulminating ulcerative colitis or toxic megacolon. This finding confirmed those already demonstrated for azathioprine by Bowen et al. (19), who suggested that immunosuppressive drugs should not be used for the treatment of ulcerative colitis. Nonetheless, we had noted favorable results in a select group of patients, which led us to adopt new criteria for instituting 6-MP therapy. Our choice of candidates included those with chronic prolonged ulcerative colitis, those who had an incomplete response to steroids, those who had complications from the steroid treatment, those who had contraindications to the use of steroids, and those in whom sulfasalazine had failed.

Perhaps the most important observation we made was that the real value of 6-MP could only be determined after long-term observation. We found that 13 of 14 patients either went into remission or improved significantly; only one remained incapacitated. Based on this study, and our later experience when the series had been expanded to 25 patients (20), a long-term, double-blind, controlled study was planned.

Coincidentally, in the late 1960s the following events occurred:

1. One of us (DHP) completed his fellowship in gastroenterology at Mount Sinai. In addition to the teacher (BIK)-student (DHP) relationship, we became friends and found that we shared common interests in clinical investigation of IBD. We were both enthusiastic about conducting a double-blind trial of immunosuppressive therapy.
2. The Ileitis Foundation was launched by Irwin Rosenthal, William Modell, and our Chief of Gastroenterology at Mount Sinai, Henry D. Janowitz. The primary goal of the foundation was to encourage and support research in

IBD, and DHP became its first fellow and research grant recipient. The early participation of BIK was encouraged by the founders because of his accumulated experience with ulcerative colitis. Soon thereafter, the name of the organization was changed to the National Foundation for Ileitis and Colitis.

3. Dr. Janowitz suggested that the protocol place more emphasis on Crohn's disease than on ulcerative colitis. It was already known that ulcerative colitis is premalignant, and there was some concern that immunosuppressive drugs might provoke an earlier onset of neoplasia. It was not yet known that Crohn's colitis also predisposed to the development of colon cancer. Also, we knew that a colectomy "cured" ulcerative colitis, but Crohn's disease recurred in most patients after surgical resection.

Crohn's Disease

In 1969, we launched a 2-year, placebo-controlled, double-blind, crossover study of 6-MP in the treatment of refractory Crohn's disease (21). Because there were no prior indices to measure the remission of Crohn's disease, we established our own for the controlled trial. These included "goals" of therapy for each case, as was done in the usual clinical management of Crohn's disease. We felt then, as we do now, that Crohn's disease has many diverse presentations and that this "goal index" was the most accurate way to interpret clinical responses in patients with chronic refractory disease. The most common goals were:

- elimination of corticosteroids
- closing of fistulas
- prevention of small bowel obstruction

Elimination of the primary bowel symptoms alone was not an objective, because steroid treatment temporarily accomplished this. Rather, symptoms had to be alleviated after stopping the steroids, which would indicate that 6-MP had been effective. It should be noted that although this study was initiated in 1969, it was until recently the only randomized controlled trial for treatment of fistulas in Crohn's disease, despite the fact that one-third of Crohn's disease patients have evidence of fistulization. Although initiated after our study was started, the National Cooperative Crohn's Disease Study (NCCDS) was then being conducted at 14 other medical centers. In that study, the newly developed Crohn's Disease Activity Index (CDAI) was used as a measure of response to compare prednisone, sulfasalazine, azathioprine, and placebo (22, 23), and showed that azathioprine was ineffective (22). Based on the results of our own ongoing study, we and others submitted a critique of the NCCDS study, pointing out its shortcomings (24, 25). Although the results of the NCCDS study were presented at the plenary session of the annual meeting of the American Gastroenterological Association (AGA) in 1980, our own abstract was not scheduled for presentation at that time. Rather, it was scheduled for presentation one day later and at a smaller forum. At our presentation, we encouraged clinical researchers not to abandon the use of immunosuppressive drugs in this disease, and stated that physicians in private practice were capable of contributing significantly in the performance of randomized clinical trials. The basis of our concern regarding the outcome of the NCCDS study was the following:

1. The study terminated prematurely at 17 weeks, too soon for many patients to respond.

2. It eliminated azathioprine because it caused pancreatitis in a few instances. Consequently, there were insufficient entries assigned to azathioprine to reach statistical significance.

3. It withdrew steroids before starting the assigned drug or placebo, thereby enhancing the likelihood of exacerbating the underlying disease.

4. The dose of azathioprine used was relatively small.

In 1980, our own study was published and showed conclusively that 6-MP was effective in the treatment of Crohn's disease (21). The following is a list of the clearest results of the study:

1. The overall success rate was greater than 66%. Of the 39 patients who participated in each year of the 2-year crossover study in which either 6-MP or placebo was administered throughout one full year, the outcomes were significant ($p < 0.0001$) (Table 1).

2. Thirty-three (33) patients completed only one year (refusing to cross over) and therefore received only one drug, either 6-MP or placebo; for the 19 receiving 6-MP, the rate of improvement was 79% as compared with 20% of the 14 patients treated with placebo ($p < 0.05$) (Table 2).

3. To determine whether the outcome of the first year of trial influenced the outcome of the second year, a separate analysis was performed for 36 patients. There was a highly significant difference for the patients receiving 6-MP, with improvement in 67% vs. 14% of patients treated with placebo ($p < 0.0001$) (Table 3).

4. In the study, steroids were completely eliminated in 55% of the patients, or the dose of steroids could be reduced by 20%.

5. The healing of fistulas was accomplished. Closure of fistulas occurred in 24% compared with placebo closure of 6%.

6. The study confirmed that the drug was slow acting (mean response time of 3.1 months) and in many instances, patients required continuation of steroids. Almost 20% of patients who would ultimately respond had not done so at 17 weeks, the time at which the NCCDS already had been completed.

7. Drug toxicity was modest and there was no early mortality.

TABLE 1
Results in 39 Crossover Patients

Treatment	Number of patients Improved*	Not improved
6-MP	26/39	13/39
Placebo	3/39	36/39

*Whereas 67% of the patients improved with 6-MP, only 8% improved with placebo. The difference is 59% with 95% confidence limits of 32 to 86% ($p < 0.0001$).

TABLE 2
Results in 33 Noncrossover Patients

Treatment	Number of patients Improved*	Not improved
6-MP	15/19	4/19
Placebo	4/14	10/14

*Whereas 79% of the patients improved with 6-MP, only 29% improved with placebo. The difference is 50% with 95% confidence limits of 20 to 80% ($p < 0.05$).

TABLE 3
Combined Results during First Year

Treatment	Number of patients Improved*	Not improved
6-MP	26/36	10/36
Placebo	5/36	31/36

*Whereas 72% of patients improved with 6-MP, only 14% improved with placebo. The difference is 58% with 95% confidence limits of 40 to 77% ($p < 0.001$).

Expanded data on fistulas of different sites followed (26). 6-MP seemed to close fistulas in one-third of the patients and it meaningfully reduced discharge from fistulas in another third, with a mean response time of 3.5 months. 6-MP (and azathioprine) proved to be the first drug to have this influence on fistulas in Crohn's disease, with the sole exception of metronidazole, which had a favorable effect only on perirectal fistulas. There has never been a controlled-trial confirmation of the efficacy of metronidazole on fistulas; in our clinical experience, many patients relapse after prolonged use of this antibiotic. Many also develop peripheral neuropathy. Abdominal wall fistulas improved or closed in 10 of 12 cases (83%), rectovaginal fistulas in 4 of 6 (67%), and enteroenteric fistulas in 5 of 7 (71%). Patients with perirectal abscesses and fistulas sometimes had diversionary operations, such as a colostomy or ileostomy. The results in many cases were disastrous, with recurrent Crohn's colitis in the stoma, diversion colitis in the rectum, and persistence of perirectal sepsis. A modified Parks' operation combined with 6-MP eradicated many perirectal abscesses and fistulas in those patients with recurrence after an incision and drainage procedure (27).

Our early observations noted that the use of immunosuppressive drugs was apparently more effective in the treatment of Crohn's disease when the colon (ileocolitis or colitis) and small bowels were both involved, rather than the small bowel alone. O'Donoghue et al. (28) had shown that the one-year remission, once established, was maintained by azathioprine in 95% of the patients compared with 59% on placebo. Early observations after completion of our own controlled trial showed maintenance of remission in 19 out of 20 patients (95%) after a mean of 37 months on 6-MP. After stopping 6-MP therapy, 81% of the 32 patients who had been studied relapsed after a mean interval of 6 months. When 6-MP was reintroduced in 16 of these patients after relapse, improvement was noted within a mean response time of 1.5 months, considerably more rapidly than had been the case for their first response (29).

Subsequently BIK and his colleagues at Lenox Hill reported a long-term experience with

6-MP in the treatment of Crohn's disease (30). Again, therapeutic goals were established for each of the 148 patients, and an index of Crohn's disease activity was calculated both before and after therapy. The goals, as defined previously, were achieved in 68% of cases. Major successes included elimination of steroids (66%; $p < 0.001$) and healing of internal fistulas and abscesses, with elimination or reduction in drainage and tenderness (64%; $p < 0.05$). Moreover, healing or marked improvement was noted in all cases of Crohn's disease involving the stomach and duodenum. Elective surgical resection was made much easier, if and when it had to be performed after 6-MP therapy, because the margins separating normal and diseased tissue were delineated much more clearly. However, prevention of recurrent small bowel obstruction and disappearance of abdominal masses were noted in only 43% and 55% of the cases, respectively.

Ulcerative Colitis

After the early success by Bean (12, 13) in the treatment of ulcerative colitis with 6-MP, uncontrolled trials of immunosuppressives in ulcerative colitis reported response rates of 70–80%. There was less enthusiasm for initiating controlled trials in ulcerative colitis than in Crohn's disease, due in part both to the risk of carcinoma of the colon and the knowledge that ulcerative colitis could be "cured" by colectomy. Furthermore, those who did undertake controlled trials of ulcerative colitis reported disappointing results, with one exception. In that study, it was noted that azathioprine permitted a significant reduction in steroid dosage (31).

Present et al. first reported, in an abstract in 1988 (Gastroenterology 1988; 94:A359), a good-to-excellent response to 6-MP in 25 patients (73%). The mean time to the response was 2.3 months. A subsequent report from Mount Sinai in 1996 (32) showed complete remission in 68 of 105 patients (65%) and partial remission in 25 (24%) with 12 (11%) failures. Although 6-MP was maintained, subsequent relapse was seen in 35% of the patients. In this group, steroids were required in 12% to restore remission. Fifteen (15) patients stopped 6-MP electively and 13 relapsed after a median interval of 14 months. Thus, it was recognized that maintenance 6-MP was important after patients had responded favorably.

Adler and Korelitz (33) reported the results of 87 patients refractory to steroids who had been treated with 6-MP. In 42 patients (48%), steroids could be eliminated, with good control of symptoms after a mean treatment period of 2.5 months. The mean steroid-free period while on 6-MP was 10.9 months. Eleven cases (13%) demonstrated an intermediate but significant reduction in steroid usage.

Hawthorne et al. (34) reported the results of a randomized, 1-year, controlled-withdrawal study of azathioprine vs. placebo involving 67 patients with ulcerative colitis who had been taking azathioprine for 6 months or longer. In the 2-year interval, 59% of those switched to placebo relapsed, in contrast to 36% of those maintained on azathioprine ($p = 0.04$).

Despite the lack of controlled trials, it has been our experience that 6-MP has proven to be both safe and effective in treating severe chronic ulcerative colitis. We have been able to avoid urgent surgery in more than 75% of cases. In many cases, surgery had been recommended without making the patient aware of the efficacy of 6-MP. Perhaps to some physicians and surgeons, this is justified by the advent of the ileal pouch-anal anastomosis. This position, however, has been compromised by the lack of universal and consistent success with this procedure (mean technical failure rate of 6%) and the inability to predict which patients will do well and which patients will exchange one affliction for another (chronic pouchitis in 6–8%) (35–37).

Toxicity of Immunosuppressive Agents

Historical Aspects

Experience with 6-MP and azathioprine has shown that bone marrow suppression can occur and is dose related. Both leukopenia and thrombocytopenia have been reported. Hepatotoxicity is seen less frequently.

6-MP and azathioprine can cause chromosomal aberrations in animals and humans, but these are reversible in humans. The drugs are carcinogenic in animals at the dosages used and therefore may theoretically increase the risk of neoplasia in humans. Again, the risk has been greater in transplant cases than in autoimmune disorders such as rheumatoid arthritis, perhaps because of the higher doses used.

Allopurinol, used to lower blood uric acid, may retard the catabolism of 6-MP and accentuate its toxicity. When the two drugs are used concurrently, the initial dose of 6-MP should be reduced by at least one third.

Toxicity to 6-MP in IBD has been compiled for 396 patients seen by the authors in their private practices (38). Four types of toxicity directly attributable to 6-MP have been identified. These are pancreatitis, bone marrow depression, idiosyncratic and/or hypersensitivity reactions, and drug-induced hepatitis.

Data on all toxicity to 6-MP has been updated since the earlier report, providing a larger number of IBD patients followed for longer periods of time with similar outcomes (39).

Pancreatitis. Pancreatitis after 6-MP was observed in 12 of 396 (3%) patients with Crohn's disease and one with ulcerative colitis (40). The peak incidence was 21 days after starting the drug, and all but one case occurred within 32 days. Clinically, each case was mild, with symptoms of abdominal pain, nausea, vomiting, and elevation of serum amylase, all resolving quickly upon discontinuation of the drug. No hemorrhagic pancreatitis, hypocalcemia, pancreatic abscess, or pseudocyst formation was observed. Seven patients were later rechallenged with 6-MP or azathioprine, and in each, the symptoms recurred rapidly. Clinically, the pancreatitis behaved like a sensitivity reaction, but attempts at desensitization were unsuccessful. Therefore, a single bout of 6-MP pancreatitis is considered a contraindication for future use, but a trial using small doses of azathioprine may be clinically warranted.

Bone Marrow Depression. In 2% of patients, bone marrow suppression sufficient to necessitate hospitalization occurred during the early years, before experience was gained in blood count monitoring and individual dosage adjustment (38). In these 8 patients, the lowest white blood count ranged from 300–2500/mm^3. Fever was present in 7, and blood cultures were positive in 3. Major septic complications were seen in one patient, but there were no deaths. Characteristically, the bone marrow depression was usually followed by prolonged remission of Crohn's disease or ulcerative colitis. This observation has also been noted by others in relation to ulcerative colitis (41). Leukopenia was noted in most patients at some time. White blood counts above 3500/mm^3 were rarely associated with clinical problems and were managed by temporarily stopping the 6-MP and then resuming it at a lower dosage.

Subsequently, Connell et al. (42) reported the experience from St. Mark's Hospital, London in 739 patients with IBD treated with azathioprine. Only 9 (1.2%) developed severe leukopenia (white blood cell count < 2000/mm^3); 5 of the 9 patients had complications which resulted in 2 deaths. Neither of the deaths was predictable, based on monitoring of the white blood cell count. Our own experience suggests that current methods of monitoring are adequate and that this severe complication is rare and may be modified by the availability of the colony-stimulating factor.

Idiosyncratic/Hypersensitivity Reactions. In addition to pancreatitis, other allergic type reactions occurred within the first 3 weeks of treatment with 6-MP in 2% of patients: drug fever was seen in 8, skin rash in 2, arthralgia in one, and abdominal pain with normal serum amylase in one. We have also seen severe muscle pain soon after initiating treatment with 6-MP. Rechallenging with 6-MP or azathioprine produced similar reactions. Nevertheless, desensitization with gradually increasing doses has often allowed reinstitution of a drug without recurring adverse reaction (43). Whether these reactions are idiosyncratic or represent an allergic phenomenon is unknown, because no definitive immunologic hypersensitivity mechanism has been defined.

Recent data confirm the proportion, nature and outcome of allergic reactions to 6-MP, including the usual failure of desensitization to tiny doses, but occasional success with crossover to AZA (44).

Drug-Induced Hepatitis. Eleven patients in this study developed a type of hepatitis (38), but in only one patient could it clearly be attributed to 6-MP. For this patient, who had severe ulcerative colitis that had remitted, results of liver function tests returned to normal after the drug was discontinued. These same tests became abnormal again after rechallenge. This is the only allergic-type form of toxicity that seems to occur late in the course in most cases. Hepatitis is also unique in that rechallenge is often tolerated. The only instance of immediate toxicity occurred at a later date in a patient whose 6-MP was initiated at 3 mg/kg of body weight. Recent studies have shown that abnormal liver function tests are often associated with high levels of 6-MP, which return to normal when doses are lowered.

Infections

Almost every type of infection reported in patients with IBD treated with 6-MP has also been reported in patients not treated with immunosuppressive drugs. This is especially true of patients with Crohn's disease, in which infectious complications are frequent.

All our patients receiving 6-MP who developed fever were instructed to discontinue the drug

regardless of whether we thought the fever was related to the underlying bowel disease, the drug, or an incidental illness such as an upper respiratory tract infection or a viral infection. Two patients developed liver abscesses that required drainage.

Five patients developed pneumonia; all responded to antibiotics and cessation of 6-MP therapy. Some patients with pneumonia responded equally well to antibiotics while continuing 6-MP. Some patients reported frequent colds and upper respiratory tract infections, and elected to discontinue 6-MP. It is difficult, however, to document any increased incidence of respiratory infection.

Herpes zoster occurred in 8 patients while they were taking 6-MP. In all cases, the "shingles" took its usual course. Many years later, one patient had a recurrence of herpes zoster on his trunk when he was again taking 6-MP, and also suffered a 3-day syndrome consistent with encephalitis. There has been no residual defect during a 9-year follow-up, and the patient's ulcerative colitis has remained in remission. Subsequent experience suggests there is no advantage to stopping the 6-MP during the course of herpes zoster if it is mild. When shingles is severe, the 6-MP should be stopped and then reintroduced after a benign course is confirmed (45).

Neoplasms

The situation in regard to neoplasms is similar to that with infections. Neoplasms occur more frequently in patients with IBD whether they have received immunosuppressive medication or not. In Crohn's disease particularly, an increased risk of extraintestinal neoplasms has been recognized (46). An appraisal of neoplastic risk was made for our patients during or after 6-MP therapy (38), and in one instance, the neoplasm was considered to be probably related to the 6-MP. This tumor was a diffuse cerebral histiocytic lymphoma in a man with Crohn's disease, who had taken 6-MP for approximately 9 months. The drug had been discontinued 11 months before the onset of headaches and the discovery of the tumor. The tumor did not respond to therapy. Two more cases of cerebral lymphoma in patients with Crohn's disease treated with azathioprine have subsequently been reported (47).

Other neoplasms occurring in patients who had earlier received 6-MP included an islet cell carcinoma of the pancreas, carcinoma of the lung in a heavy cigarette smoker, one carcinoma of the breast, and a basal cell carcinoma. One patient with ulcerative colitis developed malignant melanoma; an excision with an axillary node dissection was curative. We have subsequently seen three patients who developed carcinoma of the breast 5, 25, and 27 years after first receiving 6-MP.

Two simultaneous carcinomas of the colon occurred in one patient with long-standing ulcerative colitis who had refused the recommendation of colectomy. In these cases, the carcinomas clearly anteceded the initiation of 6-MP. Subsequently, one additional patient with long-standing left-sided ulcerative colitis, who had received 6-MP for one year, developed a carcinoma of the rectum. Benign adenomatous polyps have been encountered on sigmoidoscopy or colonoscopy in patients receiving 6-MP; the polyps have been removed endoscopically and no recurrence has been encountered despite continuation of 6-MP.

Cancer of the colon could be a complication of particular concern, because both ulcerative colitis and Crohn's colitis are diseases prone to the development of cancer even without immunosuppressive drugs. We reviewed our own experience and counted 34 patients with cancer of the colon following ulcerative colitis, during a 20-year period; two patients had taken 6-MP and 32 had not. As for cancer of the intestinal tract complicating Crohn's disease, we identified 17 patients in whom carcinoma of the ileum or colon developed; only two had been treated with 6-MP. Although these figures are not controlled and do not include a denominator, carcinoma seems to be far more common in Crohn's disease and ulcerative colitis independent of immunosuppressive therapy than associated with it. Subsequently, Connell et al. (48), reporting their data from St. Mark's, also concluded that the incidence of colorectal cancer and death from cancer in patients with IBD who had been treated with azathioprine is not greater than in those patients who had not been so treated.

Recent data from the IBD Center at Lenox Hill Hospital confirm the earlier observations of no increase in neoplasms in patients with IBD who have been treated with 6-MP or AZA (49). Nevertheless, concern persists as to whether the onset of a neoplasm is accelerated, but there are no controlled data to answer this question. Currently one of us (BIK) is investigating the possible role of sustained leukopenia as a contributing factor.

Nausea

Nausea is seen as a fairly common side effect during the first month of therapy. Occasionally the dose of 6-MP has to be temporarily reduced. Rarely does the drug need to be eliminated on this basis.

Mortality

With the single exception of the patient with cerebral lymphoma, no deaths were attributable to 6-MP. Lymphomas of the brain (50) and other lymphomas (51) also have been reported in transplant patients on immunosuppressive therapy. Although it is most likely that these tumors were caused by 6-MP, two reports (52, 53) suggest an increased incidence of lymphomas in patients with Crohn's disease who were not taking immunosuppressives.

Considerations in Pregnancy

6-MP and azathioprine cause reversible chromosome damage in humans, but the true teratogenic effect of these drugs has not been studied in a systematic or controlled manner. On theoretical grounds, most obstetricians have advised that conception is contraindicated for both women and men receiving 6-MP. We advise chronically ill female patients with persistent bowel activity not to become pregnant. Therefore, before initiating 6-MP therapy, a female patient should have her serum tested for human chorionic gonadotropin level to eliminate the possibility of early pregnancy. All couples are instructed to practice a reliable method of birth control. The authors (BIK and DHP), however, differ with respect to the continued use of maintenance 6-MP therapy after suitable remission in patients who want to become pregnant.

When pregnancy becomes a priority, BIK recommends stopping 6-MP before discontinuing contraception. In a toxicity study (38), the authors found that 16 pregnancies had occurred. In 10 patients, 6-MP had been terminated before contraception. In the remaining 6 patients, 6-MP had been continued for 3–4 weeks before the pregnancy was recognized. In 3 of the 6 patients, as well as the 10 who stopped 6-MP earlier, the pregnancies were continued. All 13 patients delivered full term. No abnormalities have been found in any of the 13 children. Additional data reported from St. Marks support the conclusion that there is little danger to the mother or the fetus by taking azathioprine throughout pregnancy (54).

A recent extensive study of DHP's patients compared the outcomes of 240 live births from 155 patients with IBD who had either stopped 6-MP before conception, or had conceived while taking 6-MP, and then either stopped or continued the drug throughout the pregnancy, to matched controls. There were no significant differences between the groups. It was concluded that 6-MP therapy either before conception or after conception and during pregnancy was not associated with prematurity, spontaneous abortion, congenital abnormalities, neonatal and childhood infections or neoplasia. These more recent data support the conclusion that 6-MP is safe when used during pregnancy (55).

Nevertheless, a study at Lenox Hill Hospital found that pregnant patients treated in their first trimester with 6-MP had an increased risk of spontaneous abortions, and (in 2 cases) chromosomal abnormalities (mosaicism and trisomy 22) found at amniocentesis, leading to therapeutic abortion (56). Furthermore a study of men with IBD treated with 6-MP, whose wives became pregnant, showed a significant increase in congenital anomalies in the offspring when the father was taking 6-MP during the 3 months before impregnation (57).

Cyclosporine

The marked difference between cyclosporine and 6-MP or azathioprine in the treatment of inflammatory bowel disease is that a favorable response, when seen, is more apt to be seen earlier after administration of the former drug, usually within 1–2 weeks rather than the 3–4 months for the latter drugs. Cyclosporine acts on T rather than B lymphocytes and inhibits their proliferation. The rapid onset of action is due to inhibiting the production of interleukin-2 and the consequent release of multiple cytokines.

The first controlled trial of oral cyclosporine (using 5–7 mg/kg/day) in patients chronically ill with Crohn's disease, performed by Brynskov et al. (58), showed a statistically significant response rate of 59%, but coincidentally, a 31% response for placebo. A subsequent controlled trial failed to confirm this response in chronically active patients, although lower doses were used (59). Another controlled trial showed no difference in relapse rate with cyclosporine as compared to placebo, using low doses of cyclosporine (less than 5 mg/kg/day) (60). A new 12-month study (61) has been reported by European investigators using 5 mg/kg/day, and no major difference has been found when comparing cyclosporine plus low-dose steroids versus low-dose steroids alone.

At Mount Sinai, Present and Lichtiger used intravenous cyclosporine to treat Crohn's disease

(62). At an intravenous dose of 4 mg/kg/day for 14 days, which was then followed by oral doses of 6–8 mg/kg/day, a favorable response rate was noted in 88% of the patients. Closure of Crohn's disease fistulas occurred in 44% of these patients and improvement was noted in another 44%. Two-thirds maintained improvement in the chronic phase, and steroids could be discontinued in 75%. Hanauer and Smith (63) showed a similar response rate using this technique. Thus, oral cyclosporine seems to be less effective than intravenous cyclosporine, which may be due to malabsorption of the drug and/or the need for higher doses in inflammatory bowel disease patients with IBD.

The most promising data on cyclosporine comes from another study by Present and Lichtiger (64), who treated patients with ulcerative colitis via the intravenous route at 4 mg/kg/day for 14 days after a 7 to 10-day trial of parenteral steroids had been unsuccessful. A mean response time of 6.4 days was observed, and colectomy was avoided in 75%. A subsequent controlled trial has confirmed the efficacy of intravenous cyclosporine under these circumstances (65). Further observation has shown that oral cyclosporine has been successful for 6 months in 69% (66). This major long-term difference between the response in Crohn's disease and in ulcerative colitis might be attributed to the malabsorption so prevalent in the former and not in the latter. Also, the oral doses used in the Crohn's disease trial are far below the comparable IV dose. It is of interest that more than one-third of the patients entered into the controlled trial were referred by the surgical colleagues of Drs. Present, Gelernt and Bauer. The collegial relationship between our surgeons and gastroenterologists has encouraged many IBD advances at Mount Sinai.

Toxicity is of great concern when using cyclosporine, particularly intravenously. The foremost concern is nephrotoxicity. Fortunately, this toxicity can be minimized by carefully monitoring the blood urea nitrogen (BUN) and creatinine, keeping the cyclosporine blood level in a therapeutic range, and avoiding nonsteroidal anti-inflammatory agents and other drugs which may enhance the levels of cyclosporine and its toxicity. The risk of lymphoma and carcinoma is of concern, but in view of the doses and duration used for the treatment of IBD, cyclosporine has not been contraindicated. Other complications, such as tremors, hirsutism, gingival hyperplasia, paresthesia, headaches, and hypertension, although common, are almost always transient.

Intravenous administration of cyclosporine in the management and treatment of very sick patients with ulcerative colitis, in whom treatment with intravenous steroids has failed, is justified. The major risk in using intravenous cyclosporine when intravenous steroids have failed is waiting too long. Although the waiting period probably should be no longer than 7–12 days, some patients are already too ill to wait even that long for any hoped-for response to cyclosporine. Patients who are that ill are vulnerable to pneumonia, sepsis, and death, when they might have been saved by a timely colectomy. On the other hand, the risk of pneumocystis has been markedly reduced in some patients by the concurrent use of Bactrim (sulfamethoxazole-trimethoprim). In addition, should there be time for a trial of intravenous cyclosporine, its success will allow for introduction of the slow-acting immunosuppressive drugs 6-MP and AZA, which may then maintain remission for many years thereafter. This decision, of course, has to be based on a finely attuned clinical evaluation of the individual patient.

Although patients who respond to intravenous cyclosporine have continued with oral cyclosporine as well, the results on maintaining remission have been disappointing, presumably due to poor absorption, even with the advent of a newer preparation (Neoral) which has been shown to be better absorbed than the original drug (67). Consideration of the use of cyclospirne has been discussed by us elsewhere (67–69).

Anti-Tumor Necrosis Factor (anti-TNF) Alpha (Infliximab, Remicade)

In a short-term, multicenter study (including Mount Sinai), using a chimeric monoclonal antibody to tumor necrosis factor, 65% of patients with Crohn's disease improved vs. 17% on placebo, including 33% of the patients on anti-TNF in clinical remission after a single 2-hour infusion, with a better response after a lower dose of 5 mg/kg than after 10 mg/kg and 20 mg/kg (70).

Subsequently, Present et al. (71) used 3 infusions of anti-TNF to treat Crohn's disease fistulas, and demonstrated at least 50% healing in 62% of patients but in only 26% of patients on placebo ($p = 0.002$). Most recently, the results of a third multicenter study by Rutgeerts et al. (including DHP) (72) best documented the rates of relapse following the 3 infusions and recommended that the infusion be repeated every 8 weeks to maintain the remission. The reported toxicity so far has not been greater than that seen with 6-MP and AZA, but the development of anti-chimeric antibodies and hypersensitivity reactions after later infusions have been reported. No data is thus far available regarding the long-term potential for neoplasm.

The Present and the Future

Of all the immunosuppressive drugs now available, 6-MP and azathioprine have had the most enduring role and continue to show the most promise for the future. Despite the disadvantage of its slower onset, 6-MP has been consistently effective in two-thirds of patients with otherwise refractory Crohn's disease and those with ulcerative colitis. Azathioprine has also been effective for the same groups of patients. Because 6-MP is a metabolic byproduct of azathioprine, presumably weight-for-weight, the favorable effect of azathioprine is not as great as that of 6-MP. Nevertheless, this has never been submitted to any controlled trial. What is more important is the answer to the question as to why favorable results of treatment are consistently about two-thirds in patients with IBD. Why is it not 100%? What accounts for the other one-third? Perhaps the answer in Crohn's disease lies with the underlying pathology, particularly of the small bowel, in which repeated attacks of inflammation result in fibrosis which to date has been irreversible. After all, success with 6-MP in preventing small bowel obstruction has been consistently less than for other indications, such as elimination of steroids and closure of fistulas. A role for 6-MP in prevention of recurrence after bowel resection for Crohn's disease has now been confirmed (73), and it is now our practice to start 6-MP in the perioperative period.

Perhaps the answer lies in the role of inducing leukopenia with 6-MP or azathioprine. In retrospect, those patients who did develop leukopenia had greater success than those who did not (74). Furthermore, the successes came earlier and lasted longer, and those who did develop leukopenia had no clinical bone marrow depression. This can be attributed in part to what we have learned about careful monitoring. Our approach is to perform complete blood counts weekly for the first 3–4 weeks, and then if the white blood count does not fall and clinically there is no indication for increasing the dose of 6-MP, the time between blood counts can be extended. If, however, at any time, the symptoms recur and the white blood count permits, the dose of 6-MP should be raised. At this point, monitoring should be done weekly for 3 weeks. Another time for particularly careful monitoring is when steroids have been reduced or are about to be eliminated. Because the steroids had served to raise the white blood count, this stimulus may be lost and the patient may be vulnerable. In all cases, the patient must call after the blood count to receive new directions as to dose and when the next count should be done. Platelets also should be counted, because thrombocytopenia is sometimes seen during 6-MP therapy.

Another question is why leukopenia develops so easily in one patient but not in another. Although some patients tolerate as much as 200 mg a day without apparent effect on the white blood count, others tolerate only tiny doses such as 12.5 mg per week, or even less. This has been attributed to the absence or low levels of the enzyme thiopurine methyltransferase, which results in loss of catalytic activity. While the resulting leukopenia may lead to a rapid clinical response of IBD, the risks of bone marrow depression and allergic complications are proportionately increased (75, 76). This has led to the measurement of 6-thioguanine metabolites in an attempt to predetermine both the efficacy of the drug and its potential toxicity (77).

When leukopenia is first recognized in these patients, they have almost improved more than those without leukopenia, but when the dose has to be reduced further and further, the value of leukopenia is replaced by loss of overall drug efficacy.

The role of anti-TNF is being clarified very rapidly. Whether repeated infusions will maintain remissions of Crohn's disease on their own, supplement the maintenance role of 6-MP or AZA (or vice versa), or serve to effect earlier remissions then better maintained by 6-MP/AZA, is yet to be determined. Furthermore it must be clarified whether the temporary remission for sick hospitalized patients with Crohn's disease is better accomplished by intravenous steroids or Remicade, since the success rate for IV steroids is 88% within 10 days (78). Data comparing long-term steroid and Remicade toxicity might play a major role in deciding which drug should be used to initiate remission.

Other Immunosuppressive Drugs for IBD

Methotrexate has been effective for Crohn's disease, just as it has been for rheumatoid arthritis, but the toxicity profile has been greater than that of 6-MP/AZA and the maintenance less enduring. It has been reserved for patients who fail or are intolerant to 6-MP/AZA (79). Recent

studies have shown that the combination of Remicade and methotrexate is very effective in rheumatoid arthritis patients. Future studies in Crohn's disease are required to see whether Remicade plus 6-MP or azathioprine is more effective than Remicade plus methotrexate.

The role of tacrolimus (FK506) has not yet been adequately tested (80). A controlled trial is currently underway using the newly formed Crohn's and Colitis Foundation of America Clinical Alliance. Other immunosuppressive drugs, including IL-10, IL-11, mycophenolate mofetil, and ICAM-1 (an anti-sense oligonucleotide) are being tried. Thalidomide has reappeared and has proved to have anti-TNF activity; since this drug can be given orally, it has already shown promise for treating Crohn's disease (81, 82).

Conclusion

Physicians at Mount Sinai and those who have trained there have played a major role in describing the clinical spectrum of inflammatory bowel disease. The opportunity to see and treat many of these patients has provided the experience to evaluate the many therapeutic innovations including the current use of immunosuppressive drugs. This evaluation is not yet completed, nor do we anticipate that treatments will be perfected until a better understanding of the pathogenesis of the disease has been achieved. The continuing clinical experiences at Mount Sinai and other institutions and the collaborative efforts of clinical and research scientists should help to attain the goal either of limiting the pain and suffering imposed by this disease or of eradicating it.

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Cancer in Inflammatory Bowel Disease

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Abstract

The first case of cancer in inflammatory bowel disease (IBD) was reported at The Mount Sinai Hospital in 1925 in a patient with ulcerative colitis (UC). In 1956, carcinoma of the jejunum was described in a patient with regional enteritis (Crohn's disease [CD]). IBD cancers are preceded by dysplasia, and the relative risk increases with duration of the IBD. CD cancers are more proximally distributed than are UC cancers. Both tend to occur at the site of the overt disease and both develop at earlier ages (47 UC, 50 CD) than in the *de novo* colorectal cancer (70 years).

The absolute cumulative colon cancer frequencies (8% UC, 7% CD) are identical after 20 years, emphasizing the importance of regular surveillance in both types of IBD. Moreover, the increased risk of colon cancer exists in patients with CD even when CD is confined to the small bowel, and patients with IBD have increased risks of developing extraintestinal and reticuloendothelial tumors in both CD and UC, as well as ano-vulval and malignant melanoma in CD. Colitic colorectal cancers are often diffuse, extensive, multiple and right-sided with insidious presentation. The prognosis is no worse after operation than that of *de novo* colon cancer.

Most small bowel cancers in CD are adenocarcinomas, rather than sarcomas, and present at a younger age, more diffusely and more distally than *de novo* cancers, usually making them undiagnosable at a curable early stage; indeed, two-thirds present with intestinal obstruction. Strictures of the colon are common in patients with IBD, and they have a 10-fold risk for colon cancer, 30-fold for UC, and 6-fold for CD. The risk increases with disease duration. The indications for surgery are absolute, relative and incidental, and the procedures include segmental resection, total proctocolectomy, subtotal colectomy and palliative procedures.
Key Words: Inflammatory bowel disease, cancer.

WE OBSERVED IN ONE CASE a malignant degeneration of the late stage of polypoid ulcerative colitis, with the frank occurrence of carcinoma of the rectal wall. In brief this was a case of nonspecific ulcerative colitis of the colon 14 years in duration. The polypoid stage was already in evidence 10 years ago. More recently the patient came under observation with renewed symptoms of his disease. The sigmoidoscopic examination revealed an extensive polypoid colitis, in addition to which one observed on the left lateral wall of the rectal ampulla, growing in a mass of polypoid excrescences, an ulcerating massive neoplasm. Section removed for histological examination revealed the presence of an adenocarcinoma. (1)

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Historical Background

For more than 70 years, surgeons and gastroenterologists at The Mount Sinai Hospital have been intrigued by the association of cancer with inflammatory bowel disease. Although Crohn is known for his description of regional ileitis, the first case of cancer in inflammatory bowel disease reported and described was actually one of ulcerative colitis-associated rectal cancer (see above) by Crohn and Rosenberg in 1925 (1). This was 66 years after the classic description of ulcerative colitis by Sir Samuel Wilks in 1859 (2). Since then, many reports have appeared confirming the high incidence of cancer of the large bowel in cases of ulcerative colitis, particularly for those with longstanding universal disease (3–5). The occurrence and significance of cancer in Crohn's

disease were not appreciated until many years after the classic description of regional enteritis by Crohn, Ginzburg, and Oppenheimer was published in 1932 (6). Carcinoma occurring in association with Crohn's disease was first recognized in the large bowel (7), then in the small bowel (8) (see below), and subsequently at extraintestinal locations (9).

Dr. Leon Ginzburg et al. described a case of "carcinoma of the jejunum occurring in a case of regional enteritis" in 1956 (8):

> This was believed to be the first report of carcinoma arising in the small intestine at the site of stenosing granulomatous enteritis. From the age of 11 until 30 this patient had been subjected to frequent bouts of crampy abdominal pain, with marked but non-bloody diarrhea, followed by relative constipation. In October of 1952 a gastrointestinal series revealed rigidity of the segments of small bowel involving the jejunum, with areas of dilatation between. A diagnosis of ileojejunitis was made. He was admitted with acute intestinal obstruction. Physical examination revealed a thin patient with distended abdomen and visible peristalsis, and hyperactive peristaltic rushes on auscultation. The entire segment from 18" to 6 feet from the ligament of Treitz, with multiple strictures, was resected. The tumor mass 40 cms from the proximal end consisted of an adenocarcinoma arising from the mucosa and invading the bowel wall. Cords of anaplastic cells invaded the serosa. Seven months later the patient was readmitted with widespread metastatic disease also involving the liver.

This case report describes a typical case of carcinoma occurring in stricturing small bowel disease. We have seen patients with cancer-complicating stricturing disease.

For several decades following the early description of granulomatous disease of the bowel by Dalziel in 1913 (10) and its fuller elucidation by Crohn, Ginzburg, and Oppenheimer in 1932 (6), it was generally accepted that cancer did not occur with Crohn's disease. There were no reports of cancer until 1948, when Warren and Sommers described the first case of carcinoma of the large bowel occurring in association with Crohn's disease (7). The number of described cases has increased dramatically over the last few decades. There are now considerably more than 128 patients in whom cancer of the large bowel has been reported in association with Crohn's colitis, ileocolitis, and even regional enteritis (11).

The first reports of cancer occurring in the jejunum in patients with regional ileitis and jejunitis were those of Ginzburg et al. (8) and Kornfeld, Ginzburg and Adlersberg (12). These authors described the following case.

> A 36-year-old white woman was admitted to The Mount Sinai Hospital in 1955. She was suffering from upper abdominal pain, persistent vomiting, loss of weight and marked weakness. Her initial gastrointestinal symptoms, characterized mainly by severe diarrhea, were first manifested eight years previously. At that time she was admitted to another institution where radiological studies revealed evidence of colitis. She continued to have four or five watery bowel movements daily which never showed evidence of blood pus or unusual quantities of mucus. Her weight fell from 125 to 75 pounds. She was treated by one of us with Aureomycin and cortisone and regained 40 pounds in weight in a few months. Despite radiologically demonstrable widespread disease she remained actively employed for five years. An obstructive episode was treated by suction and followed by four months of medical treatment. Radiologic studies revealed dilated jejunum and a rigid segment. She was readmitted with obstruction and found to have an unresectable jejunal mass and multiple areas of disease. She died with metastatic liver disease six months after a retrocolic duodenojejunal bypass.

Since this time, more than 80 cases of cancer of the small bowel have been reported in patients with Crohn's disease (13–15). Among these cases, 17 have occurred in excluded segments of bowel (13, 16–18), of which 7 cases have been reported from this hospital (Fig. 1) (19).

Brown, Weinstein and Janowitz (16) described a "carcinoma of the ileum 25 years after bypass for regional enteritis" in 1970. This 55-year-old woman was admitted to The Mount Sinai Hospital in 1969. Twenty-five years earlier, she had developed low abdominal pain and fever. At laparotomy 6 months later, Crohn's ileitis was found and an ileotransverse colostomy was constructed. Because of obstruction, this was revised to a side-to-side ileodescending colostomy (see Fig. 1, case 3 RC), leaving the proximal colon in place. At re-exploration, the terminal ileum and cecum were resected and an adenocarcinoma with two positive lymph nodes was found. She developed a subphrenic abscess and died on the 31st postoperative day.

BYPASS PROCEDURES IN SEVEN PATIENTS WITH CANCER IN EXCLUDED SEGMENTS

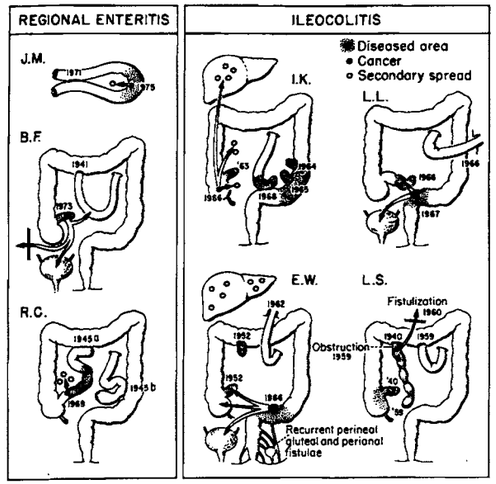

Fig. 1. Bypass procedures in seven patients with cancer in excluded segments.
JM = metastasizing cancer in jejunum four years after side-to-side jejunoileal bypass in-continuity.
BF = fistulizing cancer in terminal ileum thirty-three years after ileotransverse colostomy with exclusion.
RC = locally metastasizing cancer in terminal ileum twenty-five years after ileodescending colostomy with exclusion.
IK = metastasizing cancer in uninvolved cecum four years after diverting ileostomy and subsequent ileosigmoid bypass of terminal ileum.
LL = fistulizing cancer in diseased sigmoid colon two years after diverting ileostomy.
EW = fistulizing metastatic mixed mesodermal sarcoma in diseased sigmoid colon fourteen years after exclusion bypass of terminal ileum and four years after diverting ileostomy.
LS = cancer in multiply strictured segment of ileum, occurring at site of nineteen-year-old ileotransverse colostomy, and discovered upon malignant fistulization after secondary bypass.
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General Considerations

It is generally accepted that the numbers of cases of inflammatory bowel disease (IBD)-associated cancer in the colon in ulcerative colitis (UC) and in the small bowel in Crohn's disease (CD) have increased. The question of the colorectal cancer (CRC) risk in Crohn's disease remains controversial and will be discussed in detail below. Early reports suggested a poor prognosis for all gastrointestinal cancers in inflammatory bowel disease, but recent studies of larger series of patients have indicated a better prognosis, especially in patients with colitic colorectal cancer. In these patients, survival is similar to that in non-colitic CRC.

Clinico-Pathologic Features of IBD Cancer

Cancers occurring in IBD differ in many respects from those occurring *de novo*. In general, they occur earlier in life; the anatomic distribution is different, being influenced by sites of disease; and they are more frequently multiple and mucinous. The cancer risk is greater than in the general population (Fig. 2), and increases with longer disease duration (Fig. 3). In both diseases, cancer is preceded by dysplasia, which allows for surveillance for colorectal cancers. Both ulcerative colitis CRC (UCCRC) and Crohn's disease colorectal cancer (CDCRC) occur in association with strictures, although UC strictures are more frequently malignant.

Cancers occurring in CD, although similar in many respects, differ in some respects from those developing in UC. CD cancers have a more proximal distribution; may occur throughout the gastrointestinal tract, since CD is a diffuse disease; and may occur in association with fistulas or excluded loops. In both diseases, cancers tend to occur at sites of overt disease. In CDCRC, cancers may occur in normal-appearing bowel in as many as one-third of patients (20). We have recently described six patients (a seventh has been seen more recently) with Crohn's disease limited to the small bowel, who developed cancers of the colon and rectum (21). These observations of a wide distribution of cancer within the intestinal tract, as well as the occurrence of diffusely infiltrating (22) and multiple (23) cancers, are consistent with the fact that Crohn's disease may affect the whole gastrointestinal tract, even in the absence of overt disease (24–27). Furthermore, recent endoscopic studies have shown that one-third of patients with Crohn's disease, and even some patients incorrectly diagnosed as having ulcerative colitis, have macroscopic or histologic evidence of involvement of the upper gastrointestinal tract in the absence of any radiologic changes (28). Each of the above features of cancer in CD will be considered in detail below.

Cancer Risk

Overall Risk

Several studies have suggested an increased incidence of gastrointestinal cancer in patients

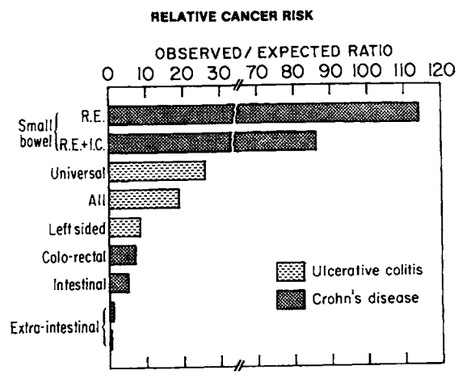

Fig. 2. Relative cancer risk in patients with ulcerative colitis and Crohn's disease.
R.E. = Regional Enteritis.
I.C. = Ileocolitis.
Universal = universal colitis involving all segments of colon and rectum.

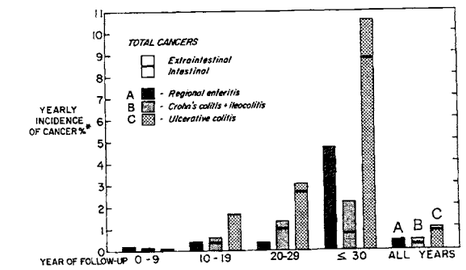

Fig. 3. Incidence of gastrointestinal cancer in Crohn's disease and ulcerative colitis for patient years at risk starting from onset of first symptoms. The cancer risk increases progressively with each passing decade for all categories of inflammatory bowel disease, but the absolute incidence rates are three times higher in ulcerative colitis than in Crohn's disease.
Bars:
A = Regional enteritis — left bars
B = Crohn's colitis + ileocolitis — middle bars
C = Ulcerative colitis — right bars
For each decade of follow up, Extraintestinal yearly incidence, in percent, is indicated by the amount above the horizontal line within each bar, while the yearly incidence, in percent, for Intestinal cancer is indicated below the horizontal line.

with Crohn's disease. Fielding et al., in 1972, found seven cancers in the gastrointestinal tract, including two in the pancreas and two in the small bowel (29). Alexander-Williams' 1976 series of 12 gastrointestinal cancers among 500 patients with Crohn's disease also included higher than expected numbers of cancers in small bowel, large bowel, esophagus, and pancreas (30). Similarly, our 1979 study of Mount Sinai patients revealed an increased incidence of both small and large bowel cancers when compared with an age- and sex-matched population (Fig. 3) (5). The incidence of gastrointestinal cancer in Crohn's disease increased with disease duration in a way similar to that in ulcerative colitis (Fig. 3) (14).

Colorectal Cancer Risk in Colitis

The risk of colorectal cancer is considerably increased for patients with ulcerative colitis, particularly for those with universal disease (all segments of colon and rectum) of long standing (7–9, 31). The overall incidences of ulcerative colitis-associated colorectal cancers (fewer than 1,000 per year in the United States) and of Crohn's colitis (less than 100 per year) are not high when compared with the total yearly incidence of 140,000 for colorectal cancers in the general population. Nevertheless, the issue of colorectal cancer risk in inflammatory bowel disease must take into account a number of important factors. First, the relative risk of colorectal cancer is much increased in age- and sex-matched populations in both ulcerative colitis and Crohn's colitis. Second, both forms of colitis colorectal cancer occur in patients younger than in *de novo* colorectal cancer. The mean age at development of cancer is approximately 56 years for Crohn's colitis and 49 years for ulcerative colitis, compared with 70 for *de novo* colorectal cancer (32). Third, since colitis colorectal cancer is a premalignant condition, cancer could theoretically be prevented in both UCCRC and CDCRC if high-risk cases could be identified early, so that timely colectomy could be carried out.

There is much controversy regarding the incidence of colorectal carcinoma with Crohn's disease. A high incidence was reported in two early publications from England. In 1965, Atwell et al. in Leeds reported three colorectal cancers among 62 patients, an incidence of 5% (33). Then, in 1968, Perrett et al. in Oxford found three cases among 82 patients with Crohn's disease, a 4% incidence (34). Although other series failed to confirm as high an incidence, Weedon et al. at the Mayo Clinic found that their patients with Crohn's colitis, whose disease onset occurred before 21 years of age, had an incidence of colorectal cancer 20 times higher than expected (35). The seven colorectal cancers in our early series of 327 patients (2%) with Crohn's colitis or ileocolitis represented an increased incidence of about 7 times what was expected (14). We now have a collected series of 30 (3 multiple) colorectal cancers among our patients with Crohn's disease. Eight large bowel cancers occurred in seven

patients with regional enteritis and 25 among 23 patients with colitis and ileocolitis.

Warren and Sommers reported the first case of adenocarcinoma complicating Crohn's disease in 1948 (7). For the next 30 years, reports of single (22, 36), and even multiple cases (23, 33, 35–38), failed to dispel the skepticism surrounding this association. More recent studies, however, have clearly demonstrated the increased risk of colorectal cancer for those patients with Crohn's disease who have extensive, longstanding, unresected colonic involvement (14, 20, 39, 40). Nevertheless, the association between Crohn's disease and colorectal cancer remains controversial, with a number of doctors disputing the association (41–45). However, each of these five populations-based studies calculated their relative risks without specific regard to the population actually at risk; namely, patients with "extensive, longstanding, unresected" colonic disease. All of these studies show an increase in relative risk of approximately 10-fold if corrected for these factors (46). A recent study from Birmingham compared the cancer risk between two hospital-referred but identically selected cohorts of patients with extensive ulcerative colitis and equally extensive Crohn's colitis (40). This study established a virtually-identical, absolute, cumulative frequency of 7% and 8%, for CD and UC respectively, at 20 years, thereby confirming the previously noted similarities between cancer incidences in these two diseases (14, 20, 39). In their prior 1994 study (47), Gillen et al. found that the relative risk of 4.9 for colorectal cancer increased to 13.3 for patients younger than 25 years of age at onset of CD, and to 18.2 if corrected for extensive colitis. If both factors were present, the risk rose to 57.2. Thus, in the presence of longstanding, extensive disease and unresected colon (this would seem to be obvious, but many authors have failed to exclude patients who have "no colon" and therefore are at "no risk!"), especially with early onset of Crohn's disease, the risk clearly is increased. In these high risk patients, it could be argued that as in ulcerative colitis regular surveillance should be carried out.

Colorectal Cancer Risk in Regional Enteritis

One question that remains unresolved is the possible association between colorectal carcinoma and small bowel Crohn's disease (42, 48). Even though seven (23%) of our patients, five of whom were previously reported (15, 21), had overt Crohn's disease confined to the small bowel, they nonetheless developed eight carcinomas. Five of these occurred in the colon and three in the rectum. It could be argued that colorectal cancer, being a common disease, appeared only coincidentally in two patients, both of whom were more than 60 years of age, with short duration disease at the time of cancer diagnosis. However, three of the seven ileitis cases presented with colorectal cancers, at ages 34, 38, and 42, suggesting a true increase in risk, and two developed cancer after 30 and 31 years of disease, at ages 70 and 78 respectively. Moreover, there were no significant differences in age at onset of Crohn's disease, age at cancer, and duration of disease to cancer, between patients with ileitis and those with either ileocolitis or colitis. This finding once again raises the question of whether small bowel Crohn's disease even predisposes someone to colorectal adenocarcinoma (42, 48), which would be consistent with the panenteric nature of this disease.

Extraintestinal Cancer Risk

Although several studies prior to 1983 failed to demonstrate a statistically significant increase in incidence for extraintestinal cancers in patients with inflammatory bowel disease (14, 20, 38, 49), a more recent study of 2,000 patients with inflammatory bowel disease has shown an increase in three specific tumor groups in patients with either Crohn's disease or ulcerative colitis (4). The first group includes reticuloendothelial tumors: leukemias in ulcerative colitis (50, 51) and lymphomas in both ulcerative colitis and Crohn's disease (4, 52). The second group comprises tumors arising from chronic perineal inflammation in Crohn's disease: squamous carcinomas of the anus and vulva (4, 53). Finally, there may be an increased incidence of malignant melanoma in Crohn's disease (4, 54). It remains to be seen whether an increased risk of any of these cancers, some of which are similar to the types that occur in immunosuppressed and/or irradiated patients (55), can be documented in other medical centers.

Colorectal Cancer

Clinicopathological Features: Colitic colorectal cancers show characteristic clinico-pathological features that tend to distinguish them from other colorectal cancers. They are more diffuse, not infrequently extending over more than one segment of bowel. They may be invisible to the naked eye, or they may infiltrate the bowel wall causing stricture formation. They are frequently

multiple, and the incidence of right-sided cancer is greater in colitis-associated than in *de novo* colorectal cancer, due largely to right-sided disease in CD and to the increased incidence of multiple synchronous cancers (32).

Cancers in colitis and regional enteritis have the unfortunate tendency of developing without giving clinical evidence of their presence in their early stages. Advanced cases are characterized by obstructive symptoms, rapid weight loss, and abdominal masses. Colorectal cancers in Crohn's disease may occur in excluded distal bowel or in association with enterovesical or colovesical (Fig. 1) (19, 56), rectovaginal (57, 58), colocutaneous (19, 59), or perianal fistulas (19, 53, 60). Crohn's disease colorectal cancers share some features with ulcerative colitis colorectal cancers. The clinicopathological features of colorectal cancer occurring in Crohn's disease, as in UC, are difficult to differentiate from the clinical features of the underlying inflammatory bowel disease. Compared to *de novo* cases, colorectal cancers in Crohn's disease occur at an earlier age (48 vs. 70 years), are more often located in the right colon (45%), and are more frequently multiple (22, 23). Multiplicity is less of a feature than in UCCRC where the incidence of multiplicity is reported to be 14–40%, compared with 4% for *de novo* colorectal cancer (32). It has been suggested that there are two separate populations among these patients. First, there are those with onset of Crohn's disease at older than 60 years of age, in whom the vast majority have had a relatively short duration of disease and in whom the Crohn's disease and cancer symptoms occurred simultaneously. This group, for example, constitutes approximately 20% of the patients in Hamilton's series (61). The second and much larger group consists of younger patients, usually with a long duration of disease. Examination of the literature prior to 1985 reveals that for all 29 patients younger than 60 years of age, for whom the duration of disease is recorded, the mean disease duration was 15 years, while for the 29 patients older than 60 years of age, the mean disease duration was 5 years. This thesis regarding two populations has been supported by a recent publication by Kyle and Ewen, who describe two such separate populations among patients in their area who developed Crohn's colorectal carcinoma (62). However, in Hamilton's series, there are also three older patients with long disease durations of 36–51 years, suggesting a third group with both older onset age and longer pre-existing disease duration (61). Six patients with onset of the disease after 70 years of age had a mean disease duration of 25 years, but two elderly patients had simultaneous onsets of Crohn's disease and cancer at ages of 68 and 72, as first described by Hamilton (61). Since onset age of Crohn's disease in the sixth decade of life is unusual and the incidence of spontaneous colorectal cancer increased in late decades, patients in this latter group could represent either coincidental spontaneous cancer or colitis-associated cancers in a setting of longstanding, undiagnosed Crohn's disease.

Cancer of the Small Bowel

Clinicopathological Features: Most cancers of the small bowel in Crohn's disease are adenocarcinomas, usually in the terminal ileum or jejunum; they are difficult if not impossible to diagnose at a curable stage. They differ from *de novo* cancers of the small bowel in many respects (13, 63). There is a lower average age at diagnosis of cancer in Crohn's disease, 45 years vs. 60 years; the site of cancer is more distal, 76% vs. 20%; and the mean postoperative survival time is less, 8 months vs. 32 months. Furthermore, sarcoma is an extremely rare form of small bowel cancer in Crohn's disease, whereas approximately one-third of *de novo* small bowel cancers are of this variety. There is also an increase in the proportion of multifocal or diffuse cancers in association with Crohn's disease. As with ulcerative and Crohn's colitis, the incidence of cancer increases with longstanding duration of Crohn's disease (Fig. 3).

In our 18 patients with known sites of intestinal cancer, the mean duration of Crohn's disease was 22 years (18 years for cancers occurring in bowel in-continuity and 28 years for cancers occurring in excluded bowel) (19). Hoffman et al. have reported similar figures, with 90% of their cases lasting more than five years, 70% more than ten years, and 38% more than 20 years from the onset of disease, yielding a mean disease duration of 18 years (63). Although the majority of cancers of the small bowel occur after a long duration of disease, Fresco et al. have drawn attention to the fact that as many as one-third of all cases may occur within the first decade of disease (64). However, the total number of patients at risk in the early onset group is much greater than in subsequent decades; hence the true cancer risk is much lower.

The most common clinical presentation of small bowel cancer is intestinal obstruction. This occurred in two-thirds of our patients (19). Other important symptoms include diarrhea, weight loss, abdominal mass, and abdominal fistulae (15, 37). These symptoms are also found in Crohn's disease without cancer. The possibility of the development of complicating cancer should be entertained if the development of these clinical features follows "a long quiescent period" (19). Small bowel cancer is rarely suspected preoperatively, the diagnosis being made in fewer than 5% of reported patients, and in only two of our nineteen. Intraoperative, postoperative and autopsy diagnoses were made in 27%, 61%, and 7% respectively, of those 44 patients reviewed by Hoffman et al., for whom the timing of the diagnosis could be determined (63).

Three key microscopic features were described by Fleming and Pollock: invisibility, mucosal dysplasia, and endometriosis-like invasion of the stroma (65). Invisibility is defined as microscopic recognition when the cancer is difficult to perceive, even on opening the operative specimen. Mucosal dysplasia, similar to that originally described by Morson and Pang in ulcerative colitis (66), is found in 25% or more of cases of CDCRC (65, 67, 68) and suggests that surveillance should be carried out in selected cases with Crohn's disease.

The prognosis of carcinoma of the small bowel in Crohn's disease is poor. Among the 44 patients reported by Hoffman et al. (63), there were only two 5-year survivors (5%), compared with the 20–30% 5-year survival rate for *de novo* small bowel cancers. The mean postoperative survival time in those Crohn's disease patients who survived surgery was only 7.8 months. All of the small bowel cancers initially reported by Greenstein et al. (14) were fatal. However, in a larger series reported more recently, although all of the five patients with cancer in excluded bowel died within 18 months, the overall survival rate at three years was 23% (Fig. 4) (15). The survival rate of more than 30% at three years for in-continuity cancer was similar to that for *de novo* small bowel cancer. The prognosis for large bowel cancers is better. With colonoscopy today, we can expect an increased and earlier preoperative detection of colorectal cancer in Crohn's disease, and thus possibly a better prognosis for the large bowel variety, but not for that in the small bowel. Small bowel enteroscopy and push enteroscopy can now be tried but there is no proof of their diagnostic value.

Strictures and Cancer

Enteric strictures are one of the common complications of Crohn's disease and are caused by marked thickening of the bowel secondary to intramural fibrotic change. The frequency of benign colorectal strictures in Crohn's disease, and the difficulty of differentiating them from malignant strictures (Figs. 5 A, B, C), makes this a topic of major importance in the attempt to diagnose cancers at an early and curable stage. Although strictures occur more frequently in the small intestine than in the colon, 5–17% of patients with colonic Crohn's disease have a colorectal stricture. One hundred thirty-two of 980 patients (13.5%) with CD involving the colon, admitted to The Mount Sinai Hospital between 1959 and 1985, developed 175 colonic strictures (69). Thirty-three patients developed more than one stricture. The frequency was twice as great in colitis (19%) as in ileo-colitis (11%). Ten malignant strictures were identified in 9 patients (3 ileocolitis, 6 colitis). One of these patients had three strictures (2 malignant and 1 benign), and two had 2 strictures (1 malignant and 1 benign).

The frequency of cancer in patients with stricture (6.8%) was higher than in those without stricture (0.7%, 6 of 848, $p < 0.001$). There were no differences in clinical symptoms between patients with benign and malignant stricture. Seventeen of 165 benign strictures (10.3%) were long, extending over more than one anatomical segment of colon, but all ten malignant strictures were short ($p < 0.0001$).

The age at the diagnosis of stricture was significantly higher in the 9 patients with malignant stricture than in the 123 patients with benign

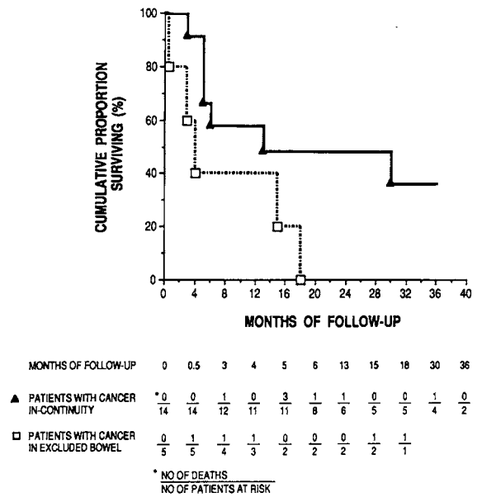

Fig. 4. Survival curves for five patients with cancer in excluded bowel and 14 patients with cancer in non-excluded bowel. The difference did not reach statistical significance. Reprinted from reference #15 with permission.

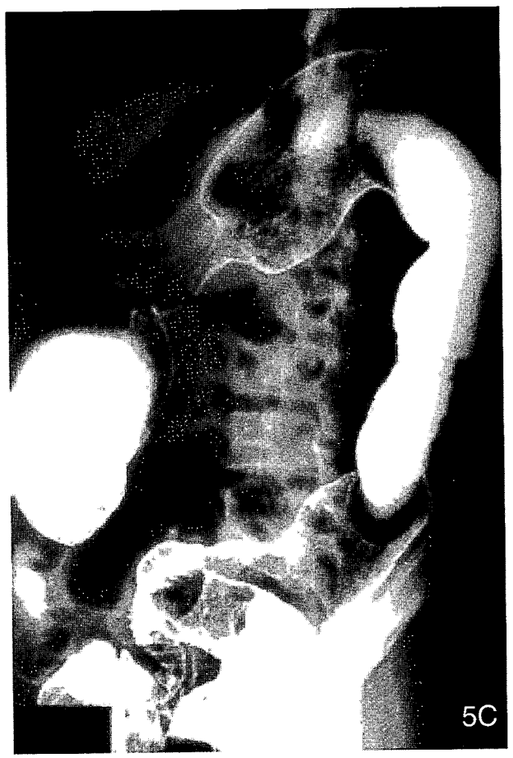

Fig. 5. Malignant and benign strictures in inflammatory bowel disease.

A. Malignant stricture in ulcerative colitis in which the cancer was missed for a year after endoscopy failed to pass the stricture.

B. Benign stricture in Crohn's disease in which malignancy was suspected.

C. Thirty-five-year-old woman who had Crohn's colitis for 20 years. She developed multiple colonic cancers. Only the malignant stricture of the transverse colon is readily apparent in this X-ray. She survived for five years following chemotherapy despite transmural metastases found at laparotomy.

stricture (mean age 57.2 vs. 41.4 years, respectively, $p < 0.01$). The proportion of strictures that were malignant increased with duration of disease, from 3.3% with less than 20 years of CD, to 11% with CD of 20 years or more. All nine patients with malignant stricture were treated surgically, and 4 of the 9 died of colon cancer during a mean follow up of 4.3 years. In view of the high rate of malignancy, 6.8%, in this series, colonoscopy with biopsy is essential in Crohn's disease patients with colonic strictures, and surgery is mandatory when a stricture cannot be fully assessed during colonoscopy. Unlike ulcerative colitis, in which proctocolectomy is required, in segmental Crohn's disease, a more limited segmental resection may be appropriate treatment in some patients. Follow-up surveillance is essential in these patients.

The frequency of colon cancer in stricture patients was 10 times higher than in non-stricture patients in our series. Although there appears to be an association between colorectal cancer and stricture, it is not clear whether benign strictures degenerate into malignancy or whether cancers present as strictures. The proportion of malignant strictures increased with increasing duration of Crohn's disease (Fig. 2). This observation is consistent with the fact that longer duration of disease is associated with increased risk of colorectal cancer, with or without stricture. Malignant disease must be ruled out if a stricture is found in a patient with Crohn's (ileo)colitis. Radiological examination is of value for detection of colonic stricture, but is not reliable for the differentiation of benign from malignant disease. Following radiological detection of a stricture, endoscopy with biopsies throughout of the length of the stricture is essential. Multiple biopsies should be taken at the proximal and distal edges, and from within the stricture, in order to rule out dysplasia, carcinoma *in situ*, or frank adenocarcinoma. Surgery must be considered whenever the endoscopist cannot visualize the entire length of the stricture.

As in Crohn's disease, any patient with ulcerative colitis who develops a stricture or obstruction should immediately be evaluated by colonoscopy. The risk of cancer is even greater in UC strictures. Gumaste et al. found that 17 of 58 patients with colorectal strictures in UC had malignant strictures (70). Seven of these 17 patients with malignant strictures in ulcerative colitis presented with partial or complete obstruction, compared with none of 42 with benign strictures. In both Crohn's disease and ulcerative colitis, a remarkable degree of narrowing, sometimes to as small as one to two millimeters, can occur without the development of obstructive symptoms, which must be attributed to the liquidity of the stool.

Surveillance of Crohn's Disease for Carcinoma

Surveillance for cancer in patients with Crohn's disease remains controversial, but should seriously be considered for selected groups of patients who are at a high risk for the development of colorectal cancer. In the 1980s, Korelitz (71, 72), and Shorter (73) suggested the need for surveillance, while Butt (74, 75), Fielding (29), and Warren (7) did not advise prophylactic measures, but they recommended "vigilance." In 1985, Hamilton (61) suggested that cost-benefit studies of surveillance protocols were needed in well-defined Crohn's disease populations.

Several factors make it difficult to propose a rational surveillance program for Crohn's disease patients. These factors include the variety of cancers which occur in association with Crohn's disease: extraintestinal (4) and intestinal (14), small bowel (3, 13, 15, 18. 64), and large bowel (2, 35, 61, 68). There are also several different modes of clinical presentation: cancers following long duration of disease (3), cancers coincident with onset of Crohn's disease (34, 37, 61, 67), cancers remote from overt disease (13, 14, 61, 76), and cancers in excluded segments (19). Finally, there are features that make the diagnosis difficult to establish even when a lesion is suspected and sought: the inaccessibility of small bowel to endoscopic examination, the difficulty of evaluating segments of bowel that are either bypassed (16, 18, 19, 77) or proximal to strictures (4, 69, 78), the "invisibility" (65) or "occult" (67) nature of the neoplasms, and the confounding of cancer symptoms with those of the underlying bowel disease.

I have proposed that regular clinical checkups should be instituted for patients with Crohn's disease, including examination of the abdomen and, because of extraintestinal cancers (see below), review of the reticuloendothelial system and skin, especially the anovaginal area. An explanation should be sought for recurrence of old symptoms or for development of new symptoms, particularly stricture, fistula, intestinal bleeding or weight loss, especially if these symptoms develop after a long period of quiescent disease. Excluded segments should be removed whenever re-operation is being performed. Patients with perianal abscesses, and internal and external fistulae should be considered to be at some risk for malignant transformation of these areas of chronic inflammation. A routine endoscopic surveillance program can be recommended for selected patients with longstanding (more the 10 years), universal disease, especially with early onset of CD. A controlled study should be designed to see if earlier diagnosis, leading to curative resection, could be made, utilizing multiple biopsies for dysplasia. In view of the occurrence of carcinoma in overtly normal appearing bowel, and in the colon and rectum in regional enteritis, biopsies of both normal and abnormal bowel would have to be made and examined for

dysplasia, carcinoma *in situ*, and infiltrating carcinoma. Biopsies would also have to be taken from elevated masses, adenomatous polyps, and especially from areas of stricture and fistula formation. Prophylactic colectomy should be advised if dysplasia develops in the absence of acute inflammation, and especially if dysplasia is found in the presence of an elevated mass. It remains to be seen whether small bowel enteroscopy will enable differentiation of benign from malignant strictures in the more proximal bowel.

The ratio of costs and risks to benefits has not been established for prophylactic colonoscopic surveillance, nor has an optimal surveillance regimen been determined. On an empirical basis, most such programs commence after 10 years of disease, often on an annual or biannual schedule. One could argue for earlier surveillance in view of the relatively high incidence of cancers in Crohn's disease during the first decade. Newer and more sensitive indicators of premalignancy, such as DNA flow cytometry, cell turnover kinetics, mucin histochemistry, lectin binding, or monoclonal antibody identification of antigenic tumor markers, may ultimately supplant routine histologic examination for dysplasia as more effective screening techniques.

Indications for Surgery

A. Absolute

1. High-grade dysplasia or low-grade dysplasia found in patients in surveillance programs in the absence of acute inflammation, with or without a dysplasia-associated lesion or mass (DALM).
2. Carcinoma proven by endoscopic biopsy.
3. A stricture that cannot be passed.

B. Relative

1. An excluded loop; although patients often refuse surgery if quiescent.
2. A poorly compliant patient on whom regular surveillance cannot be done.
3. Surveillance is impossible in the high-risk patient because of multiple, large pseudopolyps or the difficulty of differentiating the dysplasia of adenomatous polyps.

C. Incidental

1. Patients may be operated on for other indications unrelated to the cancer, such as fulminating colitis, toxic megacolon or a cancer found pathologically.

Principles of Surgery for Colorectal Cancer in IBD

The surgery for cancer in IBD is based on the principles which have evolved for cancer surgery in general: wide excision with lymphadenectomy, which should be carried out in conjunction with appropriate surgery for the inflammatory bowel disease.

In Crohn's colitis, except when the disease is extensive or universal, or severe perianal disease is present, segmental resection (SR) with reanastomosis is an option and frequently the preferred method of treatment. Although there is a high recurrence rate for colocolostomy, ileo-sigmoidostomy or ileo-proctostomy, these more limited resections allow the patient to retain the rectum, maintain intestinal continuity, and avoid a permanent ileostomy for variable periods of time. This is especially valuable in young patients. In CD, ileoanal pouch construction is at this time contraindicated. In indeterminate colitis, pelvic pouch construction may be successful with results almost as good as for ulcerative colitis (79).

Between 1960 and 1989, a total of 147 patients with cancer occurring in IBD were seen at The Mount Sinai Hospital in New York City. There were 30 with large bowel adenocarcinoma in CD, compared with 102 patients with CRC in UC (80). An additional 19 patients were seen with small bowel cancer (SBC) (15). The four groups of surgical procedures required for these patients included segmental resection (SR), total proctocolectomy (TPC) with end ileostomy or pelvic pouch (in UC only), subtotal colectomy (STC) with or without reanastomosis, and various palliative procedures (PP) including diversionary colostomy or ileostomy. The surgical procedures in our 130 patients with CC and UC complicated by CRC are listed in Table 1.

Segmental Resection (SR)

Segmental resection, right, left or distal abdominoperineal, was the preferred surgical therapy for Crohn's colorectal cancer, cancer occurring in what was often a segmental disease (Table 1). In this series, seven cases of colorectal cancer occurred in patients with regional enteritis localized to the small bowel (21). These cases were clearly ideal for SR, which was carried out in 14 patients, 46% of the series.

Total Proctocolectomy (TPC)

In CD, TPC is generally reserved for those patients with extensive or universal colitis, especially those with perianal disease in whom reconstruction of intestinal continuity is inadvisable. Although one-half of the patients with ulcerative colitis had TPC, only five (17%) of the Crohn's patients had primary TPC with a Brooke ileostomy.

TABLE 1
Surgical Procedures for Colorectal Cancer in Inflammatory Bowel Disease

	Ulcerative Colitis			Crohn's Disease		
	Subtotal	Procedure		Subtotal	Procedure	
	n	n	%	n	n	%
Total Proctocolectomy	51			5		
with ileostomy		43	43		5	17
with pelvic pouch		8	8		0	0
Subtotal Colectomy	25			5		
with ileostomy		11	11		4	14
with reanastomosis		14	14		1	3
Segmental Resection	14			14		
ileocolic		0	0		2	6
right colectomy		7	24		1	3
left colectomy		1	0		4	14
sigmoid/ant. res.		1	1		1	3
protect/Hartmann		0	0		1	3
abdomino-perineal		5	5		5	16
Palliative Procedure	5			5		
ileostomy		1	1		3	10*
colostomy/Hartmann	4	4**		2	7	
Unresectable						
inoperable/biopsy	4	4	4	1	1	3
laparotomy	1	1	1	0	0	0
TOTAL	100		100	30		100

* One with proximal jejunojejunostomy and ileoileostomy.
** One following recurrence of a rectovesical fistula after a decade-long quiescent interval.

Subtotal Colectomy (STC)

In CD complicated by carcinoma, STC was carried out in five (17%), a percentage somewhat less than the 25% in our UC patients. In only one was primary reanastomosis carried out. This is the preferred surgical procedure for UC patients who are ill, have severe active disease in addition to the cancer, are on steroids, are hypoalbuminemic and/or are severely anemic.

Palliative Procedures (PP)

Fewer than 5% of patients with CD or UC had cancers so advanced that they were inoperable. Palliative diversionary ostomy without resection was also necessary in an additional five (17%) of the patients with CD. The large number of unresectable cancers in CD was contributed to by the five patients with cancers in excluded loops. In earlier years, this operation was carried out frequently at The Mount Sinai Hospital, but is no longer done today. In most other series, cancers in excluded loops are less common.

Small Bowel Cancer in Crohn's Enteritis

Segmental resection was the preferred surgical therapy for Crohn's enteritis in 79% of patients (Table 2). Unlike the patients with colorectal cancer, only one patient developed cancer in nondiseased bowel. The four patients requiring palliative diversion, or who were inoperable, constituted 21% of the total series, a similar proportion to the 6 of 30 patients (20%) with CDCRC. Of these cancers, five occurred in excluded loops (15, 16, 18, 19).

Reticuloendothelial Tumors

Lymphomas

Lymphomas, colonic or extraintestinal (52), do not occur commonly in either CD and UC. It has been suggested that the incidence is greater than what was expected (4). For intestinal lym-

TABLE 2
Surgical Procedures for Cancer in Small Bowel in Crohn's Disease

	Subtotal n	Procedure n	%
Resection	15		79
small bowel resection		2	11
with ileostomy		1	5
with strictureplasty	1	5	
ileocolic resection and reanastomosis	11	58	
Palliative Procedures	4		21
bypass/diversion			
ileotransverse colostomy	1	5	
jejunostomy		2	11
inoperable		1	5
TOTAL	19		100

phomas, local excision is required. This should be followed by radiotherapy when indicated, and chemotherapy, which is the definitive therapy for extraintestinal lymphoma (52).

Leukemias

Leukemias are more common in ulcerative colitis than in Crohn's disease (4, 50) and occasionally may exacerbate the hemorrhage due to gastrointestinal ulceration. In one such patient with leukemia in CD, total proctocolectomy was required for massive gastrointestinal hemorrhage. Appropriate chemotherapy is necessary in all of these patients (50).

Cancers of the Anorectum

Low rectal adenocarcinomas in both forms of IBD and squamous cell cancers of the anus in Crohn's disease, usually with perianal disease, are treated by radical abdominoperineal resection of the rectum including the sphincter muscles, when necessary and resectable (53, 81). Early or advanced squamous cell cancers may be treated by local excision, or by radical excision with or without radical lymphadenectomy prior to radiotherapy and chemotherapy.

Peri-ileostomy Cancers

Cancers occurring at the site of an ileostomy are rare, but a number have been reported. Radical excision with transposition of the ileostomy is required (82).

Stricture Cancers

Cancers occurring in association with strictures constitute a particularly difficult diagnostic problem both for CDCRC (69) and UCCRC (70), in which the incidence of malignancy in strictures is approximately 30% and 5% respectively. When the diagnosis of cancer cannot be ruled out, surgical resection is indicated.

Small bowel cancer should be ruled out in all patients with multiple strictures in jejunoileitis in whom stricturoplasty is performed (15).

Cancer Occurring with Fistulae

This association has long been recognized (18, 19, 56, 59). Unfortunately such cancers are often unresectable. However, it is possible on occasion to carry out radical cancer "en bloc" resections, including the bowel on either side. This principle should be applied whenever the possibility of fistula cancer exists, even if unproven. If a complete cure is not possible, a longer period of palliation may be possible.

Long-Term Outcome Following Surgery for Gastrointestinal Cancer in IBD

Survival following surgical resection is better in colorectal cancer than in small bowel cancer in Crohn's disease. Although early series suggested a poor long-term outcome for UCCRC, recent studies have shown that survival is similar to that for non-colitic colorectal cancer. We have found a 45% 5-year survival for CRC in CD, which increases to 56% if cancers in excluded loops are omitted (unpublished data). This is comparable to the 52% survival for our 100 UC patients (80). For small bowel cancer, survival is much poorer, at best 23% at 3 years (15). Mortality for cancers in excluded bowel was 100% for both small and large bowel (see Fig. 5) (15, unpublished data).

Conclusions

Cancer in inflammatory bowel disease clearly increases in incidence in the intestinal tract and probably in certain extraintestinal sites as well. The absolute number of patients developing such malignancies are low compared to overall cancer rates in the general population, but because of higher relative risks, younger ages of onset, distinctive clinicopathological features, and difficulties in making a diagnosis, it is important that this complication of inflammatory bowel disease be widely appreciated. The prognosis today is no worse for colorectal cancers in ulcerative colitis or Crohn's disease (except for those occurring in excluded bowel) than for *de novo* cancers of the large bowel, but it remains exceedingly poor for small bowel cancers in Crohn's disease. Surveillance can probably be advised for ulcerative colitis-related colorectal cancers, although there is still some doubt as to whether it will be cost-effective or how it will affect prognosis and survival. There is even greater doubt concerning its role in monitoring patients with Crohn's disease for either colorectal or small bowel cancers. A cooperative study of endoscopic surveillance to diagnose dysplasia or malignant change in the mucosa of patients with Crohn's disease is now essential. There is increasing evidence that it would be rational to carry out surveillance for patients clearly at increased risk, namely patients with: unresected colons; longstanding disease (>10 years); and extensive disease, particularly in those with early onset of their Crohn's disease. The surgery for cancer in inflammatory bowel disease is based on a combination of the general principles for the surgery of IBD without cancer and radical excisional cancer surgery. Resection of the mesentery and lymphadenectomy should be carried out according to general cancer principles. Postoperative survival for colorectal cancer is good, approximately 50%, compared with the poor, less than 23%, survival for small bowel cancer.

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The Small Intestine

CHARLES D. GERSON, M.D.

Abstract

Clinical investigation of the small bowel at The Mount Sinai Hospital began with David Adlersberg's arrival in 1931. His research interests were in bile acids, cholesterol, carotene, and vitamin A. In 1952, he was given a Nutrition Laboratory and later, a Nutrition Clinic. His vitamin A tolerance test and interest in malabsorption led him to a comprehensive study of sprue, the separation of the tropical and non-tropical forms, and their different etiologies and treatments. Adlersberg's work was complemented by (a) Marshak and Wolf's radiologic examination of the small bowel (especially in sprue and other malabsorption disorders); (b) Gerson's perfusion experiments; and (c) Friedman, Waye and Wolf's motility studies. Lieber and his colleagues explored the deleterious effects of alcohol on the function and structure of the small intestine. Gerson explored the nutrition of patients with Crohn's disease of the small intestine, especially after extensive resection or bypass leading to ascorbic and folic acid deficiencies and hypergastrinemia. **Key Words:** Malabsorption, small intestine, jejunum, ileum, sprue, Crohn's disease, vitamin A, vitamin C, folic acid, alcohol.

The Small Intestine

THE ERA OF small bowel clinical investigation at Mount Sinai Hospital began with Dr. David Adlersberg in the 1940s. Having earlier established a reputation in the study of bile acids and cholesterol, in Vienna, he had the good fortune to be invited to The Mount Sinai Hospital in 1931 as a member of the Chemistry Department. He then extended his research interests to carotene and vitamin A. This led him to develop the use of the vitamin A tolerance test and a continuing interest in malabsorption syndromes. In 1952, The Mount Sinai Hospital established the Nutrition Laboratory under his supervision.

Celiac Sprue

In addition to the Nutrition Laboratory, Adlersberg had established a Nutrition Clinic where he followed a large number of patients with sprue. While non-tropical and tropical sprue had been recognized as clinical entities in the 19th century, their differentiation and the etiology of celiac sprue were not established until the classic report by Dicke, of the role of gluten, in 1952. However, in 1947, Adlersberg and Schein (1) published an extensive clinical description of a series of forty patients with sprue. This included findings of macrocytic anemia, steatorrhea, flat vitamin A tolerance test, and response to the diet then employed for sprue patients. Twenty-seven patients showed excellent response to a high protein, low fat, monosaccharide diet supplemented by liver extract, B complex and folic acid.

The first definitive description of villous changes in celiac sprue is attributed to Paulley in 1954 from surgical biopsy material. Schein (2), from Mount Sinai's Pathology Department, wrote an accompanying article to the above clinical description, also in 1947, from an autopsy of a patient with sprue. He described clubbing and mushrooming of small intestinal villi, "hitherto undescribed lesions of the intestine." This was clearly one of the first descriptions of an altered villous architecture in non-tropical sprue.

In 1951, Adlersberg and colleagues (3) were one of the first three groups to report on the beneficial effect of cortisone and ACTH in the treatment of sprue. The necessity for gluten restriction in the diet was not yet known so the treated patients were described as having refractory non-tropical sprue. Five of seven patients responded dramatically to steroids. In the early 1950s, this

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was a breakthrough form of therapy, as it still may be in patients resistant to a gluten-free diet.

In 1957, the *Journal of The Mount Sinai Hospital* published an entire issue devoted to sprue. Included was an article that summarized Adlersberg's experience with 94 patients with sprue (4). He was then able to define clinical and laboratory criteria that helped separate non-tropical and tropical sprue. This was the culmination of a long and productive career in the investigation of sprue.

Years later, in 1996, Kahn, Fiel, and Janowitz (5) returned to the subject of sprue with a report of a patient with celiac sprue and several autoimmune entities, including idiopathic thrombocytopenic purpura. In their article, they discussed HLA phenotypes and their possible role in the linkage of immunological conditions.

Tropical Sprue

Tropical sprue, another cause of malabsorption that is distinct from celiac sprue, was the subject of several research reports by Gerson. First, in collaboration with Lindenbaum (6), the small intestines of 68 Indian and Pakistani subjects who had come to New York were studied. Initially, these subjects were found to have functional and structural abnormalities known as subclinical tropical enteropathy. By following them sequentially, it was shown that their small bowels improved spontaneously after arrival in the United States. This indicated that environmental factors in South Asia were responsible for tropical enteropathy. Using a jejunal triple lumen perfusion technique, Gerson, Cohen, and Brown (7) were able to demonstrate the relationship between folic acid and hexose malabsorption in sprue. In the report by Meyers, Schweitzer, and Gerson (8), the occasional confusion and overlapping of findings between tropical sprue and pernicious anemia were clarified in a series of illustrative cases.

Radiology

Richard Marshak, best known for his radiologic studies of inflammatory bowel disease, was interested in all aspects of small bowel radiology. One of his interests was sprue. In collaboration with Wolf and Adlersberg (9), he published the first large series of sprue patients in 1954. With his typically critical eye, he described the radiologic characteristics of sprue that distinguished it from other small bowel diseases. He was one of the first to emphasize proximal dilatation as the earliest change. He also complemented Adlersberg's work by demonstrating x-ray improvement after steroid therapy.

Marshak published numerous articles on various small intestinal disorders, and became a national and international expert in this area. His weekly radiology conference at The Mount Sinai Hospital was avidly attended by physicians from near and far. His observations were finally recorded in a classic medical text, "Radiology of the Small Intestine" (10), published in 1970.

Motility

The next investigative work concerned small bowel motility. In the 1950s and 1960s, knowledge in this area was limited, in part due to the technical difficulties in studying the small intestine. Motility research was largely confined to the proximal small bowel. Gerald Friedman and Jerome Waye (11) developed a new technique utilizing pressure transducers and a series of three catheters with openings 7 cm apart. These were placed in the gastric antrum, and various levels of the duodenum and proximal jejunum. They began to describe, in several reports, the differentiation of various wave types in the duodenum. In collaboration with B.S. Wolf (12), they correlated pressures with cineradiographs so that pressures could be compared with motility patterns. They appreciated that there were propulsive contractions and mixing contractions. At that time, techniques for measuring the migrating motor complex, especially phase III with its "housekeeping" function, had not yet been developed.

Alcohol

Charles Lieber is best known for his work on alcohol and the liver (13). However, his experimental model of feeding alcohol while maintaining normal nutrition was also utilized to study the effects of alcohol on the small intestine. In 1969, in collaboration with John Lindenbaum (14), he published the first report to show that alcohol inhibited intestinal absorption of vitamin B_{12} despite the presence of intrinsic factor and pancreatic enzyme. This finding led to a more extended study of small intestinal structure and function. Several articles documented anatomical changes. Emanuel Rubin and colleagues (15) showed electron microscopic changes in mitochondria, endoplasmic reticulum and cytoplasmic degradation, both in jejunum and ileum. Later (16), histologic changes were demonstrated with an increase in crypt-villous ratio, cellular infiltration of the lamina propria, and some erosion of villous tips.

Perlow and Lieber (17) also measured enzyme activity in the brush border of chronic alcoholic men. There appeared to be diminution in sucrase activity and lactase activity, compared with controls. These enzyme levels increased after two weeks of abstinence; there was an increase in both enzymes, suggesting that alcohol was responsible for the findings.

Crohn's Disease

In the 1970s, Gerson published a series of papers related to the effects of Crohn's disease on small intestinal absorption and nutrition. In an effort to correlate ileal disease or resection with absorptive parameters, 68 patients with ileitis were studied (18). Resection of 90 cm of terminal ileum was a major determinant of steatorrhea, while resection of 60 cm uniformly caused vitamin B-12 malabsorption. Jejunal function was well maintained in most patients except those with short bowel syndrome whose absorption parameters were most impaired. This study emphasized the nutritional consequences of intestinal resection, which then was performed more freely than it is today.

One of the consequences of extensive intestinal resection with a resultant short bowel syndrome is gastric acid hypersecretion. In the early 1970s, Straus and Yalow were able to measure serum gastrin levels in a series of patients with short bowel syndrome in whom hypersecretion of gastrin was the probable cause of excess acid (19). It was suggested at that time that some inhibitory factor had been removed in the resected distal small bowel, but this hypothesis has still not been clearly established.

Patients with Crohn's disease often avoid fruits and vegetables because of problems with diarrhea. Because it was known that this dietary restriction may cause folic acid deficiency, Gerson and Fabry studied another vitamin present in the same foods, ascorbic acid (20). Serum and leukocyte ascorbic acid levels were significantly reduced, sometimes in the range seen in scurvy. Dietary histories showed that vitamin C deficiency was correlated with reduced ascorbic acid intake.

Because ascorbic acid is important for collagen formation, tissue ascorbic acid concentration was then measured in surgical ileal specimens from patients with and without fistulae. Both tissue and serum ascorbate levels were significantly lower in patients with fistulae. This study demonstrated that vitamin C deficiency can be a nutritional consequence of Crohn's disease.

Folic Acid Absorption

Another area of active investigation by Gerson and co-workers (21) included the use of a triple lumen tube to perfuse various substances over a 30-cm segment of proximal jejunum. Fluid aspirated from the distal port of the perfusing system could be used to measure accurately the absorption of various solutes, such as folic acid. Adding other substances to the perfusate could be shown to affect folate absorption. Glucose increased the absorption of folic acid, possibly due to solvent drag. Diphenylhydantoin (DPH), on the other hand, when added to the perfusate (22) was shown to inhibit folate absorption, thus explaining the association between DPH and folate deficiency. Folic acid absorption was found to be normal in patients with Crohn's disease (23). Acetazolamide inhibited the absorption of salt and water by the normal human jejunum (24).

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Note by Editor of The Mount Sinai Journal of Medicine

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WHILE PREPARING the material for publication, it became readily apparent that two articles originally published in 1932 merited special consideration, not only for their historical context, but also for their medical content. These articles are therefore republished here, to afford easy access both in print and electronically, via the Web. One of these articles, by Ginzburg and Oppenheimer, originally appeared in *Transactions of the American Gastroenterological Association*; the other, by Crohn, Ginzburg and Oppenheimer, appeared in the *Journal of the American Medical Association* These two articles were originally delivered as oral presentations in early May 1932, the presentation by Ginzburg preceding that by Crohn.

The article by Ginzburg and Oppenheimer has rarely been cited in the medical literature, probably because the journal was neither widely distributed nor easily available. In fact, there is some question as to whether the two listed authors ever knew of its publication, since they never cited it. A later version of this same article, embellished with relevant figures of pathological specimens and clinical radiographs, appeared in 1933 (*Annals of Surgery* 98:1046–1062).

This, of course, was not the case for the 1932 article by Crohn, Ginzburg and Oppenheimer which appeared in *JAMA*. Both articles provided valuable, if not similar, insights into a disease which often had been described earlier, as Baron points out. But now, Crohn's oral presentation catapulted this disease entity into the consciousness of the medical community. And from this moment, progress in treating the disease would be relentless, thanks to a more thorough description of its clinical course and an improved grasp of its pathophysiology, and the cellular and molecular events with which it is associated.

Landmark Article

Transactions of the American Gastroenterological Association 1932; 35:241 – 283.

Non-specific Granulomata of the Intestine*

(Inflammatory Tumors and Strictures of Bowel)

LEON GINZBURG, M.D., AND GORDON D. OPPENHEIMER, M.D.

DURING THE PAST FEW YEARS, we have encountered cases, apparently with increasing frequency, which clinically and radiologically gave the impression of being tumors or tuberculosis of the bowel. At operation, these cases were usually considered to be either hypertrophic tuberculosis or malignant disease. Microscopic examination of resected specimens, however, failed to substantiate these views. No evidence of specific disease, such as tuberculosis, syphilis, or actinomycosis, could be found. Amoebic disease of the bowel was excluded both from a study of the sections and the stool, as well as by the inefficacy of emetin therapy in suspected cases. Carcinoma, lymphosarcoma, and Hodgkin's disease could be definitely excluded. A few of these cases were quite evidently secondary to diverticulitis, but aside from these, a large heterogenous group remained, differing etiologically, but with certain common clinical and pathological findings. These cases, which showed various degrees of hypertrophic chronic inflammatory lesions in different stages of healing have long been known to the English as well as the Continental surgeons. In 1921 Tietze (1) published a thorough resume of the subject with a very complete bibliography. In 1923, Wilensky and Eli Moschkowitz (2) reported four cases which they had collected from various institutions, using the designation "Non-specific Granulomata of the Intestine," a name, which perhaps best conveys an idea of the underlying pathology. Mock (3) has recently reported a series of cases using the same designation. Clinically these cases manifest themselves either by the development of palpable masses or symptoms due to an ulcerative stricturing of the bowel. They may, therefore, with propriety, also be designated as non-specific inflammatory tumors and strictures of the bowel.

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*Presented at the Annual Meeting of the American Gastro-enterological Association in conjunction with Dr. Burrill B. Crohn. The section on localized ileitis represents a joint study.

Permission granted to reprint the article which appeared in *Transactions of the American Gastro-enterological Association* 1932; 35:241 – 283.

It is well known that both the intestine and its peritoneal covering have tremendous powers of resistance to infection and a marked ability to resolve inflammatory lesions. Furthermore, the intestinal mucosa is possessed of marked regenerative power (4). Surgeons have time and time again recorded their amazement at the rapidity and completeness of the disappearance of huge inflammatory exudates and masses from the abdomen. Similarly, both clinically and experimentally we know that there may be extensive mucosal disease or injury without any resultant permanent scarring. In some instances, however, following an infection or injury, this "restitutio-ad-integram" does not occur. The persistence of some infectious agent or irritating factor, or the inability of the tissues to overcome them, results in a cycle of reparative and destructive processes which leads to the formation of either hypertrophic extra-intestinal masses or extensive intramural hypertrophic ulcerative stenotic lesions or combinations of both.

Histological study of the various types of lesions shows simply evidences of various stages and degrees of acute and chronic inflammation with lymphocytic, polymorphonuclear and plasma cell infiltration, with varying degrees of degenerative changes or fibroblastic proliferation. In some of the peri-intestinal lesions there is considerable hyalinization, and early calcification and even early bone formation have been encountered. The presence of giant cells is a common finding. We believe that these are accidental findings due to the presence of non-absorbable vegetable matter, minute quantities of which extravasated around the lesion in perforative cases or became entrapped in the healing of ulcerative lesions. Wilensky and Moschkowitz reported the presence of large cells in the section of one of their cases. By special stain, we have been able in a number of our cases to demonstrate cells or groups of cells with much cytoplasm and little nuclear material, which are in all probability, vegetable cells. These apparently became entrapped in healing ulcers and were apparently taken up by the lymphatics, for we have found them in the serous and subserous layers of the bowel, as well as the submucous. Being nonabsorbable, they become encapsulated by foreign body giant cells. In the serosa they give rise to little nodules which are very difficult to differentiate grossly from miliary tubercles. Such foreign body tubercles, incidentally, have been experimentally produced by the introduction of emulsions containing vegetable matter into the peritoneal cavity (5). We consider them as accidental, rather than etiological factors, in the course of the disease. Their importance is two-fold; firstly, their irritant action may be a factor in producing the marked hyperplastic fibrosis seen in some cases; and secondly, they are probably responsible for the confusion of these non-specific lesions with tuberculosis.

The following is a study of fifty-two cases which have been observed and operated upon mainly on the surgical service of Dr. A. A. Berg during the last ten years. Only those cases where resection was performed or specimens obtained are considered. These sections were restudied with the invaluable aid of Dr. Paul Klemperer to help us in settling questionable points. These do not include cases of sigmoid diverticulitis or any lesions situated distal to the recto-sigmoid junction. Gastric cases and two cases of ulcerative jejunitis near the fossa of Treitze have also been excluded from this study. An accurate etiological or pathological classification is at present impossible. We submit the following classification therefore, fully conscious of its defects and overlappings, but pleading in its favor, a certain degree of clinical utility. It is our plan to discuss each group and to report in abstract some of the typical cases.

1. Extra- or peri-intestinal granulomata secondary to sealed-off perforations of the bowel.

2. Granulomata secondary to known vascular disturbances of the gut.

3. Localized hypertrophic ulcerative stenosis of the terminal ileum.

4. Localized hypertrophic colitis with or without low-grade generalized colitis.

5. Simple penetrating ulcers of the colon.

6. Lesions secondary to inflammation of the appendages of the bowel, such as appendicitis, diverticulitis, typhlitis.

I

Lesions in Which the Inflammation Reaction Is Mainly Extra- or Peri-intestinal and Which Are Secondary to Sealed-off Perforations of the Bowel

As a response to a slowly perforating lesion of the intestine that has become sealed off by omental, parietal, or visceral adhesions, large inflammatory masses, with very little or no pus formation may develop, which are intimately adherent to the serosa and sub-serosal tissues but do not actually involve the sub-mucosal and muscular layers of the gut. A classical example is the type of lesion resulting from perforation of the colon by such foreign bodies as fish bones. Usually this accident results in the formation of ordinary intra-abdominal abscesses. In some instances, however, probably due to the slow rate of perforation, the inflammatory reaction is mainly productive. As a result of the continued presence of the foreign body and the low-grade infection resulting from the penetration of the intestinal wall, a markedly hypertrophic inflammatory reaction takes place in the peri-colonic and sub-serous layers of tissue which both clinically and at the operating table may give the impression of being a colonic neoplasm. Three such cases operated upon under the clinical diagnosis of neoplasm were recognized for their true nature at the time of operation and the foreign bodies sought for and found. Perforative lesions, from whatever cause, may involve the omentum with the development of a large omental mass containing necrotic xanthematous tissue, firmer fibrotic masses, areas of calcification or discrete encapsulated miliary abscesses. The lesion in the wall of the gut may be minimal.

An exceedingly interesting group are those cases in which a pseudo-tumor of the abdominal wall itself develops as a result of a perforative lesion, becoming sealed off by the anterior parietes. In two such cases, foreign bodies (fish bone, toothpick) were found in the center of large firm tumor masses involving the rectus muscle and pro-peritoneal tissue. These tumors had been excised under the diagnosis of sarcoma of the abdominal wall. The deep side of these inflammatory abdominal wall tumors was densely adherent to the omentum but there was no evidence of adherent bowel. In two other cases, in which the same preoperative diagnosis of sarcoma was made, adherent gut was found on the deep side of the tumor mass; a perforation apparently having been sealed off by the parietal peritoneum. The "tumors" were found to be edematous, granulomatous lesions involving the parietal peritoneum and the pro-peritoneal cellular tissue.

Altogether, ten cases were encountered in this group, five of which were definitely due to foreign body. In three cases, the inflammatory mass was mainly in the serosal and subserosal layers of the flexures of the colon. In two instances, the mass was mainly omental; the original perforation being in the transverse colon in one instance and in the small gut in the other. In four cases, the main mass and granulomatous tissue lay in the abdominal parieties, and in one instance was chiefly peri-vesical. (The large group of cases with marked productive peri-cecal changes due to appendicitis and peri-sigmoidal inflammatory masses from sigmoid diverticulitis also belong in this group, and are much more common than any of the other types of lesions noted. They are so well known, however, that they have not been especially studied or included in the enumeration of this group.)

Clinically these cases are characterized by the development of a palpable mass without the appearance of symptoms due to obstruction or ulceration. Because of the lack of intramural involvement of the bowel the barium meal or enema usually shows no abnormalities. Occasionally, a persistent spasm of the bowel adjacent to the lesion may be encountered which gives the impression of a filling defect. At operation, these tumors are found not to encroach upon the intestinal lumen and intra-intestinal irregularities or ulcerations are absent. This point serves to differentiate even the very adherent and intimately connected peri-intestinal masses from neoplasm or inflammatory diseases which actually involve the bowel walls.

1. Case of large peri-intestinal inflammatory tumor originating in the small bowel

E. H., age forty-five, admitted to Mount Sinai Hospital in 1925. Two years ago a laparotomy had been performed in the lower abdomen. Did not know what operation had been performed. She was well until few months before admission when she began to experience localized abdominal tenderness,

some constipation and loss of weight. Physical examination revealed a large mass, the size of a grapefruit, to the left of the midline adherent to the scar of the old operation. No evidence of any hernia at this point. G. I. x-ray was negative. Colon enema negative.

At operation, tumor was resected with the adherent skin and fascia and muscle. On its deep surface it was intimately adherent to and apparently an integral portion of the wall of the small intestine. This portion of the bowel together with the tumor was resected.

Pathological report. — "Macroscopic specimen consists of a tumor mass, the size of a large grapefruit, adherent to the skin and by its deep surface to a small segment of small intestine. The skin and intestine appeared to be normal. The tumor itself, is of a mottled character, darker portions appearing like hemorrhagic inflammatory tissue. The lighter yellowish portions are evidently the seat of necrosis. Below the attachment to the skin is a small, hard piece of tissue which cannot be cut, and which may be either foreign body or possibly new bone formation. The portion of tumor not adherent to the gut is covered by a thin sheet of tissue probably compressed omentum. Grossly, it cannot definitely be determined whether tissue is inflammatory or neoplastic in nature. Microscopic examination: shows no evidence of neoplasm. There is considerable acute and chronic inflammation with areas of fibrous tissue, areas of necrosis, hyalinization, calcification and ossification."

The patient made an uneventful recovery. Six months postoperatively she was well. Has not been seen since.

2. Case of peri-colonic inflammatory tumor, mainly omental, simulating sarcoma of the bowel. Healed colonic perforation

D. S., age fifty-three, admitted to the Mount Sinai Hospital in 1922. Nine months before admission he had developed pain in the right lumbar region. After three months, the pain became most marked in the right lower quadrant where it had persisted to the time of admission. The pain was dull and boring, and radiated posteriorly. It was more or less continuous and bore no relation to either meals or bowel movements. There had been no change in the character of the alimentary habits. Physical examination revealed a palpable mass in the right lower quadrant opposite the umbilicus, the dorsal portion of which appears to be fixed. Wassermann was negative. X-ray showed spasticity of the transverse colon and an apparently persistent defect in the caput coli. Whether this defect was due to new growth or to spasm could not definitely be determined from the roentgenogram.

At operation a mass was found adherent to the parietal peritoneum. The peritoneum was opened below this point and separated. There did not appear to be any involvement of the inside of the bowel wall. The mass was thought to be sarcomatous and accordingly, resection of the transverse colon with the adherent tumor and omentum was performed.

Pathological examination. — Macroscopic specimen consists of resected transverse colon with a portion of mesentery and adherent omentum. At about the central portion of the specimen is a small mucosal scar extending through the wall and at this site thickened omentum is densely adherent. No definite perforation can be established. The omentum proper is markedly infiltrated and is the seat of numerous abscesses, varying from 1 to 3 cm. in diameter. Diagnosis: Inflammatory tumor of the omentum with multiple encapsulated abscesses.

3. Case of fish-bone perforation with peri-colonic mass

A. K. was admitted to the Mount Sinai Hospital in July, 1926, with a complaint of pain in the left upper quadrant of the abdomen of eight weeks' duration. The pain was localized, and did not radiate. It was more or less constant and had no definite relation to the intake of food. For the last three weeks, the bowels had moved only with the aid of cathartics. The patient also stated that the stools had become smaller in diameter. There was no melena, vomiting or diarrhea, nor were there any urinary symptoms. He had lost twenty pounds in weight since the onset of his illness. However, he appeared to be fairly well nourished and his hemoglobin was 95 per cent. In the left upper quadrant of the abdomen, and in the left flank, a slightly tender, large mass was palpable. X-ray and pyelogram of the urinary tract showed the kidney to be normal in size and in position. X-ray of the colon showed no filling defect. A pre-operative diagnosis of inflammatory tumor or carcinoma of the splenic flexure was made.

At operation, a large mass was found occupying the splenic flexure and upper portion of the descending colon. This was carefully separated into two component parts, one of which consisted of thickened, inflamed omentum; the other was a large smooth, firm peri-colonic mass. There was no evidence of any invasion of the colonic lumen. In the midst of this mass there was seen to be a depressed area, of what was apparently a healed fistulous communication with the gut. The omentum mass was then further explored and two fish bones were found lying in separate small abscess cavities. The abdomen was closed with rubber tube drainage and the patient made an uneventful recovery.

4. Case of fish-bone perforation with formation of inflammatory tumor of the abdominal wall

J. C., age sixty-five, was admitted to the Mount Sinai Hospital, April 30, 1925. For the past few months the patient had noted the development of a mass above and to the right of the umbilicus. There had been no pain associated with its development. It had never been reducible. Physical examination showed a hard, smooth, spherical mass about three inches in diameter, to the right and above the umbilicus. It was not tender and there were no signs of inflammation. There was no cough impulse. The preoperative diagnosis was that of a tumor of the abdominal wall.

An elliptical incision was made around the mass and the tissues found to be normal down to the rectus muscle. The posterior aspect of the rectus muscle, the posterior rectus sheath and peritoneum were involved in a mass of dense, grayish tissue. To effect its removal, the abdominal cavity had to be entered. The omentum was then found to be adherent to the mass, but was not apparently involved in the inflammatory process. There were no evidences of any adhesions of any of the abdominal viscera to the deep surface of the tumor. The tumor, when excised, was still considered to be a neoplasm, and the specimen was cut across for further inspection. In the depths of the mass a small collection of pus was found, and in its center was a fish bone, 2 to 3 cm. long. Culture showed staphylococcus albus and an anhemolytic streptococcus.

The pathological description follows: "The macroscopic specimen consists of tumor mass to which is attached a resected portion of omentum and some adherent muscle. The tumor mass measures about 7 to 8 cm. in diameter, is oval in shape, firm in consistency and on section presents a small sinus tract, containing a foreign body about 3 cm. long (fish bone). Microscopic examination discloses a fibroma showing numerous inflammatory areas. A few multinuclear giant cells are present, in the tissue adjacent to the foreign body."

II

Lesions Secondary to Known Vascular Disturbances of the Bowel

The most striking example of this type of lesion that we have encountered is the stenotic involvement of the bowel, resulting when badly compromised but viable gut has been replaced following operation for strangulated hernia. In these cases there is permanent vascular injury affecting the intramural vessels of the bowel. Vascularization through anastomosis is sufficient to prevent a necrosis of the muscular and fibrous layers of the bowel. It is, however, insufficient to permit of the usual marked regenerative functioning of the intestinal mucosa. Ulcerative lesions involving the mucous membrane first result, followed by secondary infection and the production of gradual fibro-stenotic reactions which may result in extreme reduction of the caliber of the intestinal lumen. Five such cases have been encountered in this series, all in the form of a tubular stenosis, i.e., cases in which the entire segment of strangulated gut underwent fibrotic involution. In the literature, cases of narrow annular stricture corresponding to the site of constriction at the neck of the sac have been reported. In this series we observed one annular stricture in which a loop of gut had been caught under an encircling band of omentum. Small mesenteric tears have been reported as causing stenosis, both clinically and experimentally, in the same manner.

The symptoms are those of gradually increasing subacute intestinal obstruction, the ulcerative phase apparently passing by unnoted. The symptoms have appeared anywhere from two weeks to six months following strangulation. Short circuiting entero-anastomosis effected relief of symptoms in four cases; resection in one. One patient came to autopsy without operation,

In these cases we have definite evidence from the history and findings at the primary operation that there had been extensive vascular insult. How large a role this vascular mechanism plays in cases where the causal connection is not so clear-cut, it is difficult to say. The fact that such lesions as repeated and self-reducing intussusceptions or recurrent partial volvulus, especially at the ileo-cecal angle, may be responsible for certain chronic inflammatory lesions, must be borne in mind, although insusceptible of proof. It must be emphasized that the end stages of a lesion in which primary vascular insufficiency permitted necrosis and secondary infection of the bowel resemble almost identically those in which a primary infectious agent has produced secondary thrombotic and degenerative changes.

I. M. L., age forty-five, was admitted to the Mount Sinai Hospital in September, 1926. She had been operated on four years ago at another hospital for a left inguinal hernia, which had apparently recurred shortly afterwards. Eight hours before admission it had suddenly become large, painful and irreducible. She had vomited three times. Examination revealed an irreducible inguinal hernia about the size of a small grapefruit.

An immediate operation was performed, and a bilocular sac containing brownish, slightly foul-smelling fluid, was found. Two loops of intestine were found to be incarcerated, one of which showed considerable cyanosis with subserous hemorrhage. After a prolonged period of observation and irrigation with warm saline, the loop was considered viable and was replaced. The subsequent course was uneventful, and the patient was discharged well at the end of two weeks.

For four months following the operation the patient was apparently entirely free from symptoms. At that time she began to experience occasional attacks of colicky abdominal pain. There was no vomiting or constipation. Shortly afterwards, the patient was seen in the return clinic and visible peristalsis noted. A gastrointestinal x-ray was taken which showed unmistakable evidence of an incomplete small intestinal obstruction. Laparotomy was advised but refused. One month later, the patient was readmitted to the hospital in a moribund condition with signs of intestinal obstruction. Her condition was too poor to warrant operation. Respirations ceased soon after admission.

Autopsy showed the following: "Eighty cm. above the ileo-cecal junction, the intestine shows a narrowing 8 cm. long. The area is about one-third the diameter of the normal intestine. The ileum proximal is markedly dilated. In the region of the stricture the wall of the intestine is markedly thickened and the lumen markedly stenotic. The mucosa is cicatricial and there are polypoid excrescences of the preserved mucosa. Microscopically the wall of the ileum is seen to be several times normal in thickness. The mucosa is denuded of epithelium; the muscularis mucosa is fragmented. There is a marked inflammatory infiltration of submucosa and subserosa."

III

Hypertrophic Ulcerative Stenosis of the Terminal Ileum

In this group of cases the terminal ileum is the seat of the lesion, the changes being most marked at the ileo-cecal valve where it usually terminates abruptly on the ileal side of Bauhin's valve. Proximately, it diminishes in severity, signs of the disease being rarely found further than 10 to 15 inches from the cecum. We have no clue to its etiology but observation of various stages of the disease in different patients lead us to believe that the following are the steps in the development of the final process. The primary lesion, we believe, are a number of oval or lenticular shaped ulcerations located on the mesenteric side of the bowel. We have found this lesion on a number of occasions proximal to the main, hypertrophic mass and separated from it by normal looking mucosa. As the disease progresses, it is characterized. by two main features; firstly, a marked tendency to perforation and secondly, by an excessive proliferative reaction in the submucosa. The end stage of the process, the one most frequently encountered, is manifested by the conversion of the terminal ileum into a thickened hose-like tube. When opened, the normal transverse intestinal folds in the terminal portion of the bowel are seen to be partially destroyed and partially flattened and broken up into polypoid masses. A series of linear ulcerations along the mesenteric border is practically a constant finding. At times, especially near the cecum, the mucosa is almost completely atrophic and there may be papillary excrescences, especially along the margins of the ileo-cecal valve. The submucosa is enormously thickened and causes a marked diminution in the caliber of the lumen. Perforation frequently occurs in between the leaves of the mesentery and the enlarged glands and exu-

date gives rise to good-sized masses. The pus may track along the cellular tissue and form secondary communications with the cecum or colon. At times the perforation occurs into the peritoneal cavity with the formation of an intra-peritoneal abscess. Drainage of these abscesses results in the formation of intractable fistulae. Clinically, these patients have presented themselves with four different pictures.

1. Simulating acute appendicitis. — The first sign of the disease may be an attack impossible to differentiate clinically from appendicitis. At operation however it is at once noted that the terminal ileum is soggy, edematous and blotchy, and that there are numerous large succulent glands in the terminal mesentery. Resection has never been performed in this stage of the disease in this series, so that we have no idea of the underlying pathological changes present during this phase. A number of these patients gradually passed into the more chronic phases of the disease. One case is symptom-free two years after exploration, although x-ray shows definite narrowing in the terminal ileum.

Occasionally these patients are admitted with an abscess already present. Drainage may result in the formation of a chronic fistula starting immediately post-operatively, or there may be primary healing with secondary breaking down, occurring weeks or months later.

2. Symptoms of ulcerative enteritis. — There may be a low-grade diarrhea, loss of flesh and strength, mild colicky pains, and a development of a secondary anemia. This type is rather uncommon.

3. Symptoms of chronic incomplete small intestinal obstruction. — This is the most common manifestation of the disease. The patient may previously have passed through one of the phases described above, but frequently the obstructive symptoms appear without any previous history. Severe abdominal cramps, visible peristalsis, and borborygmus are the most common symptoms complained of. The duration of symptoms in this group varies from one to three years. At operation the typical hose-like ileum referred to above, frequently very densely adherent or communicating with the cecum, ascending colon or sigmoid is found. The occasional presence of small tubercle-like nodules may serve to render differentiation from tuberculosis more difficult. The nature of these foreign body tubercles has been discussed above.

A mass was palpable in every subacute and chronic case. Visible peristalsis was frequently noted. The barium enema as a rule shows no abnormality, as the disease ends at the ileo-cecal valve. As a result of pathological ileo-colic or ileo-sigmoidal communications, secondary changes may occur in the colon which are reflected in the barium enema and which may lead to a false conception as to the true nature of the pathological process. In two instances, definite narrowing has been demonstrated in the terminal ileum following the barium meal. In others, dilated loops of ileum and ileal stasis have been demonstrated. In most of these cases no attempt was made to administer a barium meal because of a fear of causing a complete obstruction.

4. Chronic intractable fistulae. — These have resulted following drainage of intra-abdominal abscesses, and have resisted closure by exposure and simple suture of the internal opening plus enterostomy. They have been cured either by short-circuiting operations with exclusion of the involved loop, or resection of the diseased segment plus entero-colostomy. The findings at operation are those described tinder the chronic form of the disease plus the presence of extensive adhesions.

There have been fourteen ileo-cecal resections in this group with one death. Of the remaining thirteen cases, one patient returned with an annular stricture a few inches proximal to the site of the original resection. The other cases have done well. We have only two proven cases where a previous short-circuiting operation with exclusion had been performed, both these cases later coming to resection. In one of these, an anastomosis had been performed elsewhere apparently through disease tissue with a resultant implantation of the disease on the colonic side of the anastomosis. Another patient, on whom an entero-colostomy with exclusion had been done, developed a new focus of the disease involving a segment of gut five or six feet proximal to the original area. There were four other patients who, we believe. fall into this group, in whom entero-colostomy exclusion proved curative. No specimens were, however, removed from these patients and they are not definitely included in this group.

Relation to Appendicitis

We do not believe that this group of cases has any relation to appendicitis. Approximately half of these patients had been subjected to previous appendectomies. In some of them, it had already been noted at the time of the primary operation, that distinct abnormalities were present in the terminal ileum. In those patients in whom the appendix was still present at the time of resection, no particular abnormalities were found in it, aside from a severe peri-appendicitis.

Relation to Tuberculosis

Careful study of these sections revealed no definite tubercles, no caseation, necrosis, nor could tubercle bacilli be demonstrated. In six instances, guinea pig inoculation, inoculation into rabbits and into chickens failed to show evidence of any variety of tuberculosis. Lowenstein cultures for tuberculosis were negative in three instances.

It might be argued that evidences of tuberculosis would be difficult to find in tissue which has undergone fibrosis. However, anatomical tubercles and the Koch bacillus could not be demonstrated even in the active ulcerative lesions found proximal to the main hypertrophic mass. Even in the tubercle-like structures occasionally seen on the serosa, definite evidence of Koch infection could not be found. During the past ten years there have been only five cases of localized hypertrophic tuberculosis resected at operation at the Mount Sinai Hospital. There have been a number of instances of multiple tuberculous foci in the intestines found at laparotomy. There have also been a number of cases with active or advanced pulmonary tuberculosis with x-ray evidence of involvement of the ileo-cecal region. In the latter instance, operation was never resorted to.

To sum up our impressions of localized hypertrophic tuberculosis, it has been our experience that most of the supposedly localized ileo-cecal tuberculosis proved on microscopic examination to be non-tuberculous, while on the other hand, most of the indubitably tuberculous lesions proved to be unsuitable for resection because of their multiplicity.

Case of hypertrophic stenosis of the terminal ileum, foreign body tubercles present

A. P., age thirty-six, was admitted to the Mount Sinai Hospital, July, 1930. Eight years ago an appendectomy had been performed, apparently for chronic appendicitis. The present illness was of two years' duration, first manifesting itself by weakness and loss of weight. Eighteen months before admission severe peri-umbilical pain had developed and had gradually increased in severity until it was almost continuous. She had suffered from moderate constipation until the last few weeks, when mild diarrhea movements, three to five per day, occurred. She was asthenic and had lost thirty pounds in two years. Physical examination revealed a mass, the size of an orange in the right lower quadrant, behind the old appendectomy scar. Hemoglobin was 50 per cent, Wassermann was negative. Stool showed no blood, ova or parasites. Barium enema showed dilatation of the entire colon with marked redundancy of the transverse colon. X-ray following barium meal showed some degree of ileal stasis. A preoperative diagnosis of either carcinoma or tuberculosis of the ileo-cecal region was made.

Operation revealed a large inflammatory mass involving the terminal ileum, cecum and ileo-cecal mesentery. There was a large mass of nodes along the right colic artery. Tubercle-like structures were found on the serosa of the terminal ileum. The post-operative diagnosis, following a resection of the terminal ileum, cecum and ascending colon was ileo-cecal tuberculosis.

Pathological description. — "Resected specimen consists of 12 cm. of ileum, cecum and ascending colon. Ileo-cecal junction is markedly thickened, forming a tumor the size of a tangerine. The mucosa of the ileum shows areas of ulceration as well as some areas of mucosal hyperplasia. Some of the ulcers appeared to be surrounded by tubercle-like structures. The ileo-cecal orifice was markedly narrowed and the wall of the valve infiltrated by dense connective tissue. The cecal wall also appeared hyperplastic but the main lesion seemed to stop at the valve. The serosa of the ileum and cecum presented a few discrete millet-sized tubercles."

Histological examination.—Marked thickening of all the layers of the gut due to fibrous proliferation with diffuse infiltration of large and small lymphocytes, monocytes, plasma cells and occasional polynuclear leucocytes. There are also areas of lymphoid hyperplasia. The mucosa shows ulceration. No tubercle bacilli seen. No anatomical tubercles seen. No evidence of caseation necrosis.

Numerous giant cells were seen and large cells and groups of cells with pale cytoplasm and small nuclei. These were considered vegetable cells with foreign body reaction.

Portions of the lesion were ground up and injected into rabbits, guinea pigs and chickens for tubercle bacilli identification. All were negative. Final pathological diagnosis: non-specific chronic and acute productive and ulcerative inflammation of the lower ileum.

8. Hypertrophic stenotic inflammation of terminal ileum with obstructive symptoms, spontaneous perforation into sigmoid. Preoperative diagnosis: Carcinoma of sigmoid

Male, D. H., age twenty-six, admitted to the Mount Sinai Hospital in October, 1928. For three years he had been suffering from severe abdominal colic and constipation. At times diarrhea had been present. There was no bloody stool. He had lost considerable weight, the exact amount was unknown. No anemia. Physical examination revealed moderate abdominal distention. Rectal examination showed a mass rather toward the left side of the pelvis which could be palpated bimanually and was interpreted as being a sigmoid mass, prolapsed into the cul-de-sac. Barium enema showed a stricture of a mid-sigmoid which, at that point was narrowed to the size of a quill. Preoperative diagnosis was carcinoma of the sigmoid.

Operation. — Terminal portion of ileum was found densely adherent to cecum and both were bound down to mid-sigmoid. Upon freeing the adhesions it was seen that there was an ileo-sigmoidal fistula. Aside from this site of perforation, the sigmoid appeared normal. It was realized that the main lesion was in the terminal ileum. The opening in the sigmoid was therefore closed in layers and a typical ileo-colectomy performed for the removal of the mass involving the ileum and cecum.

Pathological examination. — Resected specimen consists of 33 cm. of ileum and the cecum. The proximal 17 cm. of the specimen consist of normal but markedly dilated small gut. The distal half of the resected gut is considerably narrowed and its walls thickened. The narrowing of the lumen and the thickening of the wall increase toward the cecum. The thickening is due mainly to hyperplastic changes involving the submucosa and the mucosa. A series of superficial irregular ulcerations with reddish green base are seen throughout the stenosed portion of the ileum always at the mesenteric insertion. About 6½ cm. from the cecum there is an irregular hemorrhagic area about 1½ cm. in diameter with a centrally placed irregular perforation. About 1 cm. from the ileo-cecal junction is a large superficially ulcerated area from which pus escaped on pressure. Aside from these ulcerated areas the mucosa is edematous and has a cobble-stone appearance. The lymph nodes are hyperplastic.

Histological examination.—Marked mucosal ulceration with acute and chronic purulent inflammation. Diffuse thickening of all layers of the gut especially the submucosa due to edema granulation tissue and diffuse infiltration with large and small lymphocytes, plasma cells and occasional polynuclear leucocytes and occasional giant cells. No tubercles or tubercle bacilli seen. Final pathological diagnosis: Hyperplastic chronic ulcerative inflammation of ileum. Picture resembles hyperplastic tuberculosis of the ileo-cecal region but there is no evidence of tuberculosis in this instance.

9. Operation for acute appendicitis. Diseased terminal ileum noted at the time. Gradual development of obstructive symptoms. No relief from ileo-colostomy. Resection performed.

S. W., age thirty, operated at another institution on March 1, 1929, with a preoperative diagnosis of acute appendicitis. At operation, it was noted that the ileo-cecal junction and the terminal ileum were red and thickened and the serosa dull and opaque, and covered with plastic exudate. Many large mesenteric glands were seen. Gland was excised and reported as hyperplastic lymphadenitis. The appendix was reported as chronic atrophic appendicitis. He was readmitted to that institution in January, 1930, with a history of pain in the lower abdomen, repeated vomiting and obstipation for two days. A diagnosis of fibrosis of the terminal ileum causing intestinal obstruction was made and the patient was subjected to a

laparotomy. The terminal ileum was found narrowed and fixed by numerous adhesions. An ileo-transverse colostomy was performed without division and exclusion of the loop. The patient did not do well after operation and continued to have increasing abdominal colic and marked loss of weight.

When he was admitted to Mount Sinai Hospital in June, 1930, patient was emaciated and visible peristalsis was noted in the lower abdomen. Repeated studies with barium meal and enema failed to cast much light upon the condition in the abdomen. It was thought that the symptoms were due to entrapment of intestinal contents between the site of the ileo-colostomy and the stricture in the terminal ileum. With this diagnosis patient was subjected to a laparotomy which revealed an exceedingly complicated series of conditions. Near the site of the old ileo-colic anastomosis a small abscess was encountered, penetrating into the transverse mesocolon. Exploration revealed this to be due to a perforation of a piece of toothpick through the small intestine with considerable degree of stenosis and kinking at this point. As it was impossible to close the perforation about six inches of the small intestine were resected and an end-to-end anastomosis performed. Following this, further exploration revealed that the terminal ileum distal to the anastomosis and the transverse colon were the seat of chronic inflammatory disease. A rapid resection of the terminal ileum, cecum colon, ascending colon and transverse colon to a point distal to the old ileo-colic anastomosis was undertaken and a new ileo-colostomy performed. Patient did remarkably well after this procedure and was discharged greatly improved seven weeks later. Patient has been followed for the past year, has gained forty pounds in weight, and aside from a small sinus communicating with the closed end of the transverse colon, showed no symptoms.

Pathological findings. — The macroscopic specimen consists of a resected portion of the terminal ileum, ileo-cecal junction, cecum, and ascending colon, and a portion of the ileum which has been anastomosed with the transverse colon at previous ileo-colostomy. The terminal ileum is markedly dilated to a circumference of 10 cm. and contains several small serpiginous ulcerations. The ileo-cecal junction is markedly stenosed and barely admits a medium sized probe. The stenosis is due to a large proliferating polypoid mucosal mass overlying the junction and surrounded by numerous ulcerations. The ascending colon, from the ileo-cecal junction to the old ileocolostomy is normal. At this point the mucosa on both sides of the anastomosis is found hypertrophic with numerous ulcerations and small polyps. The lymph nodes in the mesentery are enlarged and hypertrophic. In addition, there is a separate portion of resected small intestine at the center of which there is a perforation in the vicinity of which the wall of the bowel shows marked thickening, fibrosis and annular narrowing. Microscopic examination shows ulceration of the mucosa of acute and chronic suppuration. The walls of the gut are infiltrated with numerous large and small lymphocytes and plasma cells. There are a few eosinophiles and polymorphonuclear leucocytes. There is extensive fibrosis involving all the coats, most marked in the submucosa and the muscularis. No evidence of tuberculosis or amebae disease.

Diagnosis. — Ileo-cecal stenosis due to polypoid ulcerative non-specific ileitis involving the terminal ileum and transverse colon.

10. Operation for supposed appendix abscess. Appendix not badly diseased. Development of fistula in right lower quadrant eight months later. Diseased terminal ileum at operation three years later, for intractable fistulae.

H. C., age twenty-eight, first admitted to the Mount Sinai Hospital in January, 1928. At that time he complained of colicky pains in the abdomen, unrelated to meals of three weeks' duration. The morning before admission, the pain became more severe and was referred to the lower abdomen, especially on the right side. There had been no vomiting, or chills. Temperature had not been taken.

On admission, temperature was 104. Blood count was 20,000 with 92 per cent polys. There was tenderness, rigidity and a mass in the right lower quadrant. Clinically the case was considered a case of appendix abscess. Laparotomy was performed and a large mass, the size of a large grapefruit was found in the iliac fossa. After packing off the intestinal contents, the mass was unraveled and found to consist of the cecum, appendix, terminal ileum and its mesentery and a loop of sigmoid. The appendix was lying in a bed in the mesentery of the terminal ileum, which was about two inches thick and oozing pus. The appendix was removed and rubber-dam drain led down to the necrotic tissue. Aside from a wound infection, patient did well and was discharged one month later. Pathological report of the appendix was acute and chronic inflammation.

Patient was readmitted to the hospital in May, 1931. He had been well for eight months after the operation at which time the scar broke down in one place and for two months drained greyish, odorless fluid and then closed spontaneously. For the next one and one-half years, patient had no symptoms. Two weeks before the second admission he began to experience pain at the site of his scar, which gradually became more severe. On admission, patient's temperature was 103, and beneath the scar a fluctuant mass was present. Upon incision, about 1 ounce of thick, yellowish pus was evacuated. From this abscess cavity a tract led down toward the abdomen. Tube drainage was instituted. Patient drained feces for several days, and lipiodol injected into the wound seemed to run into the cecum. After about ten days the fecal discharge ceased and the wound began to granulate. Barium enema at this time revealed no abnormality in the cecum.

The patient was seen again in July, 1931, at which time, an exudate was still present in, the right lower quadrant. Conservative therapy was continued until November, when an exploratory laparotomy was undertaken. At operation, the terminal 2 feet of ileum were found to be greatly thickened, edematous, hyperplastic and in one of the loops was found, the inner opening of the fistulous tract. It was recognized that the fistula was not of appendicular or cecal origin but probably had at its base, a non-specific ileitis. Accordingly, resection of the 2 1/2 feet of terminal ileum, cecum and part of the ascending colon was undertaken and an ileo-transverse colostomy performed.

Pathological findings. — The specimen consists of 40 cm. of terminal ileum, 12 cm. of large bowel and attached skin. From the skin a fistulous tract leading to a point in the ileum, 4 cm. from the ileo-cecal junction. There are some enlarged, moderately firm glands in the ileo-cecal angle. Examination of the interior of the specimen shows cecum and colon to be normal. Beginning at the ileo-cecal valve and extending proximately for 30 cm. there are marked mucosal alterations. The mucosa is markedly thickened, congested and thrown up with irregular folds. Rugae have lost their identity. The surface presents numerous hemorrhages, erosions and ulcerations interspersed with areas of mucosal hyperplasia. Lymph follicles are enlarged. The submucous layer is moderately thickened and fibrotic.

Microscopic examination. — Marked mucosal ulceration with acute-chronic purulent inflammation. Diffuse thickening of all layers of the gut, especially the submucosa, due to edema, granulation tissue and diffuse infiltration with large and small lymphocyte, plasma cells and occasional polynuclear leucocytes. No tubercles or tubercle bacilli seen.

Pathological diagnosis. — Hyperplastic chronic ulcerative inflammation of the ileum.

IV

Localized Hypertrophic Colitis

In addition to a purely localized definitely palpable inflammatory colonic mass, some of these cases at one time or another presented evidence of a low-grade general colitis, much milder in type than the ordinary severe, diffuse ulcerative form. In others, the disease remained localized. That ulcerative colitis may affect predominantly or almost exclusively certain segments of gut has been emphasized by Dr. Berg for years, and recently, Bargen has reported a series of cases illustrating the same point. In most of the present cases there were no roentgenological or sigmoidoscopic evidence of generalized colitis at the time of operation, and the symptoms were attributed entirely to the localized colonic disease. In a few of these cases, persistence of symptoms after resection led to renewed investigation, which in some instances showed evidences of mild colitis, which responded to medical therapy. In those cases where definite evidence of colitis involving other portions of the colon could be shown, coincident with the presence of a mass, it was sometimes possible to obtain a good result by a short-circuiting entero-colostomy. In only one case did definite symptoms appear first in a segment of gut other than in which the hypertrophic mass ultimately developed (case 11).

The cecum and ascending colon were the seat of the disease five times; the recto-sigmoid, three times; the mid-sigmoid, once; and the junction of the sigmoid and the descending colon, three times. In the right colon, the disease usually extended upward until a few inches from the hepatic flexure. The mucosa showed, at times, large irregular ulcerative areas up to 1/2 inch in diameter with areas of hypertrophic mucosa in between them. In other cases the ulcers were smaller and were overshadowed by the bullous polypoid mucosa. Papillomatous and polypoid changes were common in the mucosa. The submucosa was moderately thickened and edematous. The serosa was opaque, and there was marked thickening and hypertrophy of the subserosal fat both in the gut and meso-colon. Glands in the ileo-cecal angle were enlarged. Numerous adhesions to the omentum and surrounding loops of gut were found at operation.

In the sigmoid, the pathological changes were more of a fibrostenotic nature with narrower limits of involvement and relatively little ulceration and with more tendency to stricturing and papillary proliferation in the mucosa. Microscopically the picture was simply that of various stages of inflammatory disease. In addition to tuberculosis, careful search was made in these cases for amoebae. Evidences of neither were found.

Most of these patients had been sick for about six months when they appeared for operation. Abdominal pain, diarrhoea and bloody stools were the most common complaints in the right-sided lesions. When the sigmoid was involved, constipation and painful defecation were present. At times, the symptoms were mainly obstructive. A palpable mass was found either by abdominal examination or in the cul-de-sac by pelvic examination in every case. X-ray showed either an irregular filling defect or an area of narrowing in the involved segment. When the filling defect was unusually extensive, the presence of inflammatory rather than neoplastic disease was suggested. In two cases, radiological evidence of coexisting colitis, in addition to the presence of a local lesion, could be shown. By and large, however, radiological differentiation from neoplasm or tuberculosis was not possible with certainty. The sigmoidoscope is of value in diagnosis not only for removing specimens for microscopic examination but also for demonstrating multiple foci of disease.

At operation, the determination of the exact nature of the pathological changes is again very difficult. Most of these cases were resected under the operative diagnosis of carcinoma or tuberculosis. Ulceration on the inside of the bowel, projection of papillary growths into the lumen and the presence of annular infiltration mimic neoplasm very closely.

On the right side, ileo-colic resection was performed five times with no mortality; no other procedure being adopted for this form of the disease. One of these patients had a mild recurrence of symptoms which cleared up under dietetic treatment.

In the lesions involving the upper and mid-sigmoid, a Mikulicz operation was performed three times, and an exclusion anastomosis to the lower-most point of the pelvic colon once. In another case, where definite evidence of generalized colitis could be demonstrated, in addition to a recto-sigmoid mass, a cecostomy was performed. Marked subsidence in the size of the mass, and diminution in the severity of the symptoms followed. In two localized lesions at the recto-sigmoid junction, abdomino-perineal resection with restitution of continuity by an extra-peritoneal presacral anastomosis was performed according to the technique of Dr. A. A. Berg. The only alternative in these cases would have been a left inguinal colostomy which would probably have resulted in a stricture of the bowel below that site and prevented any attempt at closure of the inguinal anus without a secondary and more difficult resection of the involved area. There were no mortalities in this left-sided group.

11. A patient in whom the development of an inflammatory mass in the cecal region was preceded by a three-year history of intractable perianal inflammations. A period of recovery following resection of the inflammatory mass was followed in a few years by extension of the inflammatory condition to the adjacent distal segment of the colon.

I. F., age forty-four, admitted to the Mount Sinai Hospital for the first time in 1927 with a history of vague abdominal symptoms, and a history of recurrent peri-anal abscesses and fistulae. Examination at this time revealed a number of perianal ulcers and superficial fistulae. Sigmoidoscopy showed a congested mucous membrane covered with shreds of mucus. Stool was negative for blood. Ewald test meal showed an anacidity but neutral red appeared in the gastric contents fol-

lowing injection. Wassermann was negative. Physical examination revealed no other abnormalities.

Following this, there were a series of readmissions for intractable peri-anal ulcers and fistulae and fissures which proved recalcitrant to the ordinary operative measures. Tuberculosis was suspected but the excised specimen proved negative. Three years following his first admission, he was readmitted to the hospital with a history of peri-umbilical and right lower-quadrant pain of four months' duration. He had occasional periods of diarrhea, but in between his bowels were normal. On one occasion, he passed a moderate amount of bright red blood in his stool.

Physical examination showed a man, chronically ill, and moderately anemic (hemoglobin 68 per cent). In the right lower quadrant, a firm mass, about the size of a small grapefruit, was palpable. It was fairly fixed. Sigmoidoscopy revealed no abnormalities. Barium enema revealed a marked and constant irregularity and filling defect involving the cecum and ascending colon. The findings were considered suggestive of an intrinsic lesion, probably neoplasm.

Patient was operated upon under the preoperative diagnosis of either neoplasm or hypertrophic tuberculosis of the colon. At operation, a large mass, involving the cecum and the ascending colon was discovered to which there were numerous adhesions of omentum and transverse colon. An ileo-colic resection was performed.

Pathological report. — Macroscopic specimen consists of the resected portion of the cecum and ascending colon together with the appendix and small portion of the ileum. Cecum is very definitely thickened and narrowed by an inflammatory process beginning at the ileo-cecal junction and extending upward for 12 cm. This portion of the cecum shows a large, irregular ulcerative process, finely granular and red with numerous interspersed areas which have the appearance of hypertrophic granulations plus hypertrophic mucosa. Around the margins, of the ulcerated area, mucous membranes show a polypoid hypertrophy. Jutting out from this main area are numerous finger-like ulcerative areas surrounded by hypertrophic mucous membranes. The appendix is apparently involved in the inflammatory process. It is red and infiltrated and through its intestinal orifice there is a projection of polypoid mucosa. The distal 4 cm. of the ascending colon, in contrast to the remaining portion, is smooth, pale and atrophic. Numerous shotty lymph nodes are found in the meso-colon, appearing grossly hyperplastic. Cultures from the bowel show enterococci and colon bacilli. Guinea pig, rabbit and chicken inoculations for tuberculosis are negative.

Histological examination. — Showed acute and chronic inflammation. There are no evidences of tubercle or caseation necrosis.

Diagnosis. — Non-specific inflammatory disease of the cecum and the ascending colon.

Following operation, patient did well for about two years; he gained weight and his peri-anal ulcers healed. Recently he commenced to lose ground again. X-ray at the present time shows an apparent extension of the same type of inflammatory lesion previously present in the cecum, to the distal transverse colon.

12. Case of localized ulcerative colitis

I. L., age fifty-five, admitted to the Mount Sinai Hospital in 1924. The chief complaint was pain in the right lower quadrant and diarrhea of four months' duration. Pain in the right lower quadrant was dull and gnawing, frequently started after meals and continued for one-half to one hour. Bowels moved six to seven times a day. Occasionally they were tarry. Five weeks before admission, a mass became palpable in the right lower quadrant.

The appendix had been removed seventeen years previously.

Physical examination showed a man, chronically ill, apparently having lost considerable weight. The abdomen was slightly distended and in the right lower quadrant, a mass, the size of an orange, slightly tender, and slightly movable, could be palpated. Hemoglobin was 88 per cent. Wassermann was negative, stool contained small quantities of blood. X-ray showed a filling defect in the cecum and ascending colon. The rest of the colon appeared normal. Preoperative diagnosis of carcinoma of the cecum was made, and an ileo-colic resection performed.

Pathological examination. — Specimen consisted of about 10 cm. of cecum and 18 cm. of ascending colon. Colon and ileo-cecal angle were covered with a large amount of hyperplastic fat, almost obscuring the peritoneal covering. Where the peritoneum was visible, particularly over the ileum, there were small peritoneal nodules, suggestive of miliary tubercles or lymphoid infiltration in fatty deposits. On section, the ascending colon down to the cecum was the seat of an ulcerative colitis with polypoid infiltration. The very terminal portion of the ileum also showed evidence of superficial erosion.

Histological sections showed simply various grades of acute and chronic non-specific inflammation. No evidence of tuberculosis or amebiasis could be found.

Following operation, patient developed a small fistula and continued to have diarrhea. This persisted for about six months when the diarrheal symptoms disappeared, and the fistula closed spontaneously. This patient has been observed in the Gastrointestinal Clinic of the Mount Sinai Hospital for the last seven years and has been noted to have occasional flare-ups of low-grade colitis, which at times could be seen to involve the lower sigmoid segment. His general condition is good.

13. Case of localized hypertrophic colitis. Fistula following previous appendectomy

A. S., age twenty-three, admitted to the Mount Sinai Hospital in 1929, complaining of severe cramps and diarrhea of three weeks' duration. The pain was increased after ingestion of food. Stool varied in consistency from liquid to mushy but contained no blood or pus.

Physical examination revealed a tender mass in the right lower quadrant. At this time the hemoglobin was 85 per cent and the white blood count was 23,000 with 81 per cent polys. Temperature varied between 100 and 101 degrees. Examination of the stool showed some pus; no parasites, ova, or amebae. Course of emetin had no effect. X-ray following barium enema showed a defect involving the cecum and ascending colon. Barium meal showed the same picture. Chest x-ray was negative.

Exploratory laparotomy revealed cecum and ascending colon to be rather thick and injected. No evidence of tuberculosis could be seen in the external covering of the bowel. No definite ulcerations were palpable inside the bowel. Appendix was removed and the patient was discharged.

Two months later he was readmitted with a loss of weight, continued diarrhea and persistent fistula in the right lower quadrant. Stools were negative for tubercle bacilli, actinomycosis and amebae. Another course of emetin was given without avail. One month later, as symptoms persisted, exploratory laparotomy was performed and ileo-colic resection plus an ileosigmoidostomy was performed.

Pathological description. — Macroscopic specimen consisted of cecum, ascending colon and a small portion of the terminal ileum. The mucosa of the colon showed marked edematous polypoid hyperplasia giving the mucosa a cobblestone appearance. Between the polypoid projections were occasional, irregular small ulcerations. There were a few papillary mucosal projections. Peri-intestinal lymph nodes appear hyperplastic. There does not seem to be much involvement of the deeper layers of the gut, except for an inflammatory edema.

Microscopic examination showed areas of ulceration in the mucosa with hemorrhagic and acute and chronic purulent inflammation. At other points the mucosa was hyperplastic. The submucosa showed mainly edema with round-cell infiltration. The muscularis was thickened and showed moderate fibrosis. There were no evidences of tubercle bacilli or anatomical tubercles. No amoebae seen on section.

Pathological diagnosis. — Non-specific ulcerative colitis and polyposis.

Patient made uneventful recovery and has remained well to date.

14. Localized hypertrophic sigmoiditis and peri-sigmoiditis with diarrhea and bloody stools

R. H., age 27, admitted to the Mount Sinai Hospital in September, 1922. Chief complaint was diarrhea of two years' duration. She had six to seven movements per day, and the stool frequently contained fresh blood. At times, there was severe cramp-like pain. She had lost 15 pounds in the past year. Red blood count was 3,500,000. Hemoglobin was 35 per cent. Stool showed fresh blood; no amebae, ova or parasites.

A mass was palpable in the left lower quadrant. Sigmoidoscopy showed an ulcerative infiltration 15 cm. from the anus, mainly on the anterior and right lateral wall. A specimen removed was reported as chronic inflammatory tissue. The fresh secretion was examined for amebae but none found. An appendicostomy was performed and the cecum was reported as being hard and indurated as though the seat of chronic inflammation. Patient was given a course of emetin and irrigation was performed through the cecostomy. Barium enema showed a narrowing of the sigmoid and a filling defect in the region of the descending colon and sigmoid. The rest of the colon appeared normal. Sigmoidoscopy again showed a granular infiltrating mass which the sigmoidoscopist considered carcinoma, but which was reported as inflammatory tissue. The mass in the left lower quadrant became larger and patient showed no signs of improvement.

At the second operation, a large mass, the size of a grapefruit, densely adherent to the latero-pelvic wall and surrounded by firm adhesions was found. Resection was performed.

Pathological examination. — Macroscopic specimen consisted of resected sigmoid about 20 cm. in length, showing a tremendous productive inflammatory process, infiltrating its wall, constricting the lumen and involving peri-sigmoid tissue. The mucous membranes showed a rather polypoid appearance with marked thickening of the sub-mucosa, apparently inflammatory in nature, and without ulceration or diverticula. In the center of the specimen where the inflammatory process was most marked there seemed to be a necrosis of the intestinal wall.

Microscopic examination showed acute and chronic inflammation. No signs. of neoplasm or tuberculosis. Pathological diagnosis: Chronic and acute sigmoiditis and peri-sigmoiditis.

15. Hypertrophic colitis (sigmoid) with gradually increasing obstructive signs

H. B., age 67, admitted to the Mount Sinai Hospital in May, 1926. Chief complaint was gradually, and markedly increasing constipation of a few months' duration. There had been occasional appearance of blood in the stool. One month before admission, barium enema showed a constriction with an incomplete but fairly tight obstruction at the junction of the descending colon and sigmoid, approximately at the level of the brim of the true pelvis. The appearance of the descending colon, judged by the barium in it after evacuation suggested colitis. At this time, a mass could be felt in the left lower quadrant. Since the x-ray had been taken patient had become gradually more obstipated, until upon admission he was passing only small quantities of gas.

Because of the increasing obstruction, it was felt advisable to resect or short-circuit the mass, regardless of its nature. At operation, a mass, 3 inches long, densely indurated, and very adherent to the parietes was found and a Mikulicz operation performed.

Pathological report. — Hypertrophic colitis. No signs of malignancy. No diverticula found.

The artificial anus was later closed, and when last heard from two years after operation, the patient was feeling well.

16. Localized inflammatory annular stricture with polypoid hypertrophy of mucous membrane just above recto-sigmoid junction

F. S., age 53, admitted to the Mount Sinai Hospital in June, 1925. She had been sick for a year, with increasing constipation and rectal bleeding. The severity of both symptoms had increased considerably, just before admission. On examination a mass could be felt in the left iliac region. X-ray showed a stricture at the recto-sigmoid junction. Proctoscopy showed no abnormality in the lower rectum, and a stricture was encountered at the recto-sigmoid junction.

Because of the increasing symptoms, it was decided to operate in spite of the fact that the exact nature of the lesion could not be definitely determined. It was felt that a colostomy would simply result in the production of a complete stricture if the lesion were benign. It was, therefore, decided to resect the involved lesion, which was done according to the technique of Dr. A. A. Berg by abdomino-sacral excision with restitution of continuity by end to end extra-peritoneal presacral anastomosis.

Pathological description. — Macroscopic specimen consists of resected portion of sigmoid 10 cm. in length containing an annular lesion 5 cm. in diameter, causing constriction at that site. There is a marked polypoid hypertrophy of the mucous membrane in this region. The muscular wall of the bowel above the lesion is thickened. The lymph nodes are slightly enlarged. Microscopic examination shows polypoid hyperpla-

sia of the mucosa, diffuse fibrosis and round cell infiltration of the rest of the wall of the sigmoid.

This patient was readmitted about six months later for dilatation of stricture developing at the site of the anastomosis. Following this procedure, patient has remained well to date.

V

Simple Penetrating Ulcers of the Colon

This term is applied to a group of cases which show one or more clean-cut penetrating ulcers which look almost like punched out peptic ulcers. It is apparently a purely local disease; the surrounding colon not appearing to be grossly diseased. In two cases, penetration had occurred through the colonic wall and had become sealed off by adhesions of omentum or epiploic appendices, with the formation of rather firm inflammatory masses, which gave the impression of being penetrating or perforating neoplasms. Both these lesions were situated in the ascending colon and, clinically, were operated upon with diagnoses of acute appendicitis. At operation they were mistaken for carcinoma of the colon and were resected as such.

Another patient, who probably belongs in this group is one who developed signs of incomplete obstruction in the transverse colon and who, at operation, was found-to have a narrow, inflammatory annular stricture. There were no evidences of disease of other portions of the colon, and the narrow, local, annular stricture can probably be best explained as a result of the healing of a penetrating ulcer.

Another manifestation of the same type of lesion was encountered at autopsy in a patient who had experienced severe repeated hemorrhages from the bowel, one of which finally proved fatal. Twelve cm. from the rectum a group of punched out ulcers was encountered. At the base of one of these was an arteriosclerotic vessel which had been eroded by the penetrating ulcer.

We have no exact idea as to the underlying etiology of these lesions. It is possible that they are due to injuries by ingested foreign bodies. There is also a possibility that they are of vascular origin due to blocking of a small vessel. Some point is lent to this latter view by our experience with a case encountered a few months ago. This latter patient was admitted to the hospital as a perforated duodenal ulcer with x-ray evidence of free air in the diaphragm. Exploration showed, however, that perforation had occurred in the lowermost ileum which contained four sharply punched-out perforations, about 1/2 cm. in diameter. These were sewn up and an ileostomy performed. The patient did well for a few days, then suddenly went into collapse, commenced to drain blood through the ileostomy tube, and died shortly thereafter. Autopsy showed a mesenteric thrombosis. The area of ileum where the perforation had occurred was normal except for the sharply punched-out ulcers. Our interpretation of this course of events was that the thrombus had originally been parietal and that small emboli had broken off, plugged some of the terminal arteries or arterioles and given rise to the rapidly perforating ulcers, and that later the parietal thrombus had become complete. These are the only facts which we can adduce, which at all throw any light on the etiology of this type of ulcers.

17. Penetrating ulcers and annular stricture

E. R., age 23, admitted to the Mount Sinai Hospital in December, 1928. For two months she had complained of increasing pain and constipation, borborygmus and occasional blood in the stools. She claimed to have experienced a similar attack one year ago, which lasted for a few weeks and then disappeared.

Physical examination revealed a sausage-shaped mass in the upper abdomen. There was occasional intestinal erection noted. The x-ray revealed an irregular narrowing of the transverse colon for a distance of two inches.

Laparotomy revealed a stenosing lesion of the colon, annular in nature, in the middle of the transverse colon. Resection with side to side anastomosis was performed.

Pathological examination. — Specimen consists of a portion of resected transverse colon 7 cm. in length, which was divided into two portions by a narrow linear stricture approximately 1 cm. wide which presents small nodular elevations in mucosa and a small polyp as well as several small irregular ulcerations. The gut proximal to this area is dilated to approximately twice the circumference of a normal bowel and the thickness of the wall approximately twice that of normal.

Microscopic examination showed acute and chronic inflammation. No evidence of malignancy or tuberculosis.

Pathological diagnosis. — Ulcerative stricture of the colon, non-specific in character.

VI

Inflammatory Masses Secondary to Appendages of the Bowel (Appendicitis, Typhlitis, Diverticulitis)

Probably the best known type of this variety of inflammatory mass is that which is secondary to sigmoid diverticulitis. These have been so much discussed in recent years that we feel there is no reason for including them in the present study. We wish, however, to emphasize in passing, that in addition to the large peri-sigmoidal inflammatory masses caused by perforation of a diverticulum or extension through it of infection from the lumen of the bowel there is another and less common type. In this, there is a gradually developing submucous infiltration of the sigmoid as well as an adherent peri-sigmoiditis, with the development of a considerable degree of intramural fibrosis and hyperplasia and a considerable degree of stenosis. This type is clinically and radiologically extremely difficult to differentiate from malignant stenosing lesions of the sigmoid and even at operation, differentiation may be impossible.

The relation of the appendix to the development of certain hypertrophic masses in the ileo-cecal region is a moot point. In many cases an unresolved appendicitis is undoubtedly responsible for the formation of a hyperplastic fibrotic mass, the so-called "appendicitis fibroplastica," but this does not account for all the lesions found in this region. In these cases, the appendix is found buried in the cecal wall or as in one case of this series, in the terminal ileum; and forms part and parcel of the inflammatory mass. The extension of the inflammation in these cases is simply by contiguity and as might be expected is mainly peri-cecal with involvement of the sub-serosal tissue. The submucous layer of the gut does not appear to be involved. Occasionally tiny abscesses between the appendix and the cecum will be uncovered when the former is mobilized. These are quite common, their true nature is usually appreciated and resection is rarely performed.

There is another, and much rarer type of lesion, however, which may he called chronic typhlitis, in which the appendix though thickened and indurated lies free and non-adherent.

Both it and the cecum show a marked submucous thickening, edema and fibrosis. The lesion does not extend up into the ascending colon or into the ileum except at the ileo-cecal valve, points which serve to differentiate it from the two other types of non-specific inflammatory disease encountered in this region, which have been discussed above. Large masses of firm glands are found in the ileocecal angle. Upon examination, the pathological alterations involving the appendix and cecum are seen to be continuous. If the route of spread were by direct extension, it would have to be through the contiguous submucous layers of the appendix and cecum. However, from the clinical standpoint, it is well known that inflammation of the appendix usually stops short of the extreme base even in the most virulent form of the disease. Dr. Klemperer, who was at one time greatly interested in the extent of the basal involvement in acute appendicitis, was able to substantiate our clinical observation from his pathological studies.

The question then arises as to whether the extension is into the cecum from some unusual form of acute appendicitis involving the base, or whether the ileo-cecal changes were primary, the appendix participating simply as a component portion of this segment of gut. We are inclined to believe that the type of chronic cecitis with extensive submucous-intramural involvement, but without evidences of mucosal ulceration is secondary to a partially resolved acute or chronic typhlitis.

There is no doubt about the existence of acute typhlitis as a clinical entity. On an active emergency service three or four such cases are encountered every year. Clinically and on physical examination they present the picture of acute appendicitis. Operation, however, reveals a succulent edematous, inflammatory lesion without much peritoneal injection or fibrin deposition. involving the cecum, the retro-peritoneal tissue, the appendix, and the ileocecal glands. The appendix does not appear to be more acutely involved than any of the adjacent tissues. In some of these cases, the appendix and a lymph gland from the ileo-cecal angle were removed. On pathological examination these revealed only acute inflammatory hyperplasia. In one subacute case, where ileocecal resection was performed, a small ulcer was still present in the cecum. The submucosal proliferative reaction was all out of proportion to the size of the ulcerative lesion. Most of these acute cases clear up, probably, either with or without operation. An especially severe case was recently encountered which came to post-mortem examination. The cecum was found greenish-black and gangrenous. There were numerous cecal ulcerations, two of which had gone on to perforation. The appendix was gangrenous. Jennings has recently called attention to this type of case.

In other cases, repeated attacks finally result in the formation of a chronic submucous and subserosal inflammatory infiltration. In these chronic cases, there are no ulcerative, polypoid or papillary changes in the mucosa; the glands are firm; the cecal wall thickened and indurated, and there are few adhesions present.

The symptom usually complained of is recurrent attacks of pain in the right lower quadrant without any history of blood in the stool, diarrhea or constipation. At times, the chief complaint is that of a mass. Radiologically, filling defects or irregularities in the cecum are present. The general condition is usually good, operation being mainly undertaken because of the presence of a mass. At operation, differentiation from tuberculosis may be difficult and most of the cases subjected to resection have been operated because of their similarity to that condition.

19. Peri-typhlitis. A case of so-called appendicitis fibro-plastica chronic productive peri-appendiceal inflammation leading to the formation of a large mass

L. K., age 18, was admitted to the Mount Sinai Hospital in October, 1929. For 2 1/2 months he had been suffering recurrent attacks of pain in the lower abdomen. Two days before admission, an especially severe attack had begun in the lower abdomen and had finally localized to the right side. There was nausea, but no vomiting. Examination showed tenderness and rigidity in the right lower quadrant. Preoperative diagnosis was acute appendicitis.

At operation the entire ileo-cecal region was found to be involved in a moderate sized, hard, stony mass which infiltrated the cecal wall. The ileo-cecal angle contained numerous glands of the same stony hardness. The appendix could not be visualized and seemed to be part of the large conglomerate mass. After considerable debate, an ileo-colic resection was performed.

Pathological examination. — Specimen consists of terminal ileum, cecum and part of the ascending colon. There is no intrinsic lesion of the mucosa of any of the resected bowel. In the ileo-cecal angle, surrounding the appendix and involving the terminal mesentery, is a chronic inflammatory mass of tissue including a large number of hyperplastic lymph nodes. The appendix, 7 cm. in length, appears to be chronically inflamed and stenosed, particularly in its distal two-thirds.

Microscopic examination showed a marked fibrosis of the appendix involving all the coats with a marked lymphocytic infiltration. The cecum simply showed chronic peri-typhlitis.

Diagnosis. — Chronic appendicitis and peri-typhlitis.

20. Case of chronic productive typhlitis resembling tuberculosis

A. B., age 35, admitted to Mount Sinai Hospital in March, 1930. One year ago patient had a severe attack of pain in the right lower quadrant which persisted for two weeks. She had no generalized abdominal pain at that time, no vomiting. She believes she had fever. Five days before admission she again developed pain in the right lower quadrant with rather marked severity, much more so than the occasional dull pain which she had been experiencing in the interval. She had no diarrhea or blood in the stool. There had been no increasing constipation or loss of weight. Physical examination revealed a mass, the size of an orange, in the right lower quadrant, rather firm, slightly irregular. The preoperative diagnosis was appendix abscess.

Exploring revealed a mass occupying the ileo-cecal region covered by thickened omentum. When the omentum was separated the appendix was found lying free and did not appear acutely inflamed. There was a marked infiltration of the ileo-cecal angle and cecum. It was thought that the lesion might be a hypertrophic tuberculosis and an ileo-cecal resection was performed.

Pathological description. — Specimen consists of terminal ileum, cecum and ascending colon. The region of the entrance of the ileum into the cecum appears firm, nodular and edematous. Upon opening the specimen the mucosa of the resected bowel appears grossly normal except for some edema of the ileo-cecal valve and the caput-coli. The mesentery

of the ileocecal junction appears firm, and infiltrated and on section seems to contain some succulent lymph nodes, surrounded by firm, hard, inflammatory tissue. The appendix was not adherent and appears moderately thickened. An inflammatory mass extends from the mesentery of the ileo-cecal junction and appears to involve the wall of the cecum. It is firm and irregular. On section of this area, the cecum appears to be markedly thickened, shows edema and infiltration of all the coats, especially the submucosa. Microscopic examination shows diffuse infiltration of the submucosa with round cells and with considerable edema. There is a moderate amount of fibrosis. There is a considerable thickening and edema of the serous coat as well as the mesentery. The appendix shows signs of chronic inflammation, fibrosis, but little inflammatory infiltration.

Diagnosis. — Chronic typhlitis, peri-typhlitis, chronic appendicitis.

21. Subacute, ulcerative and phlegmonous typhlitis

D. W., age 31. Was admitted to the Mount Sinai Hospital in March, 1930. He had been ill for two days with peri-umbilical pain and nausea. He had had two similar previous attacks, which were supposed to be due to appendicitis. Previous history was negative except for respiratory symptoms coming on during the winter. Examination showed slight tenderness and rigidity in the right lower quadrant; temperature was 101, and leucocyte count was 12,000 with 80 per cent polys. At times it was thought that a mass could be palpated in the right lower quadrant, but this could not be established with certainty. X-ray of the chest showed a chronic pulmonary phthisis.

At operation, which was undertaken with the preoperative diagnosis of appendicitis, the appendix was found to be normal, but there was a tumor in the cecum about the size of a pigeon's egg. An ileo-colic resection was performed.

Pathological examination. — Specimen consists of cecum, appendix 12 cm. of ileum, and a few cm. of the ascending colon. The ileum shows no gross lesion. The appendix shows some external signs of inflammation in the distal third. In the cecum, near the base of the appendix, but not involving it, there is an extensive ulcerative, necrotizing inflammation over an area about 3 cm. in diameter, with a gangrenous membrane about 2 cm. in diameter, and minute ulcerated areas covered with a yellowish sloughing base. The wall of the cecum is much thickened, the serosa inflamed. Regional lymph nodes are enlarged. Aside from this area, the cecum appears normal as does the ascending colon.

Microscopic examination. — The ulcerated area shows necrosis of mucous membranes with a diffuse purulent infiltration consisting of lymphocytes and polymorphonuclears through all the coats of the gut. There is considerable edema, small areas of hemorrhage extravasation. The ileum and ascending colon are normal. The appendix shows some slight increase in the submucosa, some injection of the serosa, but no signs of intrinsic inflammatory changes.

Diagnosis. — Ulcerative and phlegmonous inflammation of the cecum.

Summary

1. A study is reported, fifty-two cases exclusive of sigmoid diverticulitis manifesting themselves as tumors or strictures of the bowel.

2. Clinically, radiologically, and at operation these were usually regarded as malignancy or localized hypertrophic tuberculosis.

3. Microscopic examination of these resected specimens showed various stages and degrees of acute and chronic inflammation with the production of large quantities of fibroblastic and fibrous tissue.

4. No exact pathological or etiological classification is attempted. For clinical purposes they are divided into six groups, some of which are overlapping. 1. Peri-colonic or peri-intestinal granulomata due to sealed-off perforation. 2. Intestinal stenosis due to known vascular lesions of the bowel. 3. Localized hypertrophic ulcerative ileitis. 4. Localized hypertrophic colitis. 5. Local penetrating ulcers of the colon. 6. Granulomata secondary to inflammation of appendages, or diverticula of the bowel.

5. The various groups are discussed and illustrative cases briefly reported.

6. Localized hypertrophic tuberculosis of the bowel in patients without evidence of pulmonary tuberculosis, is less common at the Mount Sinai Hospital than the non-specific variety.

The authors are greatly indebted to Dr. A. A. Berg for so generously placing his extensive material at their disposal. To Dr. Paul Klemperer they wish to express their appreciation and thanks for his patience and kindness in aiding them in the study of the pathological phases embodied in this communication. To Drs. Harold Neuhof, Edwin Beer and Richard Lewisohn, Dr. I. C. Rubin and Dr. Maurice Rashbaum they are indebted for the use of individual cases.

Discussion

Dr. George Morris Piersol: I can think of no one more fit to discuss the subject of Intestinal Tuberculosis than Dr. Lawrason Brown, who has had a tremendous experience with this condition. He was speaking, of course, of secondary intestinal tuberculosis. The importance of this subject to the clinician must be obvious when one considers, as Dr. Brown has already remarked, that it is the most common complication of pulmonary tuberculosis. Autopsies indicate, I believe, that over 50 per cent of cases of pulmonary tuberculosis exhibit some evidence of intestinal tuberculosis.

In the past the great difficulty has been that the diagnosis of intestinal tuberculosis was never arrived at sufficiently early to make it possible really to do anything for the condition. The reason for this was that the diagnostic methods available were inadequate and clinicians acquired the habit of looking for what were regarded as the classical signs of this condition which in reality were terminal or late manifestations. Such symptoms as pain or localized signs in the abdomen, and the appearance of blood and pus in the stools were looked upon as the criteria necessary to make the diagnoses of intestinal tuberculosis. Dr. Brown and his associates when they recognized the x-ray manifestations of intestinal tuberculosis made a noteworthy advance in the early diagnosis of this condition. Since this method of diagnosis has been generally adopted many cases have been recognized sufficiently early to do something for them. We must all acknowledge the debt which we owe to Dr. Brown and his associates for having pointed out this important aspect of the subject.

Frequently the finding of tubercle bacilli in the stools has been looked upon as evidence of intestinal tuberculosis. In this connection it is important to remember that many times tuberculous individuals swallow their sputum so that the tubercle bacilli are found in the stools without intestinal tuberculosis being present. Therefore, the mere finding of the bacillus in the stool is not enough to make the diagnosis.

The cases Dr. Brown discussed were chiefly the usual ulcerative variety. He did not touch upon some of the sequelae which result in these cases. In the last paper, reference was made to certain sequelae found in some of the cases in whom proliferative changes occur in and around the bowel. They present great difficulty in diagnosis and are often mistaken for neoplasms and require surgical intervention. The type of case Dr. Brown discussed is, of course, not surgical. They only become so when, as the result of tuberculous ulcerations, stenoses develop and symptoms of varying degree of intestinal obstruction supervene. That, of course, is another aspect of intestinal tuberculosis that has to be borne in mind and which calls for a different type of therapy. I should like to ask Dr. Brown in conclusion how often they found tuberculous peritonitis in their cases of intestinal tuberculosis.

Dr. Franklin W. White: I am sure the members of this Association realize the great service which Dr. Brown and his co-workers have given in studying this disease and in practically creating this diagnosis. If we look back a dozen years ago when his papers were first published, we find a condition which was very different from today. We find the best clinicians considering the early diagnosis of intestinal tuberculosis as practically impossible, and the evidence of later disease very uncertain. Now Dr. Brown comes here and shows us the figures of his positive diagnoses of 98 per cent accuracy in cases which have been checked up by autopsy and operation. Certainly something has happened in these twelve years, largely due to the work of Dr. Brown and his associates.

He has shown us the great frequency of intestinal tuberculosis in pulmonary cases with indigestion and abdominal symptoms and also the great rarity of intestinal tuberculosis in patients who have no tuberculosis elsewhere. How has this change in diagnosis come about? Not so much, it seems to me, by clinical study. We know that the early symptoms are much like the symptoms of pulmonary tuberculosis, slight, vague and indistinct at first. In our physical examination we do not find much in the abdomen in the early cases. We do not get much that is really helpful from the stools as far as my experience goes. Of course the proctoscope doesn't help us much because it doesn't get up high enough to see the things we are searching for. It seems to me the roentgen-ray has been our mainstay in bringing about this great change to better diagnosis. First, by finding the changes in function which come in the earlier stages of the disease, the spasm, the hypermotility, the vacant irritable areas in the bowels, and later in the more advanced cases by finding the actual deformity of the local lesion itself.

The question of whether to give a barium meal or a barium enema is not an important one, they both have their uses. I have been struck several times with the value of the double contrast enema by giving the ordinary barium enema and after letting the barium run out, inflating the bowel with air, thus bringing out the projection of masses in the wall into the lumen of the bowel. This brings them out much more clearly than the simple enema and takes only ten minutes more to do. Inflate the bowel under the fluoroscope and take an additional film and you have a picture which may show a great deal.

Of course Dr. Brown has not claimed that the x-ray picture was diagnostic in itself, but the presence of irritation and ulceration and the fact that it occurred in certain parts of the bowel, and that it also appeared in patients who had pulmonary tuberculosis makes a very strong combination which leads us to our diagnosis. Dr. Brown has emphasized the importance of finding constant defects, not merely in one examination which might be so misleading in the bowel, but on repeated examination. I was also struck with the changes which he was able to demonstrate by following the same patients over a period of time so that the progress of healing might be studied and followed very much as we do in gastric ulcer.

Dr. H. Bockus: Mr. President and Members of the Society: This paper of Dr. Ginzburg and Dr. Crohn is of decided interest, not because these lesions that they are describing are at all common, but because of their rarity I think we are very apt to overlook them. As far as I know, this series of cases which they are reporting is the largest group of cases of this sort in the literature, although I ran across an article by H. E. Mock in *Surgery, Gynecology and Obstetrics*, written last year who reported a series of cases almost approximating that of Dr. Ginzburg and Dr. Crohn. They mentioned the same etiological factors which were discussed by the essayist here this morning. One of the particular things discussed in the paper mentioned is the fact that many of these cases of so-called inoperable carcinoma reported to have recovered are probably cases of non-specific granulomata. He stressed particularly the necessity for taking biopsy material even in the cases in which inoperable carcinoma seems to be present. I naturally have had very little experience with this condition and consequently, can't add anything particularly to the discussion from the practical standpoint, but there are several questions that I should like to ask.

I happen to have seen a patient within the past two weeks who possibly has a non-specific granuloma, but who certainly has a peri-sigmoiditis, with blood in the stools which followed almost immediately after deep x-ray and radiation therapy for carcinoma of the cervix. There is at present no indication of carcinoma in the pelvis. I am wondering whether in any of these cases Dr. Ginzburg or Dr. Crohn have noted the development of a granuloma following deep radiation or x-ray therapy.

Dr. Ginzburg mentioned the fact that amebic disease can cause this condition and very recently three cases of this sort were reported following a persistent isolated amebic ulcer and in all three of these cases it was only in the resected material in which the ameba could be found. So it is quite possible an amebiasis may account for some cases of non-specific infective granulomata. My experience comprises only two proven cases and interestingly enough, both of these cases occurred in luetic individuals. I don't mean to infer that these people had syphilomata; one was a case of old duodenal ulcer in which the gall bladder, pancreas and stomach were all bound up in a granulomatous mass which was not carcinomatous; the other case, a solitary ulcer of the ascending colon near the hepatic flexure, with a granulomatous mass associated with it.

I should like to say a word about the terminal ileitis, which I have never seen in my own practice. I went up to see the cases at Mount Sinai with Dr. Crohn and I have been thinking a good deal about it since that time. I don't know very much about anatomy, not being a surgeon, so I went out to Dr. Batson, professor of anatomy at the Graduate School, and saw some of his very excellent so-called extra-peritoneal dissections. He dis-

sects the peritoneum away from the fascia so he can throw all the peritoneal contents encapsulated within the peritoneum to one side and inspect the blood supply. He pointed out to me the fact that the ileo-colic artery, ascending branch, which supplies the cecum is more or less fixed in most specimens, but the terminal branch of the same artery which supplies the lower 6 to 12 inches of ileum is capable of a good deal of rotation. We were wondering whether in some individuals with undue ptosis the factor of disturbed circulation might be a contributing factor in the production of terminal ileitis by twisting the artery or by undue stasis in the vein (terminal branch). I should like to ask whether the habitus of these patients that have been described is of the visceroptotic type, the type in which ptosis and stretching of the mesentery is most marked.

Dr. Walter C. Alvarez: In view of the difficulties of early diagnosis of intestinal tuberculosis perhaps the logical thing to do would be to treat every patient with active pulmonary lesions as if he had trouble in the bowel and give him a smooth diet and plenty of vitamins from the start. Some of my friends who specialize in tuberculosis tell me that that is what they are doing, and that they are pleased with the results.

Some writers have stated that the physician can suspect the development of intestinal tuberculosis when the patient who was formerly optimistic becomes anxious and pessimistic. It is generally assumed that disease in the lungs does not produce the reactions on the brain that are produced by disease in the bowel. I haven't enough experience with these patients to say, whether or not this is true but I know any disturbance in the bowel that is associated with nausea is extremely disheartening.

There are good reasons for giving a smooth diet to these patients. If, in a dog, one takes a section of gut, reverses it end for end, and restores the lumen of the bowel with two anastomoses, the bowel looks exactly the way it looked before, with just as good a lumen. The difference is that the reversed loop will pass fluids but not solids. The dogs must be kept on a cellulose-free diet; otherwise they soon die of intestinal obstruction due to the accumulation of a mass of indigestible material immediately above the orad suture line. It is evident that before one can get solids through the digestive tract, one must have a normal downward gradient of forces. An irritant lesion of the bowel tends to reverse the gradient and this makes it hard for indigestible residues to go through.

The lesions that have been described by Dr. Crohn and Dr. Ginzburg interest me. I think I must have seen instances of this disease in the past; granulomas which I thought might be tuberculous but in which I could not find the characteristic histological structure. Unfortunately for the progress of our knowledge in some of these cases, the surgeon does a short-circuiting operation and the patient disappears. One must be careful not to tell these people that they have carcinoma. A prominent surgeon claims the credit for building a beautiful Christian Science Church. In a wealthy woman he found what he thought was an inoperable cancer of the bowel; he short-circuited it and sent her home with a hopeless prognosis. Later, when he had seen more of these lesions he understood why his patient didn't die.

I have long felt that there must be such a thing as terminal ileitis. I think it is a fairly common disease and some day I would like to disappear into a pathological "lab" to hunt for it myself. Ileitis would account for many of the cases of appendicitis in which the patient doesn't get well after one or more operations.

There is a reason why we should expect trouble in the terminal loop of ileum and this is because it is the one place in the bowel in which the gradient appears to be reversed. This, I think, accounts for the fact that all big gall stones that slough through into the bowel stop some 9 or 10 inches orad to the ileocecal sphincter. To explain it, authorities state that this is the narrowest part of the gut. This may or may not be true. For years I have been trying to plan an experiment which would show whether the gall stone stops where it does because this is the narrowest place or because it represents the place where the gradient is reversed. Finally a woman very obligingly performed the experiment that I wanted. She ate bran until she had to be operated on for the removal of a mass of it impacted right at the danger spot. The case was reported recently in the *Journal of the American Medical Association* (Davis, M. B., 97:24-25, July, 1931). This experiment indicates to me that it is not a narrowing of the gut but a reversal of the gradient that causes the trouble. We can see now why fish bones or any other indigestible remainders will tend to stagnate in this region.

Dr. Harlow Brooks: Mr. Chairman and Members of the Society: I think the work which Dr. Gray has done is a very hopeful harbinger for the future. If the gastro-enterologists particularly will pay some more attention to the problems that we internists have and help us more effectively in the study of general disease it will add greatly to our mutual benefit. Then I have been very much interested in the work he has done because for eight years I was pathologist to a large tubercular service which comprised nearly 50 per cent of active cases of tuberculosis. I never saw a tubercular ulcer of the stomach although we found, even by our crude methods of that day, tubercle bacilli present in the mucus of the stomach swallowed from the sputum of the infected lung. The walls of the stomach have no immunity against tubercular infection. I know that because in subacute or even in active miliary tuberculosis the process starts in the peritoneal coat and through to the mucosa in quite frequent instances. All of you may confirm that by simply doing autopsies in miliary tuberculosis, particularly in the subacute type. On the other hand, in a very large number of active cases of tuberculosis which I saw in my medical youth, I never saw a tubercular ulcer originating from the mucosa of the stomach. I saw two instances which I thought might be of this nature, but when we examined these two ulcers histologically they were prepyloric ulcers and of the typical peptic ulcer type. We carefully examined the edges of these ulcers and I fully expected to be able to demonstrate the formation of tubercles, but that we were unable to do. In other words, there is no immunity against peptic ulcer in tuberculosis cases, but when a peptic ulcer occurs it does not, I think I may say with some assurance, become infected with tuberculosis when this ulcer is located this side of the pylorus. I think that this possibly has some bearing on the mucin or the protection which it affords to eroded surfaces of the mucous membrane.

Dr. Julius Friedenwald: Dr. Gray has presented a very important and interesting paper. Last year Dr. Morrison and I completed a study of the secondary gastric disturbances occurring in pulmonary tuberculosis which we, presented at the section on gastro-enterology of the Southern Medical Association. In the report we selected 100 cases of pulmonary tuberculosis of which fifty presented the initial and fifty the terminal types of dyspepsia. In the initial type the ages of the patients ranged from twenty to seventy years. Of these 76 per cent were females and 24 per cent males. In the instances of initial dyspepsia the gastric contents revealed hyperacidity in 42 per cent, normal acidity in 44 per cent and subacidity in 8 per cent and achylia in 8 per cent. The motor function of the stomach was normal in the early stages but became reduced with the progress of the affection. In the terminal dyspepsia the ages of the patients ranged from twenty-three to fifty-eight years, of which 82 per cent were female and 38 per cent male. In these cases the digestive disturbances were severe in 72 per cent, moderate in 24 per cent and mild in 4 per cent. According to our experience, as the mucous membrane becomes involved in an extensive secondary chronic gastritis the secretion of free hydrochloric acid is rapidly diminished and a true achylia is finally produced, and at the same time the motor function of the stomach becomes impaired. The gastric content at this stage reveals an absence of free hydrochloric acid and the presence of a considerable amount of mucus much in the form of swallowed clumps. In our series of cases of advanced pulmonary tuberculosis the gastric contents presented a normal acidity in 10 per cent, hyperacidity in 6 per cent, diminished acidity in 30 per cent and achylia in 54 per cent. There was, therefore, present in these cases a combined hypochlorhydria and achylia in 84 per cent. The stomach in the stage of terminal dyspepsia, therefore, ordinarily presents a high grade of motor and secretory insufficiency. These changes may occur due to the production of toxins as well as from the developing chronic gastritis. As a result there is a delayed gastric evacuation or atony. The acidity is usually reduced as well as the pepsin concentration, but the latter does not run parallel with the reduction of acidity. On the other hand, Rehfuss has pointed to the importance of visceral focal infections in resistant cases of pulmonary tuberculosis. He has been able to demonstrate in some instances infection of the bile of the gastric mucous membrane as well as of the intestinal tract with various organisms which he considers potent in causing a lessened pulmonary resistance. The secondary gastric disturbances due to pulmonary tuberculosis are, therefore, of unusual interest. This is due largely to the fact that in this disease, especially in its incipiency, the primary symptoms are frequently entirely gastric in character and consequently often overshadow the pulmonary signs. In the advanced forms, on the other hand, we are dealing with more or less severe types of chronic gastritis with marked secretory and motor changes which at this stage may result in symptoms so intense as to cause serious complications or may even overshadow those due to the primary affection.

Dr. Gray's paper is of great interest and his findings regarding the frequent presence of tubercle bacilli in the gastric contents, in the presence of lowered gastric acidity, is a valuable contribution.

Dr. Lawrason I. Brown (closing): Mr. President, tuberculous peritonitis is rare as a complication of pulmonary tuberculosis. We think that in some instances where there is a great deal of pain associated with intestinal tuberculosis that the cause of the pain may be due possibly to a localized peritonitis over the base of the ulcer. It is interesting to recall to Dr. Alvarez that when intestinal tuberculosis is most rare, pessimism is most common, i.e., in the early cases in the minimal cases. They very often start out by being exceedingly pessimistic and as the disease advances and hope is lost more and more and intestinal tuberculosis becomes more and more frequent, they become more and more optimistic.

Dr. Irving Gray (closing): We have reported this morning our findings of the studies that have been carried out for the past year.

The gastric chemistry apparently is not influenced by pulmonary tuberculosis except that there appears to be a decrease in gastric secretory power in the female group.

The intestinal complications of chronic pulmonary tuberculosis occur in many patients. There is certainly a fertile field for study relative to the prevention and treatment of tuberculous lesions of the small bowel. Undoubtedly, most of the cases of tuberculosis of the small intestine are secondary to pulmonary tuberculosis. The primary complex of tuberculosis may occasionally be found in the small bowel as pointed out by Walter Koch, of Berlin. On autopsy of the soldiers who came from South Africa, he (Koch) found after careful survey, there was no evidence of pulmonary tuberculosis in the lungs and that the primary complex with an active tuberculosis was present in the small bowel.

In the temperate zone one rarely meets with a case of intestinal tuberculosis in whom pulmonary tuberculosis is not present.

I know of a physician's wife who developed intestinal symptoms chiefly, diarrhea, with a fever between 101 and 102 degrees daily in the late afternoon. Tubercle bacilli were found in the stool and on animal inoculation, tuberculosis was established.

Studies are now being made to differentiate between the human and bovine type. Active intestinal tuberculosis will occasionally occur in humans who have no active pulmonary tuberculosis. The diagnosis depends entirely upon the findings of tubercle bacilli in the stool.

Dr. Burrill B. Crohn (closing): Dr. Ginzburg, Dr. Oppenheimer and I have been studying benign granulomata of the intestinal tract from the surgical and pathological standpoint for some time. I wish particularly to emphasize the condition which we have named terminal ileitis because that is a clinical condition to which my interest has been, for some time, directed.

Terminal ileitis presents a very definite clear-cut clinical entity. The patient presents himself apparently with symptoms of colitis. For several weeks, months, or sometimes for one or two years, one observes the complaint of diarrhea, the passage of some blood and mucus, a low grade temperature, a mild anemia. In each instance the primary diagnosis had been one of colitis. To my surprise the proctoscopic examination was regularly negative. A form of ulcerative colitis localized to the right colon or cecum suggested itself. Not only have we had experience with this localized form, but Bargen of the Mayo Clinic has described these localized areas of colitis where the transverse colon or ascending colon or splenic flexure are affected without involvement of the sigmoid or rectum. But the barium enema was again negative and we were forced to assume the existence of some lesion in the small intestinal tract to explain the condition.

In this manner we encountered a series of fourteen cases in which there existed a lesion which we did not recognize from the literature, a lesion involving eight, ten or twelve inches of the terminal ileum; a condition characterized anatomically and pathologically by tremendous thickening of the ileum, necrotizing ulcerating lesions of the mucous membrane, and the progress of this hyperplastic inflammatory condition to a stage of stenosis where the obstruction presents itself as a clinical manifestation. Sometimes the stenosing character of the lesion is apparently the first manifestation, and these cases present originally a high intestinal obstruction of a benign character. Another outstanding characteristic of this condition which we term "terminal ileitis" is the tendency to form fistulae. Persistent abdominal fistulae are common in the experience of surgeons; medical men are not commonly called upon to analyze the for-

mation and rationale of such persistent fistulae. Those who work in large general hospitals will find that the internists are occasionally called to the surgical side to explain why a fistula persists after an appendix operation. Terminal ileitis has similarly a great tendency to form fistulae, which tracts run usually from the terminal ileum to the cecum, sometimes to the ascending colon, very frequently to the sigmoid, sometimes through the mesentery, and sometimes to the floor of the pelvis. Sooner or later a mass appears, usually at the right side of the lower abdomen and coincident with this mass the stenotic manifestations occur. Practically all of our cases have been operated upon by Dr. A. A. Berg; the cases are today all well except one, who died at the time of operation. The other fourteen cases are well; not only are well, but they remain perfectly well after the primary lesion has been removed or sidetracked.

We have been unable to find any etiological factor which can be proved to account for this disease. We took pains to eliminate tuberculosis, syphilis, and every other recognizable agency.

One may mistakenly think that we are demonstrating a very rare lesion. Now that we are aware of the clinical condition, we are seeing at Mount Sinai at least three, four or five cases a year. We had one case two months ago, and I have now a case which will be operated upon on our return. At a session of the New York Surgical Society about four weeks ago, one of the members of that association presented a case of granuloma of the terminal ileum; to my surprise he was showing this same condition. The chairman asked for general discussion; six surgeons of large experience with abdominal conditions discussed the subject. Several men recounted having seen a case six years ago or twelve years ago, upon which he had operated with good result. These were surgeons with wide experience; several of those surgeons in the course of a lifetime had seen such lesions, but had apparently not been able to recognize or identify the underlying pathological process.

(*Slide.*) Anatomically the terminal ileum is involved for 8, 10, or 12 inches. Dr. Ginzburg mentioned 24 inches because we have such an occasional case. The terminal part of the lesion ends abruptly at this point (indicating). The depth and greatest intensity of the lesion is along the line where the mesentery is attached to the small bowel. The thickening of the wall can be seen here, the tremendous thickening of the ileum, three, four, or five times the usual thickening.

(*Slide.*) This is another specimen of the lesion, first, the normal ileum, then the beginning diseased process and the terminal part of the ileum with its maximum involvement. The stilet shows one fistula formation, here another formation. The fistula burrowed through the mesentery and made an exit at the ascending colon. In one instance while doing a sigmoidoscopy, I saw a nipple-like projection on the mucosa of the sigmoid. I was actually seeing the end of a fistula which had burrowed from the terminal ileum into the sigmoid.

(*Slide.*) This is a photograph of one of the specimens exhibited; one notes the very abrupt ending of the lesion at the ileocecal valve with the tremendous thickening at the wall of the ileum, causing what will eventually be an obstruction.

The barium enema shows a narrowing of the proximal part of the transverse colon at this point; a tentative diagnosis of a carcinoma of the transverse colon was made. However, this was a case in which a fistula had burrowed through and into the transverse colon, simulating a malignant lesion. The case was operated upon as a supposed malignancy and the benign condition was discovered at this point.

(*Slide.*) This is the last slide, demonstrating barium meal by mouth, showing the strand-like terminal ileum. At this point one sees a small fistulous tract going up to the splenic flexure.

Dr. Ginzburg (closing): I just wish to answer a few of the questions, first Dr. Bockus' question about the sigmoiditis following deep x-ray therapy. We have had no such personal experiences, but cases of that type have been reported in the literature. We know that deep x-ray therapy is very apt to cause sclerosis of the smaller vessels and I imagine the changes taking place in the sigmoid were secondary to vascular changes. Such ulcers have also been reported following deep therapy in the bladder.

As far as amebic granuloma is concerned, this report is based mainly on resected specimens and in none of them were ameba found either on section or by searching the stool. We did have a case of amebic granuloma which we thought was carcinoma of the recto-sigmoid. The removal of a specimen revealed its real nature.

As far as lues is concerned, I do not recollect any of our patients that had a positive Wassermann. I don't believe it has anything to do with the condition.

The point that Dr. Bockus brought out about the blood supply and the tendency to twist of the terminal ileum, had also entered our minds. In relation to the question of vascular changes to chronic granulomata, we said that repeated partial volvulous or intussusception may have something to do with these granulomata in the ileo-cecal region. Most of the cases as I remember them were of the slender visceroptotic type. However, we had a few patients quite the opposite, definitely stenic types.

On the question of appendicitis and terminal ileitis: At least half of the cases that finally came to operation had had their appendix removed at some earlier time. In some of those cases it was noted even at the first operation that there was something wrong with the terminal ileum. The surgeons had apparently thought, however, as they weren't quite sure what the nature of the lesion was, that they had better adopt a conservative course.

As far as tuberculosis is concerned, we have injected triturated material from the bowel wall into rabbits, guinea pigs and chickens in eight or ten instances and we have never been able to achieve any definite result. We have never been able to demonstrate tubercle bacilli in sections; never been able to demonstrate coagulation necrosis, never been able to demonstrate typical tubercles.

We have only two cases showing a definite x-ray finding with barium meal which Dr. Crohn showed. This is due mainly to the fact that a great many of these cases come in with signs of subacute obstruction and naturally one is rather loath to give them barium by mouth for fear of completing the incomplete obstruction.

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Landmark Article

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Regional Ileitis:

A Pathologic and Clinical Entity

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We propose to describe, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction of the remaining walls of the involved intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas.

The disease is clinically featured by symptoms that resemble those of ulcerative colitis, namely, fever, diarrhea and emaciation, leading eventually to an obstruction of the small intestine; the constant occurrence of a mass in the right iliac fossa usually requires surgical intervention (resection). The terminal ileum is alone involved. The process begins abruptly at and involves the ileocecal valve in its maximal intensity, tapering off gradually as it ascends the ileum orally for from 8 to 12 inches (20 to 30 cm.). The familiar fistulas lead usually to segments of the colon, forming small tracts communicating with the lumen of the large intestine; occasionally the abdominal wall, anteriorly, is the site of one or more of these fistulous tracts.

The etiology of the process is unknown; it belongs in none of the categories of recognized granulomatous or accepted inflammatory groups. The course is relatively benign, all the patients who survive operation being alive and well.

Such, in essence, is the definition of a disease, the description of which is based on the study, to date, of fourteen cases. These cases have been carefully observed and studied in their clinical course; the pathologic details have resulted from a close inspection of resected specimens from thirteen of fourteen patients operated on by Dr. A. A. Berg.

Relationship of Regional Ileitis to Other Benign Intestinal Processes

There exists in the medical literature a heterogenous group of benign intestinal lesions which have now and then been described under the caption of "benign granulomas." The latter loose term covers a multiplicity of conditions in which both large and small intestines may be involved; it includes all chronic inflammatory lesions of the intestine whose etiology is either unknown or attributable to an unusual physical agent. It represents a hodge-podge or melting-pot in which are thrown all those benign inflammatory intestinal tumors which are neither neoplastic nor due to a specific bacterial agent. Within this group one finds descriptions of foreign body tumors, chronic perforating lesions with gross inflammatory reactions, traumas of the mesentery with intestinal reactions, Hodgkin's granuloma, a late productive reaction to released strangulated hernias of the intestinal wall and numerous other and similar conditions. The so-called benign granulomas all present a tumor-like inflammatory mass which usually simulates carcinoma but which eventually unmasks itself as probably an infectious process of unknown causation. The multiplicity of the possible sites of gastric, intestinal or colonic involvement and the accompanying protean clinical manifestations defeat any effort to include them all in a clear cut clinical entity. The very confusion defies classification.

In this literature, however, there have appeared on occasions references and descriptions that approach the picture that we are about to describe. The entire literature of benign granulomas was reviewed in 1920 by Tietze (1), who not only described his own cases but covered all previous medical publications. There is nowhere in his encyclopedic article a description which resembles that of regional ileitis. In 1923, Moschcowitz and Wilensky (2), in describing four cases of benign intestinal granuloma, detailed one case of a disease involving the terminal ileum which closely resembled that in our cases. They grouped it with various other and similar colonic masses as granuloma. Mock (3) in 1931 again described granuloma, but included no example that resembled the cases we have studied.

Just as the generic term of typhus originally included various diseases, from which group eventually typhoid fever, Brill's disease, Rocky Mountain fever, tabardillo and others were split off, so, similarly, do we aim to disintegrate from the general group of varied diseases spoken of as a "benign granuloma" a specific clinical entity with constant and well defined characteristics, which we propose to name "regional ileitis."

Pathologic Anatomy of the Disease

All the specimens obtained by resection were in patients who had been ill for at least a year. We therefore have no specimen exhibiting the very early phases of the disease. The latter are sometimes encountered at the operating table following an illness of from one to two weeks and diagnosed, as a rule, as acute appendicitis. At this time the terminal ileum is found thickened, soggy and edematous; the serosa is a blotchy

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red. The mesentery of the terminal ileum is greatly thickened and contains numerous hyperplastic glands. Owing to the possibility of spontaneous resolution, resection has never been performed at this stage, so that we have no knowledge of the intra-intestinal changes present at this time.

The inflammatory process is not, however, a static one, nor is the entire diseased segment affected at one time. The oldest lesions begin apparently at, or just oral to, the ileocecal valve, and the more recent ones are situated proximally. In some of our relatively early cases, we have found isolated lesions separated from the main hypertrophic mass by normal mucosa. These isolated areas are, in our opinion, the earlier and primary lesions of the disease; they consist of oval mucosal ulcerations, about 1 cm. in diameter, located on the mesenteric border of the small bowel and lying in the long axis of the intestine, where a sort of groove is naturally formed by the attachment of the mesentery.

The characteristic, fully developed hypertrophic process is, as a rule, limited to the distal 25 to 35 cm. (10 to 14 inches) of the terminal ileum, including the ileal side of Bauhin's valve and terminating rather abruptly at that point. The most advanced pathologic changes are present at the valve, which in some instances becomes converted into a rigid diaphragm with a small irregular opening. Proximally the severity of the process gradually abates, shading off into normal mucosa. The normal intestinal folds are distorted and broken up by the destructive ulcerative process and rounded and blunted by edema, giving a bullous structure to the mucosal aspect of the intestine, or frequently a cobblestone appearance of the surface of the mucosa may result. A series of small linear ulcerations lying in a groove on the mesenteric side of the bowel is almost always present. Whether these are the remnants of the original ulcerative lesions or whether they are mechanical erosions due to the formation of a *darmstrasse* by the shortening of the fibrotic mesentery, it is impossible to say.

The submucosal and, to a much lesser extent, the muscular layers of the bowel are the seat of marked inflammatory hyperplastic and exudative changes. As a result of these, the wall of the bowel becomes enormously thickened, frequently reaching two or three times its normal density. The lumen of the bowel is greatly encroached on, becomes irregularly distorted and, at times, is only large enough to admit a medium-sized probe. The intestine proximal to the involved segment frequently, but not invariably, becomes greatly dilated and may show superficial irregularly placed tension ulcers. When seen at the operating table, the involved loop is a soggy hoselike mass.

In the older phases of the disease, the exudative unusual reaction is replaced by a fibrostenotic process, and the mucosa appears atrophic with occasional superficial erosions and islands of papillary or polypoid hyperplasia. The serosa loses its gloss and frequently exhibits tubercle-like structures on its surface. The mesentery of the affected segment is greatly thickened and fibrotic, as is the subserosal intestinal fat.

A marked feature is the tendency toward perforation. Free perforation into the peritoneal cavity has not been encountered in this series. The chronic perforation apparently occurs slowly enough to permit of walling off by adhesions to a neighboring viscus, to the parietal peritoneum or to the omentum. There is a marked tendency to the formation of internal fistulas, the sigmoid having been the seat of fistulous involvement four times and the ascending colon and cecum once each. The walled-off abscesses resulting from slow perforation into the peritoneal cavity are, as a rule, considered appendicular in origin. When drained, they give rise to chronic intractable fecal fistulas which defy attempts at simple closure because of the persistence of the underlying inflammatory disease in the bowel. Indirect perforation of the cecum may result from perforation of the ileum into the terminal mesentery with secondary cecal termination of the fistulous tract. Pericecal fibrotic and inflammatory changes which result from the proximity of the ileal focus to the cecum are probably responsible for the roentgenologic changes in the contour of the ascending colon and cecum, such as may be easily confounded with the defect of hyperplastic tuberculosis.

Microscopically, no specific features can be demonstrated. The stained histologic sections showed various degrees of acute, subacute and chronic inflammation, with variations in the predominance of polymorphonuclear, round cell, plasma cell and fibroblastic elements. In the early stages the lesion is a diffuse one, involving mainly the mucosa and submucosa, with the presence of some inflammatory serosal reaction. The mucous membrane shows areas of marked destruction, and at times the glandular structure is almost completely gone, leaving an atrophic layer of epithelium, the result of a regenerative process. In later stages of the disease, the inflammatory reaction is more focal in character. These focal areas of inflammation in the serosa give the appearance, on gross examination, of tubercles.

In some of the cases, the presence of giant cells is quite striking. Special stains have occasionally demonstrated the presence of large pale cells, or groups of cells, probably vegetable in nature, in the vicinity of the giant cells. They could be demonstrated frequently in all the layers of the intestine. These and the giant cells are probably not an essential feature of the pathologic changes in this condition. They are, more likely, accidental findings due to the inclusion of small particles of vegetable matter which have become entrapped in the ulcers, entered the lymphatics and become encapsulated in the process of healing. The resultant foreign body reaction around these nonabsorbable particles results in the presence of the giant cells. To some extent they may be contributory to the marked hypertrophic scarring which occurs. We believe that the attempts, by some authors, to classify this granulomatous condition as an exudative unusual form of tuberculosis were, to a great extent, predicated on the assumption that the giant cells were, necessarily, evidences of tuberculosis.

It is quite likely that in the past this granulomatous condition was confounded with ileocecal tuberculosis, and so missed as a clinical and pathologic entity. The failure of the pathologic reports in our cases to substantiate a suspicion of tuberculosis led us to exercise still greater caution in eliminating a Koch infection as the etiologic agent. With the assistance of Dr. Paul Klemperer in determining moot points, sections from the various cases were again reviewed. No evidences of tuberculosis, syphilis, actinomycosis, Hodgkin's disease or lymphosarcoma were found. Guinea-pig, rabbit and chicken inoculations of triturated material from mesenteric glands and from the intestinal wall proved negative for tuberculosis in five cases. Löwenstein tubercle cultures were also negative in three instances. It is interesting to note that none of these clinical cases presented any evidence of pulmonary tuberculosis; there were no positive Wassermann reactions in this series.

The relation of appendicitis and previous operations to the development of the disease is of some interest. Half the patients had been subjected to appendectomy before the final resection was performed. In about half of those cases, abnormalities of the terminal ileum were already noted at the time of that operation. In those cases in which there had been no previous appendectomy, the mucosa of the appendix was not involved, as might be expected from the fact that the disease stops on the ileal side of the valve. Inflammation of the outer coats of the appendix, due to the presence of adjacent inflammatory disease, was common.

The Clinical Features

Etiologically, young adults comprise the largest number of patients. Only two of the patients studied were over 40 years, the average incidence being at 32 years of age; the youngest patient was 17, the oldest 52. Males predominate over females in the proportion of nearly 2:1. There are no known predisposing factors.

Cases of regional ileitis run, in general, a fairly constant and typical clinical course. Most of the patients had been ill for from several months to two years before coming under observation. During this time the outstanding complaints were fever, diarrhea, continuous loss of weight and a progressive anemia. The clinical picture resembles that of a nonspecific ulcerative colitis.

Fever is rarely high, long periods of apyrexia being interspersed with shorter and irregular cycles of moderate temperature. Occasionally, though rarely, the temperature rises above 103°F. Some of the cases run the complete course without fever.

Diarrhea is usually an outstanding feature, though the number of movements and the intensity of the actions never approach those of a true colitis. The average patient has from two to four loose or semisolid daily defecations, sometimes with blood and always with mucus. The stools are rarely mushy or liquid and contain free pus, coagulated lumps of mucus and streaks of blood, but tenesmus is always lacking. There are none of the perianal fistulas, condylomas or perirectal abscesses that characterize the complications of true colitis, for in this disease the rectum and colon are never involved. At times, particularly when the stenotic factor predominates, as in the later periods of the course, constipation rather than diarrhea predominates.

Vomiting characterizes the stenotic type of cases, is never marked or persistent and is usually accompanied by abdominal pain and visible peristalsis.

Pain distributed over the lower abdominal parietes is a common feature of the disease. This pain is dull and cramplike and accompanies, or is followed and relieved by, defecation. It is usually localized to the right lower quadrant and is occasionally referred across the abdomen to the whole lower abdominal region. Occasionally, and not infrequently, when the sigmoid, as is not unusual, becomes adherent to the necrotizing hyperplastic ileum, fistula formation occurs between these two hollow viscera. In these cases the pain is mainly localized over the left lower abdominal quadrants; the mass which is then felt abdominally and per rectum may appear to be an integral disease of the rectosigmoid area.

The general symptoms are those of weakness, usually a rapid and progressive loss of weight, and an anemia which ordinarily is moderate, but which may progress to a severe degree. In the milder cases, however, there may be little or no emaciation and no anemia. The stools contain constantly occult blood. Appetite is poor, particularly during the febrile bouts.

A moderate leukocytosis characterizes some of the cases; in most, the white blood count is normal. Even in the stenotic cases the blood plasm findings that accompany marked obstructions of the upper alimentary tract are rarely seen.

Physical Examination

Certain physical findings characterize this disease, the most constant ones being (1) a mass in the right iliac region, (2) evidences of fistula formation, (3) emaciation and anemia, (4) the scar of a previous appendectomy and (5) evidences of intestinal obstruction.

1. A moderate-sized mass is usually felt in the lower right iliac region or in the lower midabdomen. The mass is usually the size of a small orange, tender, firm, irregular and only slightly movable. This mass is composed of the tremendously hyperplastic ileum, the stenotic inflamed ileocecal junction, which may and often does assume a size of from two to five times that of a normal valve of Bauhin, and frequently an adherent section of the colon or sigmoid to which a fistulous tract has been created. When the sigmoid is adherent and involved, the mass may lie more to the left; when the cecum or ascending colon or hepatic flexure constitutes the distal end of the fistulous tract, the mass may lie more to the right and higher in the abdomen. When the fistulous tract burrows into and through the mesentery, the necrotic process may cause a diffuse mesenteric suppuration which participates in the formation of the mass. The tumor is usually palpable per rectum, though felt only very high with the examining finger.

2. Fistula formation is a constant feature of the disease process. The most common site of adherence is the sigmoid; next in frequency is the cecum and the ascending colon and occasionally the hepatic flexure. As the necrotizing process of the mucosa of the ileum progresses through its several coats, the serosa becomes involved. Any hollow viscus, usually the colon, now becomes adherent to the point of threatened perforation. A slowly progressive perforation is thus walled off, but results in a fistulous tract being formed between the two viscera. In one case the uterus formed the limiting organ of a threatened perforation. In another case, on sigmoidoscopic examination, a nipple-like papillomatous projection was seen high in the rectum, or just above the rectosigmoid angle. This observation was noted at the time, but the proper interpretation was overlooked; it was the colonic end of a perforating fistulous tract. In still another case, the anterior abdominal wall presented a fecal fistula, particularly such as persists after a fruitless appendectomy. These fistulas are usually regarded as cecal in point of origin; they are always, however, communications between the necrotic ileum and the anterior abdominal wall.

3. There are evidences of emaciation and anemia.

4. In at least half of the cases the appendix had been removed at some previous operation. This appendectomy usually antedated by several months or years the present symptoms. In many cases the appendix had been removed several months previous, at which time thickening and tumor-like massive inflammation of the small intestine and mesentery had been noted, though nothing beyond the appendectomy had been attempted. It seemed quite evident that in these cases the lower right abdominal symptoms had resulted in the discovery or in the overlooking of the real pathologic process in the terminal ileum. In all such cases the pathologic report cited "acute and chronic inflammatory changes of the appendix," a report which really whitewashed this organ as a participant in the disease process. In fact, we now know that the process never transcends the limit of Bauhin's valve, and that the appendix is always free from guilt and free from changes.

5. In those cases in which the process has progressed to a stenotic stage, the physical findings are those of intestinal obstruction. Loops of distended intestine may be visible through the emaciated abdominal wall, and puddling is frequently observed in the flat x-ray plates. Visible peristalsis is not uncommon and is accompanied by borborygmus and the passage of gas with evident relief. The visible loops of the distended intestine are usually localized to

the lower midabdomen. General distention and ballooning of the whole abdomen are unusual.

Clinical Course of the Disease

There are four various types of clinical course under which most of the cases may be grouped: (1) acute intra-abdominal disease with peritoneal irritation, (2) symptoms of ulcerative enteritis, (3) symptoms of chronic obstruction of the small intestine, and (4) persistent and intractable fistulas in the right lower quadrant following previous drainage for ulcer or abdominal abscess.

1. *Signs of Acute Intra-Abdominal Inflammation.* — It is impossible to distinguish these cases preoperatively from those of acute appendictis. There are generalized colic, pain and tenderness in the right lower quadrant and fever up to 101° or 102°F. The white blood count is elevated. The development of symptoms seems to be somewhat slower than in appendicitis. The presence of a mass even without actual abscess formation is a fairly constant feature. The picture encountered at operation is that of a greatly thickened, red or blotchy terminal ileum, with marked edema of the surrounding tissues and slight exudate of the ileal wall. The mesentery is thickened and edematous, and contains numerous large glands. There is usually clear fluid present in the abdomen. The appendix may appear, and shows evidence of a periappendicitis without mucosal involvement. In some cases an abscess is encountered; in our experience the pus has been thick and grumous, and not as foul smelling as an abscess of appendiceal origin. The future course of these cases cannot be predicted. Some seem to undergo resolution, others to pass into one of the more chronic phases of the disease. Those cases which are drained may develop intractable fistulas.

2. *Symptoms of Ulcerative Enteritis.* — These patients complain of colicky periumbilical or lower abdominal pain. There is a tendency toward looseness of the bowels (from three to five movements a day). The stool is usually liquid or mushy and contains pus, mucus and occult or visible blood. There is no gross melena. A constant fever is present, but the temperature is rarely above 100°F.

With the progress of the disease, a marked secondary anemia may develop, reaching as low as 35 per cent hemoglobin. Considerable loss of weight and strength may occur. In some instances disturbances of general nutrition are slight. This course may continue for as long as a year until exhaustion sets in, or more commonly the cases pass gradually into the stenotic phase of the disease.

3. *Stenotic Phase.* — This is the type most commonly encountered. The symptoms in this stage are those of a subacute or small intestinal obstruction of varying severity. The obstruction, as in most obturating lesions of the small bowel, is not complete. Violent cramps, borborygmus, occasional attacks of vomiting and constipation are present. Visible peristalsis and intestinal erection are common. A palpable mass is practically always present in the lower right quadrant. In this phase of the disease fistulous communications with the colon or sigmoid may lead to the signs and symptoms of colitis, and mask the true nature of the disease. Occasionally the stenotic phase occurs as a primary manifestation of the disease; again, the symptoms may have been present for years (four years in one of our cases).

4. *Persistent Fistulas.* — Even before we had had a resected specimen to confirm our suspicion, we felt that a certain number of the persistent and intractable intestinal fistulas which followed on the drainage of a supposedly appendiceal abscess were in reality due to a nonspecific inflammatory disease involving the terminal ileum. This belief was founded on the following observations:

1. In a number of instances at the time of the second or third operation for closure of the fistulas, the appendix was found intact and not diseased.
2. Removal of the specimens from the sinus tract and from the intestinal end of the fistula failed to reveal any evidence of tuberculosis or other specific disease.
3. The occurrence of ileal without cecal origin of the sinus tract was noted.
4. The tendency of fecal fistulas of simple appendiceal origin is to close spontaneously or to be susceptible of closure by excision of the tract and inversion of the stump.

However, in two instances resection of the intestine and fistulous tract revealed the typical pathologic picture of ileitis. We assume, therefore, that fistulas which are of supposedly appendiceal origin, but which have ideal openings and which have resisted simple surgical closure are, in the absence of tuberculosis, to be considered as cases of regional ileitis. One peculiar feature of these fistulas may be remarked: They may develop a few months after the original drainage operation, the wound meanwhile having healed and having remained healed for a few months. An abscess then develops in the wound; when this abscess mass is investigated, a communication with the intestine may be demonstrated.

Roentgenographic Observations

Two outstanding facts, one negative and the other positive, are regularly noted. Since the disease simulates regularly the clinical characteristics of ulcerative colitis, the barium enema is first attempted. This procedure results in a negative report. The reason for this is evident in the light of the pathology of the disease. The colon is uniformly free from changes, even though the ileocecal valve is the seat of greatest intensity of the process.

The barium meal, however, when carefully interpreted, gives definite positive findings. These usually consist of distended loops of terminal ileum, in which a fluid level is discernible, and a definite delay in motility of the meal through

Roentgenogram of the barium meal given by mouth, showing regional ileitis. Note the extent of the strictured area.

the distal end of the small intestine. In the four, six and nine hour observations this delayed motility is usually present, though only in the late or stenotic stages is the delay striking. The milder degrees of stasis and puddling in the deal loops may easily be overlooked by any but a careful roentgenologist. Even when the condition is plainly indicated, the true significance of these reported results may be glossed over by the clinician and an exact diagnosis may thus be missed.

When the ascending colon is the seat of a fistulous communication with the ileum, one may note some stricture deformity of the ascending colon or hepatic flexure, with delayed motility at this point. When the sigmoid is similarly involved in a fistulous tract, a true narrowing and delay at this flexure may simulate carcinoma and so create the necessary indication for operation. Both these areas of stenotic deformity of the large bowel are incidental to only one of the complications of the disease, namely, the formation of fistulous tracts. The entire colon is otherwise exonerated as a primary site of the granulomatous inflammation.

Differential Diagnosis

Regional ileitis must be differentiated from several analogous conditions which produce a mass in the right iliac region with diarrhea and fever. The most important differentiation is that of regional ileitis from nonspecific ulcerative colitis. The sigmoidoscopy and the barium enema suffice for the recognition of colitis in the largest percentage of cases. But there are types of colitis which involve only the proximal segments of the colon, and in which the sigmoid and the rectum are free from pathologic: changes. While these instances are few and relatively uncommon, they do occur and lead to much confusion; they may be recognized by the deformity and spasm of the cecum and ascending colon when the latter areas are the seat of the segmental phenomena of colitis. Only in severe cases of ulcerative colitis does the process involve the terminal ileum, and then only for a few inches. In regional ileitis, all of the damaged tissue is proximal to the valve. The diagnosis is purely roentgenographic, the clinical differentiation being impossible. Colitis does not cause fistulas except about the anus and rectum; a mass is rarely palpable in colitis.

Ileocecal tuberculosis as a primary process should be easy of differentiation from regional ileitis. We are inclined, however, to agree with Moschcowitz and Wilensky (2) in the skepticism with which they view the actual occurrence of a primary tuberculous process at the ileocecal junction. To repeat their arguments, the latter disease must be rare, for only three cases have been seen at Mount Sinai Hospital in several years. Pathologic examination of all such suspected tuberculous masses has uniformly failed in the demonstration of tubercles or of tubercle bacilli in the sections or smears. Practically all cases mistakenly suspected of, or diagnosed as, ileocecal tuberculosis have been eventually classed as new growth, as appendicitis with abscess or as benign nonspecific granuloma. In all of our first cases of regional ileitis the diagnosis of ileocecal tuberculosis was the unvarying best possibility; operation was undertaken only after the customarily accepted methods of treatment for tuberculosis had been exhausted. Fibroplastic appendicitis or typhlitis is a disease better known to the surgeons.

Lymphosarcoma, intestinal or mesenteric tuberculosis and Hodgkin's disease simulate regional ileitis in many of its features. The exact differentiation is possible only at the operating table or by the examination of pathologic specimens. Sarcoma of the intestine is usually multiple, causing dilatations at various levels, and involves the jejunum as well as the ileum and not particularly just the terminal 8 to 12 inches of the small intestine. Hodgkin's disease may give its characteristic monocytic blood picture, or a regional lymph node may reveal the true nature of the process.

Actinomycosis of the ileocecal region with fistula formation to the external abdominal wall must always be mentioned in the differentiation from ileitis. The extreme rarity of actinomycosis in this region of the body and in this climate makes this differentiation more theoretical than necessary.

From carcinoma of the terminal ileum or of the ileocecal valve the differentiation cannot be made with any certainty; both conditions call for surgical intervention and both lead to cure by successful and early resections.

Treatment

Medical treatment is purely palliative and supportive. The diseased area cannot be reached by colonic irrigations or enemas, and any attempts by medical means to reach a necrotizing, ulcerating and stenosing inflammation of the terminal ileum is purely and essentially futile. True, one case, discovered in the course of a cholecystectomy for stones, progressed to spontaneous healing or at least to a cessation of the intestinal symptoms.

But in general, the proper approach to a complete cure is by surgical resection of the diseased segment of the small intestine and of the ileocecal valve with its contiguous cecum. The restitution to complete health in thirteen out of fourteen cases as a result of the radical resection of the pathologic process or of a short-circuiting operation speaks vehemently in favor of surgical methods as the logical successful therapeutic procedure.

In one instance recurrent symptoms were accounted for by the finding of an annular stenosis a short distance proximal to the new anastomosis (ileotransversostomy). Apparently in this case the resection had not been carried out sufficiently oral to the lesion completely to eradicate the disease.

Our experience with short-circuiting anastomoses is limited. In one case a short-circuit ileocolostomy was performed through a segment of ileum that was apparently normal at the time of operation. The pathologic process did not heal; on the contrary, the disease progressed to the proximal loop of the anastomosis. In two cases of intractable fistulas and in one case of inflammatory pelvic mass, ileocolostomy with exclusion has given excellent results. The best operation, as devised by Dr. A. A. Berg, consists of dividing the ileum 3 feet (91 cm.) from the ileocecal junction, closing both ends of the divided ileum and implanting the proximal terminus of the ileum by a side-to-side anastomosis at the transverse colon.

Abstract of Discussion

DR. J. A. BARGEN, Rochester, Minn.: This presentation would seem timely, for, with improved roentgen technic and more intensive study of intestinal disease, the condition may prove to be less common than it is now supposed to be. Intensive roentgenologic investigation often becomes necessary to determine the nature of disturbances of the ileocecal coil. Undoubtedly some of these cases have been overlooked. In the last few years, several cases annually of this type have come to operation at the Mayo Clinic. Usually the appendix has been removed for complaints similar to those for which the patients presented themselves, that is, recurrent and intermittent attacks of right abdominal pain and discomfort. Some of these conditions were diagnosed preoperatively because of the suggestive roentgenographic and roentgenoscopic signs. The lumen of

the intestine in this region is narrowed, and the wall is thickened and shortened. The gross appearance of the removed specimen resembles closely that of the colon in advanced chronic ulcerative colitis. The lesion is inflammatory, containing fibrotic elements and granulation tissue as well as evidence of more acute changes. The evidence points to a regional inflammatory disease perhaps on the basis of localized decrease in resistance to some bacterial invasion. I am wondering whether the designation "terminal" is adequately descriptive. To some it has conveyed the meaning of agonal. Perhaps the modifying adjective "regional" or some other word suggesting its localized nature, instead of the end, would be more suitable: I should like to emphasize that this presentation is an important one, that possibly these cases will be discovered earlier and more frequently in the future, and if so, one instead of two operations may be performed, and that I believe the lesion is infectious.

DR. JULIUS FRIEDENWALD, Baltimore: I am reminded of two cases quite a number of years back in which this condition was evidently present but which were regarded at the time as instances of carcinoma. Both patients, men, presented almost identical symptoms; the one was 50 and the other 58 years of age. The condition arose in the midst of good health and was associated with rapid loss of flesh, diarrhea, indigestion, slight fever and anemia; it terminated in progressive constipation and in attacks of partial and almost complete obstruction. In both instances an indefinite mass could be detected in the cecal region. At operation an extensive obstructive mass was detected in the terminal ileum. A diagnosis of inoperable carcinoma was made by the surgeon and a lateral anastomosis performed. The patients made a surprisingly rapid recovery and remained well. The recovery could not be explained at the time, but the condition was evidently ileitis, as described by the authors. Since then I have observed a number of instances of a milder type which at operation presented a somewhat similar appearance. In a woman, aged 62, who was operated on about two years ago and who presented symptoms of lower right-sided abdominal pain with loss of flesh and attacks of alternating diarrhea followed by intense constipation, this condition was observed in the terminal ileum in a mild form. The surgeon, not realizing its significance, simply removed a chronically inflamed appendix. Since then the attacks have continued, the distress becoming more marked. The authors have undoubtedly described a clinical entity of great importance, a condition that may occur in so severe a form as to simulate carcinoma or intestinal tuberculosis or, in a milder form, presenting the appearance rather of a chronic appendicitis. The possibility of its occurrence must constantly be borne in mind in the differential diagnosis of chronic abdominal disease.

DR. LOUIS J. HIRSCHMAN, Detroit: I have just such a case under my observation, which presents an interesting phase which has not come under the observation of the authors, at least but rarely, as I recall their paper. This is a youth, aged 18 years, who has been suffering from chronic ulcerative colitis since 9 years of age, half his life. His weight has gone down in the last few months to 78 pounds (35.4 kg), so much so that when he was sent to me for surgical relief for his chronic ulcerative colitis, having hemorrhages, I decided on intestinal rest and enterostomy was performed. A diagnosis of benign papilloma of the ileum was not made. He was sent for relief from the chronic ulcerative colitis. At operation, about 12 inches (30 cm) of a large, doughy, thickened ileum was discovered. It was resected and ileostomy done, with immediate relief. The appendix also was involved. It was done about eight weeks ago and the patient has gained weight so that he weighs now about 130 pounds (59 kg). The interesting point to me is that when the specimen was opened the ileum was almost occluded with granulomas. It was a wonder he had any peristalsis or intestinal movement. I gathered from what the authors said that it is uncommon to have an ulcerative colitis in connection with a granulomatous infection of the terminal ileum. In this case there was no evidence of fistulas in connection with either the terminal ileum or the large intestine and I wondered why, since there is the granulomatous formation they described.

DR. SIDNEY A. PORTIS, Chicago: What were the bacterioscopic observations on the excised portion of the ileum? Did you make any sections of the ileum to find out whether any bacteria were deeply seated in the walls of the ileum?

DR. BURRILL B. CROHN, New York: In a disease of this type, in which an attempt is being made to establish the etiology of the disease, we have naturally taken great pains to exclude every known etiologic factor. Histologic sections were made of the tissues and stained with various types of stains. Cultures were made. Ground material was injected into guinea-pigs and fowl. Various types of laboratory animals were used to eliminate any possible form of tuberculosis. Löwenstein cultures were made. Dr. Klemperer, the pathologist, exhausted all the known possible scientific methods of finding an etiologic factor. I can say that no etiologic factor was found. It is refreshing to address a medical organization of this kind, where one can count on meeting men of large clinical experience and find that Drs. Bargen, Friedenwald and Hirschman have seen cases of this type. I have not had many occasions, in fact this is the first, to read this article. I have spoken extemporaneously at one or two previous meetings and wherever I spoke of this subject, the older clinicians, men with broad experience, surgical or medical, always have said: "We have seen such a thing in past years. We have met with it in surgical experience and didn't know what to do with it." The chairman of the New York Surgical Society, at the time the subject was brought up, said: "I have to operate in such a case and I don't know what to do. I don't know the nature of it." I forgot to mention an important physical sign; namely, the mass that occurs. In these cases a mass develops in the lower abdomen, usually in the right ileac region, consisting of agglutinated coils of ileum massed together. Sometimes the mass will move over from adhesions to the sigmoid and will present more in the left lower abdomen. The mass can usually he felt by rectum. It is a hard mass and a movable mass. it does not feel carcinomatous, though I must say some of the best cases we met had previously been condemned as inoperable carcinomas. In addition to the agglutinated loops of ileum, an inflammatory reaction is set up by the fistulas that travel through the mesentery of the ileum to the loops of the colon. I am thankful for the discussion. I had come to the conclusion that only the abdominal surgeons knew about the condition. I am glad to find that men with older and larger medical experiences have also met with the manifestations of the disease.

DR. FRANK SMITHIES, Chicago: You never found free fluid, did you?

DR. CROHN: Yes, a small amount, not demonstrable by physical signs but a small amount such as one would find in any inflammatory peritoneal lesion — real ascites.

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Planting Seeds of Knowledge about Inflammatory Bowel Disease:
Half a Century of Science, Prescience, and Prophecy in the Pages of Mount Sinai's Journal

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Abstract

This is a review of those clinical observations, innovative concepts, and predictions concerning inflammatory bowel disease that were first published in *The Journal of the Mount Sinai Hospital*, renamed in 1970 *The Mount Sinai Journal of Medicine*. The review was based on a hand search of every volume of *The Journal* from its inception in 1934 to the present day.
Key Words: Crohn's disease, ulcerative colitis, inflammatory bowel disease, The Journal of The Mount Sinai Hospital, The Mount Sinai Journal of Medicine.

THIS IS SURELY THE AGE OF "Evidence-Based Medicine." In the courtrooms of academia, the only "admissible evidence" these days seems to be fullypowered randomized clinical trials. By this restrictive criterion, though, we pay attention only to the final product — the harvested fruit. But what about the seeds? What about the original observations and seminal ideas that bore fruit only after many years of cultivation?

In March of 1997, the distinguished physician and editor, Frank Davidoff, lectured at Medical Grand Rounds at The Mount Sinai Hospital. His talk, entitled "In the teeth of the evidence: The curious case of evidence-based medicine," included the following statement (1): "All good science begins with good observations, but observations serve largely to generate hypotheses rather than confirm them." The speaker clearly intended to emphasize the importance of "confirmation," harvesting the fruit. In this essay, by contrast, I intend to emphasize the "generation," the planting of the seeds.

A pair of "Theme Issues" in this journal last year has already surveyed the many contributions of Mount Sinai doctors to the field of inflammatory bowel disease (IBD). I have, however, set myself a rather different agenda.

Specifically, I shall review those "good observations," innovative concepts, and predictions concerning IBD that were first published in *The Journal of The Mount Sinai Hospital*, renamed in 1970 as *The Mount Sinai Journal of Medicine*. This review is based on a hand search of every volume of *The Journal* from its inception in 1934 to the present day.

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Anatomic Distribution

Although "regional ileitis" had been thoroughly described in two nearly simultaneous presentations in May 1932 by Crohn, Ginzburg, and Oppenheimer (2, 3), it took more than 20 years before the same pathologic process in the colon was firmly classified as part of the same disease (4). Nonetheless, Ginzburg and Oppenheimer's initial compilation of cases of "non-specific granulomata of the intestine" (2) meticulously described "localized hypertrophic colitis" associated with perianal fistula, an observation repeated by Crohn, Garlock, and Yarnis 15 years later and further emphasized in a *Journal of the Mount Sinai Hospital* abstract (5) regarding the entity of "segmental right-sided colitis": "Peri-anal and peri-rectal fistulas are very common."

While it was the team of a British surgeon, H.E. Lockhart-Mummery, and pathologist, Basil Morson, who argued most strongly for classifying granulomatous colitis as an integral part of Crohn's disease (6), this concept received its major impetus in the United States from the work of Mount Sinai radiologists, particularly

B.S. Wolf and especially R.H. Marshak (7). Indeed, the classic, most exhaustive description of the features and differential diagnosis of ulcerative and granulomatous colitis appeared in a 59-page article in *The Journal of the Mount Sinai Hospital* by Marshak and Lindner in 1966 (8). This radiologic magnum opus was often reproduced and modified by its authors — as in a *Mount Sinai Journal of Medicine* paper (9) that prefigured a chapter in their classic W.B. Saunders textbook, *Radiology of the Colon* — but the clarity and thoroughness of the 1966 publication was never surpassed. Indeed, as Henry Janowitz foretold in his introduction to the 1966 paper (10): "This exhaustive study and detailed illustration of the radiographic features of the major inflammatory disorders of the colon by Drs. Marshak and Lindner will, I believe, contribute enormously to our sorting out of this baffling group of diseases."

A different view of ulcerative and granulomatous colitis, however, from a colonoscopic perspective, was outlined in 1975, in a paper by Jerome Waye (11), comprising "an in-depth review based on a personal experience of several thousand colonoscopies." This whole topic of recognizing Crohn's disease of the colon has also been reviewed in *The Mount Sinai Journal of Medicine* by one of the pioneering investigators of this disorder, Arthur Lindner, a former fellow in gastroenterology at The Mount Sinai Hospital (12).

Meanwhile, as Crohn's disease was being increasingly recognized in the colon, other *Journal of the Mount Sinai Hospital* publications and abstracts throughout the 1950s were calling attention to involvement of the stomach, duodenum, and jejunum (13–15). (It is interesting that the lure of studying IBD at Mount Sinai was so strong that the principal review of Crohn's gastroduodenitis (14) was written by Alexander Richman, chief of the Liver Clinic who was primarily a specialist in hepatic and pancreatic diseases). Further classic descriptions of gastric and duodenal Crohn's disease, accompanied by magnificent radiographs, appeared subsequently in the "Radiologic Notes" section of *The Mount Sinai Journal of Medicine* edited by C. Bloch and H.M. Peck (16, 17).

Natural History and Epidemiology

Throughout the 1960s, even before establishing himself as the pioneer of immunosuppressive therapy for IBD in the United States, Burton Korelitz, then a young gastroenterologist at The Mount Sinai Hospital, was a leading chronicler of the natural history of ulcerative colitis and Crohn's disease. As early as 1962, he had begun to publish, together with a pediatrician, Donald Gribetz, their observations on the course of ulcerative colitis in children. In 1968, *The Journal of the Mount Sinai Hospital* carried Korelitz's seminal paper on the prognosis of granulomatous colitis in childhood (18). By 1979, Korelitz had accumulated experience with more than 350 patients with Crohn's disease. His report in *The Mount Sinai Journal of Medicine* that year (19) was a landmark in establishing the scientific value of clinical experience garnered by scholarly specialists in private practice.

From a broader perspective of global epidemiology, Mount Sinai's chairman of surgery, Arthur Aufses, Jr., made a remarkably accurate prediction at an IBD symposium in 1982 marking 50 years' experience with IBD and celebrating 25 years of Henry Janowitz's directorship of Mount Sinai's Division of Gastroenterology. On that occasion, Dr. Aufses said (20): "If I had to venture a guess, I would say that granulomatous [Crohn's] disease, which has been on a marked increase in the northern parts of the world, will slowly plateau and then begin to decline. That will be followed by increases in its incidence in other parts of the world, where they don't see very much of it now." As usual, Aufses's crystal ball proved reliable.

Complications

Although Mount Sinai physicians in 1987 were most strongly emphasizing the external origins of upper gastrointesinal (GI) fistulas in Crohn's disease (21), *The Journal of the Mount Sinai Hospital*, as early as 1948, carried a paper recognizing duodenal fistula as colonic in origin, and describing its surgical correction by simple closure of the duodenal hole and definitive resection of the diseased colon (22). Similarly, an early paper on "gastrocolic fistula" clearly identified this complication as arising from "transmural colitis" and at one point in its text used the more accurate term, "cologastric fistula" (23). A much rarer complication involving the upper GI tract is pancreatitis supposedly associated with primary Crohn's disease of the duodenum. One of the earliest reports (actually only the third paper) describing this association appeared in *The Mount Sinai Journal of Medicine* in 1987 (24).

Important observations concerning the much more common complication of lower GI tract fistulization were reported by Korelitz in *The Mount Sinai Journal of Medicine* in 1984 (25). His review of 22 patients with ileosigmoid and ileorectal fistulae called early attention to two cardinal principles, both insufficiently appreciated even today. The first point was that "the entero-enteric fistula does not require surgical intervention for its own sake," since it was often asymptomatic and even in cases requiring treatment might well respond to medical therapy. The second key concept was his emphasis on identifying "the segment of origin" — in other words, carefully distinguishing the perpetrator (site of origin) from the innocent bystander victim (the site of re-entry).

Another set of Crohn's disease manifestations largely clarified by Mount Sinai investigators comprised urologic complications. Although a number of Mount Sinai papers from the 1960s are often cited as the earliest publications on this topic, the urologic complications of regional ileitis were first described by Ginzburg and Oppenheimer in the *Journal of Urology* in 1948 and abstracted shortly after in *The Journal of the Mount Sinai Hospital* (26). It should be noted that this same Gordon Oppenheimer of "Crohn, Ginzburg, and Oppenheimer" fame was in fact an eminent urologist. In this article, patients were reported as presenting with retroperitoneal abscesses; but their characteristic symptom of lower extremity pain and limp — prominently described in 1969 by Daniel Present et al., one of IBD's most productive investigators (27) — had actually been emphasized some years before in a radiological vignette in *The Journal of the Mount Sinai Hospital* (28). In this brief report, a patient was described with "severe pain in the lumbosacral region radiating to both legs, associated with difficulty in walking." The paper called attention to the complication of presacral abscess presenting as hip pain and being confused with an orthopedic problem. The correct diagnosis was revealed by a plain film of the spine showing air in the presacral space!

Two other rarely recognized associations or complications of IBD that received some of their earliest attention in *The Journal* were the presentation of regional ileitis as gross rectal bleeding (29) and the co-existence of ulcerative colitis with hemophilia A (30). Yet the tradition of "good observations" in *The Journal* is not restricted to papers from long ago. A very recent issue of *The Mount Sinai Journal of Medicine* carried only the second published case report of a preoperative diagnosis of gallstone ileus in Crohn's disease, and the only one without biliary-enteric fistula (31).

Extraintestinal Manifestations

Few Mount Sinai papers on IBD, at least since the landmark *JAMA* article of 1932 on regional ileitis (2), have been cited as frequently in the medical literature as the 1976 review of extraintestinal manifestations in *Medicine* by Greenstein et al. (32). This analysis of 700 cases of IBD distinguished between "colitis-associated" conditions and those attributable to "small bowel pathophysiology." Yet it is noteworthy that this attempt at classification was foreshadowed more than 20 years earlier in the pages of *The Journal of the Mount Sinai Hospital* by Albert Cornell, then chief of the Gastro-Intestinal Clinic of The Mount Sinai Hospital (33). Moreover, one of the early efforts at treating an extraintestinal complication on the basis of a pathophysiologic rationale was described in *The Mount Sinai Journal of Medicine* when Gelernt and Kreel reported on the use of cyproheptadine, a platelet deaggregrator, in the management of pyoderma gangrenosum (34).

Cancer

It is already well known that Burrill Crohn was an author of the first report of colon cancer in ulcerative colitis (35), and that Leon Ginzburg co-authored the first report of small bowel cancer in regional enteritis (36). It is less widely appreciated, however, that half a dozen key observations about the relationships between cancer and IBD were first published in *The Journal*.

1. Pathology. In 1952, the redoutable Mount Sinai pathologist, Sadao Otani, and the legendary Mount Sinai clinician, Isidore Snapper, teamed up to clarify the relationships among adenomatous polyps, inflammatory polyps, and cancer associated with ulcerative colitis (37). A generation later, Mount Sinai's most prolific surgical author on IBD, Adrian Greenstein, spearheaded a study of the clinical and pathologic features distinguishing colitis-associated from sporadic colorectal cancer (38).

2. Small bowel cancer. Although, as we have seen, Ginzburg et al. first reported jejunal carcinoma complicating Crohn's disease in 1956 in the journal, *Surgery* (36), B.S. Wolf in that same year described the radiologic findings in detail in *The Journal of the Mount Sinai Hospital* (39).

3. Cancer in bypassed loops of bowel. The first American report of ileal cancer in a bypassed bowel segment with Crohn's disease appeared in *The Journal of the Mount Sinai Hospital* in 1970 (40). This paper did not speculate heavily on the pathogenesis of such neoplasms, but it stressed two of the most important clinical implications: first, that these cancers were clinically silent ("...the presence of a clinically silent neoplasm in a bypassed or excluded loop of intestine is extremely difficult to diagnose radiologically...."); and second, that bypass surgery, while efficacious in the short term ("...bypass usually leads to quiescence of the inflammatory process..."), could be detrimental in the long term ("[We] emphasize the possible long-term dangers inherent in this type of surgery."). While many subsequent investigators proposed a variety of biological mechanisms for the occurrence of cancer in excluded loops of bowel, my analysis published in *The Mount Sinai Journal of Medicine* in 1983 (41) indicated that the apparently high frequency of this phenomenon was simply a statistical artefact of the confounding factor of disease duration: "...it is not the bypassed loop itself that puts the patient at risk for cancer; it is the long duration of the disease."

4. Left-sided ulcerative colitis. While conventional wisdom had held that only patients with ulcerative pancolitis were at significantly increased risk for colorectal cancer, our 1979 study in *The Mount Sinai Journal of Medicine* pointedly called attention to the risk in less-than- universal colitis (38): "It is important to recognize that after a sufficiently long interval, cancer may develop in left-sided as well as in universal colitis."

5. Mortality. Another prevalent concept dispelled in this same 1979 paper was that the case-fatality rate in colitis-associated colorectal cancer was much higher than in sporadic cancer (38): "The long-term mortality from colitis-associated cancer did not appear to be worse than that from colorectal cancer in the general population."

6. Cancer in Crohn's colitis. Perhaps the most tenacious myth concerning colorectal cancer in IBD has been that the risk is much greater in ulcerative colitis than in Crohn's disease of the colon. Although the final nails were not driven into the coffin of this widespread misconception until 1994 (42, 43), the strongest prediction of the actuality had appeared in *The Mount Sinai Journal of Medicine* as early as 1983 (41): "When cases of ulcerative and Crohn's colitis of similar anatomical extent are followed for similar durations of time, the two diseases may ultimately prove to have similar increases in risk for colorectal cancer." Subsequent studies indicated that the risks were not only similar, but virtually identical (42).

Medical Therapy

The many contributions of Mount Sinai doctors to the medical therapy of IBD have been amply recounted in previous issues of this journal (44–46) and do not need to be repeated here. Yet it is worth noting how often the most seminal therapeutic principles found early and forceful expression in the pages of *The Mount Sinai Journal of Medicine*. Two symposia in particular provided occasion for giants in the field, from both home and abroad, to demonstrate their prescient vision in the area of medical treatment.

First was the celebratory Anniversary Symposium of 1982 already mentioned in the section on Natural History and Epidemiology above. It was ambitiously entitled, "Inflammatory Bowel Disease: The Next Fifty Years," and even then five of the most vital current trends in therapy were foreseen. First, Korelitz predicted the modern movement toward earlier introduction of 6-mercaptopurine (6-MP) in the management of Crohn's disease (47): "Perhaps when we feel more comfortable with its use it might be justified even earlier in the course, when the disease is still considered mild." In the same presentation, he also accurately foretold two more guiding principles in present-day immunosuppressive treatment: its indefinite continuation for long-term maintenance of remission, and its efficacy in ulcerative colitis as well as in Crohn's disease: "The results have been impressive and suggest that the response rate in ulcerative colitis is similar to that in Crohn's disease.... There is no longer justification for the belief that predisposition to carcinoma in long-standing ulcerative colitis warrants postponing double blind trials of 6-MP similar to those conducted in Crohn's disease."

A fourth "new wave" of therapy was predicted by both Henry Janowitz and John Lennard-Jones at that symposium nearly 20 years ago, namely, the ascendancy of antibiotics in the treatment of Crohn's disease (48, 49). Lennard-Jones — to this day still unsurpassed in his genius as a clinical investigator in IBD — foresaw the 21st century's emphasis on designing biological agents to target specific points in the pathogenetic pathway of the diseases (48): "I think we'll find out how the treatments affect...pathogenetic mechanisms.... I suspect that our medical treatment is going to improve because we are going to be able to design the treatment to affect those pathogenetic mechanisms." This statement was made fully 15 years before the introduction of infliximab and related revolutionary anti-cytokine therapies!

In fact, in his 1983 remarks, Lennard-Jones's prescience extended beyond the boundaries of medical treatment into accurate visions of modern pathogenetic research: "We'll take a particular interest in the bacterial flora of the gut and its relationship with the genetic immunological status of the host." Fifteen years later, a mountain of experimental evidence has borne out his prediction. Similarly, "We'll learn a lot about chemical transmitters in the gut wall." Today's pharmaceutical research on IBD is, of course, focused almost entirely on these chemical transmitters. On this same occasion, Lennard-Jones made yet another bold prediction regarding etiology and epidemiology: "I think we'll also find that there is an environmental factor which accounts for differences in epidemiological incidence in various countries." I find this concept highly attractive, but so far insufficient evidence has been accumulated to permit submission to any jury, grand or otherwise.

A second, more recent Mount Sinai forum for "science, prescience, and prediction" regarding IBD took place in December 1989, at a Symposium entitled, "Inflammatory Bowel Disease Therapies for the 1990s: Scientific Basis and Clinical Experience" (50). Here again, the published proceedings in *The Mount Sinai Journal of Medicine* provided glimpses into at least three more innovative therapeutic avenues that would eventually culminate in clinical trial "evidence" in subsequent years. First, the indefatigable pioneer of cyclosporine treatment for ulcerative colitis, Simon Lichtiger, presented the first reports of the effectiveness of this agent both for severe steroid-resistant ulcerative colitis and for fistulizing Crohn's disease (51).

Second, Korelitz advanced the concept of pushing progressively higher doses of 6-MP, when required, to achieve therapeutic benefit (52): "There does seem to be correlation with dosing and effectiveness, because if we start at one dose and it isn't successful, very often I see that when the dose is raised, within a brief time something begins to happen.... If the patient's white cell count has not fallen and we haven't achieved therapeutic effectiveness, I will push for a bigger dose." If they had had to wait for the "admissible evidence" demanded by current academic fashion, countless patients would have been denied the benefits of this incontrovertibly correct approach.

And finally, Henry Janowitz, the father of academic gastroenterology at Mount Sinai, accurately predicted both the modest effectiveness of 5-aminosalicylates (5-ASA) and the greater effectiveness of immunosuppressives in the prevention of relapse of Crohn's disease (53): "I think that 5-ASA will offer a modest degree of protection against relapse in maintenance studies in Crohn's disease as it does in ulcerative colitis when studied against placebo. We now look forward to the continuing follow-up of the immunosuppressive agents in these diseases."

Surgery

As with medical therapy, surgery for IBD has been greatly advanced by the staff of The Mount Sinai Hospital (54). While most of these contributions have of course been published in the wider medical and surgical literature, *The Mount Sinai Journal of Medicine* has recorded its share of seminal observations. For example, an early report of the use of a rectal mucosal advancement flap for rectovaginal fistula appeared in a 1983 issue (55). With even broader impact, *The Mount Sinai Journal of Medicine* in that same year reported Irwin Gelernt's unrivaled early experience in the United States with 300 patients receiving a continent ileostomy (Kock pouch) for ulcerative colitis (56).

Looking even farther into the future, however, John Lennard-Jones, speaking at Mount Sinai, predicted the eclipse of the continent ileostomy by newer sphincter-sparing procedures on the horizon (57): "I don't think that continent ileostomy is the full answer. I think that the full answer is going to leave anatomy much more as it is, that is to say with the use of the anus. Then I think surgery will be more acceptable and I think we as physicians will be recommending it more frequently and our patients will be accepting it more readily." Speaking at the same venue, the distinguished British surgeon, John Alexander-Williams, agreed with this assessment and also provided his audience and *The Journal*'s readership with an early overview of the newly emerging intestine-sparing procedure of strictureplasty (57).

Of course, predating all the continent variations on the technique was the standard Brooke ileostomy, a procedure extensively studied and perfected by a senior Mount Sinai surgeon, Albert S. Lyons. The founder of patient-oriented

ileostomy associations in the United States, Lyons focused on the central importance of patients' psychosocial adjustment to ileostomy, in a 1983 article in *The Mount Sinai Journal of Medicine* (58), only shortly after Mount Sinai's first paper on the subject (59) and long before surgical "quality of life" studies in IBD had become academically fashionable. More recently, *The Mount Sinai Journal of Medicine* again provided the forum for a ground-breaking study bringing quantitative science to bear on such elusive but critical issues as individual coping mechanisms and family dynamics in the course of IBD (60).

Postoperative Recurrence of Crohn's Disease

It has often been said that the inexorable tendency of Crohn's disease to recur following surgical resection is still the thorniest single problem in present-day management of inflammatory bowel disease (61). The medical and surgical literature of the past 20 years is replete with studies of this phenomenon, its natural history, and attempts at its prevention. But as early as the 1950s, papers in *The Journal of the Mount Sinai Hospital* were already focusing this troublesome issue. An interdisciplinary conference of ten Mount Sinai clinicians in January 1952 devoted the great bulk of its attention to detailed discussions by Burrill Crohn and the surgeon, Ralph Colp, concerning cases of postoperative recurrence of ileitis and ileocolitis (62). In this context, it is noteworthy that even at this early date, Mount Sinai surgeons and gastroenterologists were prefiguring the surgical conservatism of today; in Colp's words, "In the present state of our knowledge, we are operating on these patients only when our hand is forced by intestinal obstruction, fistulae, and abscess formation."

Fully forty-five years ago, in a *Journal of the Mount Sinai Hospital* Symposium edited by Dr. Crohn, Henry Janowitz provided an overview of "Problems of Regional Enteritis" that has scarcely been improved upon to the present day (63). His review included several pathophysiologic insights (e.g., the suggestion that "the noxious agent is present in the intestinal stream") that are currently being validated (64). With particular regard to the problem of postoperative recurrence, Dr. Janowitz drew both pathophysiologic and therapeutic conclusions: regarding the former, "The hypothesis of widespread initial lesions...might explain the high incidence of recurrence following operation even though biopsy at the site of resection or by-pass may be entirely negative"; and regarding the latter, "With the increasing recognition that the rate of recurrence is a function of the length of follow-up, and with increasing numbers of recurrences, the [surgical] approach to therapy is now in a disillusioned phase." It must be noted that what Janowitz so confidently alluded to in *The Journal of the Mount Sinai Hospital* as "increasing recognition" in 1955 was validated by "admissible evidence" in the *New England Journal of Medicine* only 20 years later (65)!

History

This essay was not undertaken to replicate last year's historical review of Mount Sinai's contributions to the study of IBD (66), but it has instead tried to assess the unique role of *The Mount Sinai Journal* over the last half century as a seedbed and sounding board for innovative and forward-looking thoughts about the nature and management of these disorders. Yet this assessment would not be complete without some mention of several remarkable historical reviews that have appeared in these pages in years past, especially since these historical perspectives have looked not only backward but also forward.

Before the current set of three theme issues edited by Jeremy Hugh Baron and Henry D. Janowitz, there were at least seven other historical surveys published in this journal between 1945 and 1993 that deserve citation:

1. 1945. In a retrospective of "Gastroenterology at The Mount Sinai Hospital" prepared for the Moschowitz Anniversary Issue of *The Journal of the Mount Sinai Hospital* (67), Burrill Crohn was especially gracious in his discussion of the disease that ultimately came to bear his name:

> ...in 1932, dated from The Mount Sinai Hospital, appeared the first paper or papers [note the plural!] on a new clinical entity "regional ileitis." The earlier pathological and clinical studies on intestinal granulomata had been laid down by Drs. Eli Moschowitz [whom this issue of *The Journal* was honoring] and A.O. Wilensky as early as 1923. The pathological studies of these granulomata had been re-begun by Drs. Leon Ginzberg [*sic*] and Gordon Oppenheimer. The combination of these studies with the clinical and surgical observations of myself and Dr. A.A. Berg led in 1932 to the formulation of the entity of "ileitis." With practically no hesitation, with little scientific criticism, but with many constructive additions, the medical profession has accepted ileitis, or regional enteritis, as an established clinical concept.... The Attending Staff of this hospital have thus been given proper credit for the recognition of a disease, which knows no limited geographical incidence and which provides an ample and new arena for extensive surgical operative skill and original initiative.

2. 1951. In the Albert A. Berg Memorial Issue of *The Journal of the Mount Sinai Hospital*, Crohn once again downplayed his own role and lavished primary credit upon Dr. Berg, Mount Sinai's late chief of surgery, for developing the concepts of regional ileitis and "right-sided or segmental ulcerative colitis," as well as for advancing the "increasing utility of ileostomy for severe ulcerative colitis and the feasibility of subsequent total colectomy for otherwise incurable forms of universal colitis...." (68).

3. 1955. Under the editorship of Dr. Lester R. Tuchman, *The Journal of the Mount Sinai Hospital* in 1955 published the first in a series of symposia to "cover areas in which workers at The Mount Sinai Hospital are at the present time engaged on a broad front, or fields to which they have made significant contributions." The topic was "Regional Ileitis." In an even-handed bow to two men who were both colleagues and rivals, Dr. Tuchman concluded his editorial introduction (69): "Since the seminal paper on Regional Ileitis was by Drs. Crohn, Ginzburg and Oppenheimer, it is fitting that the first be Guest Editor and the second the author of the article on its surgical management." In his "Reminiscences," Crohn paid tribute yet again to the contributions of Berg, Ginzburg, and Oppenheimer to the recognition of regional ileitis as a clinical and pathologic entity (70). Remarkably, both in the closing paragraphs of this article, as well as in a 1949 paper (13), Crohn prefigured a designation of inflammatory bowel diseases that has only very recently taken shape as the "Rome" (71) and "Vienna" (72) Classifications of Crohn's disease!

4. 1966. The first section of this paper, "Anatomic Distribution," opened with a review of *The Journal*'s contributions to an understanding of involvement of the colon by Crohn's disease. For those interested in a more detailed review of the evolution of the history of this concept, an historical gem is nestled in the pages of a 1966 issue of *The Journal of the Mount Sinai Hospital* (73). Entitled, "Granulomatous colitis: An attempt at clarification," and authored by Crohn and Yarnis, this article provides a fascinating, step-by-step chronicle of what Lindner (12) much later referred to as "Recognizing Crohn's disease of the colon." In their historical retrospective, Crohn and Yarnis credit British workers of the 1950s for first recognizing the connections between "segmental" or "right-sided" colitis and the granulomatous disease, regional ileitis. They go on to acknowledge frankly, "Many of us, myself [presumably Crohn] in particular, altered opinion slowly, hesitating to admit that the segmental [cases of colitis] were truly granulomatous in nature. But over the course of years and with more extensive study on the part of the pathologist, it would seem that not only because of fact, but also in the interest of simplification one must accept as truly granulomatous disease all cases of so-called right-sided colitis." These two giants in the field of IBD also called attention to the phenomenon we now call "rectal sparing," and they confessed ignorance concerning its cause: "The most interesting fact here is that even when observed for years, this process [of granulomatous disease involving the entire colon] will not pass the rectosigmoid. It would almost appear that the rectosigmoid area constitutes a barrier to the progression of the pathological process *provided no surgery is performed* [italics added to emphasize yet another of their seminal observations!]. Why the lesion halts at this nodal point is difficult to understand." Thirty-five years later, we are none the wiser on this question.

5. 1973. In a memoir written for *The Mount Sinai Journal of Medicine* (74), Leon Ginzburg pulled off an extraordinary feat. He published a four-page article chronicling the history of regional enteritis without once mentioning the name of Burrill Crohn — except in a dismissive six-word footnote in very small type, appended to his description of the twelve cases that he and Oppenheimer had so laboriously collected and meticulously studied: "*Dr. Crohn later added two more." The insertion of this footnote seems reminiscent of the practice of bequeathing one dollar to a particularly unfavored relative, just to prove the point that the disinheritance was not the result of an innocent oversight. By the time of a subsequent memoir ten years later (75), Ginzburg's rhetoric may have

softened somewhat, but not his heart, in the judgment of those of us privy to his uninhibited correspondence and conversations.

6. 1983. In a more objective vein, Dr. Janowitz provided an overview of "The road to Crohn's disease" that emphasized three cardinal points (76): (a) that the disease was relatively new in appearance and increasing in incidence; (b) that it affected the entire GI tract as well as "overflowing" into surrounding tissues; and (c) that it had systemic effects ("an impact on the organism") beyond the gastrointestinal tract and its immediately adjacent organs.

7. 1993. At the dedication of the Dr. Henry D. Janowitz Division of Gastroenterology at Mount Sinai on December 8, 1992, Dr. Daniel Present delivered a review of "Advances in knowledge of inflammatory bowel disease at Mount Sinai Medical Center" (77). In so doing, he paid homage to our teacher and mentor, Dr. Janowitz; modestly understated his own many contributions; and paid tribute to all those who have played, are playing, and will play important roles in the continuing study, elucidation, and amelioration of these cruel and baffling diseases.

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Hepatology at Mount Sinai:

The Present and the Future

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Abstract

The Division of Liver Disease at Mount Sinai, now into its fifth decade, has evolved through two remarkable periods in its development and is on the cusp of a third exciting era. The first, extending from the division's creation in 1957 to the retirement in 1988 of its first division chief, Fenton Schaffner, was characterized by brilliant clinical and pathophysiologic insights derived from the unique collaboration of Schaffner, a master clinician, with Hans Popper, a world renowned pathologist widely acknowledged as the father of the modern discipline of hepatology. The second, extending from the appointment in 1988 of Paul D. Berk as Schaffner's successor to the present day, has witnessed enormous growth in the clinical and scientific activities of the division, together with the emergence of a world-class liver transplant program at Mount Sinai. During this recent period, an extensive program of formal clinical research was established; the basic research program then expanded into the areas of hepatic transport, molecular virology, and the cellular and molecular pathogenesis of hepatic fibrosis; and both the clinical and research productivity of the division increased dramatically. A major undertaking, now in its second year, has been the creation of the Center for the Study of Primary Biliary Cirrhosis; Mount Sinai has contributed important advances toward the understanding of this disease. Funding for the Center, from the Artzt Family Foundation Trust, supports a series of interrelated basic studies on the immunology and pathobiology of the disease, as well as creation of a unique clinical database, a serum and tissue bank, and a program of clinical studies. This integration of basic and clinical research in pursuit of new methods of diagnosis and treatment serves as a model for the division's continued leadership role.

Key Words: Hepatology, history, Mount Sinai, primary biliary cirrhosis, Popper, H., Schaffner, F., hepatitis B, hepatitis C.

Origin

A LONG HISTORY OF CLINICAL EXPERIENCE and outstanding scientific investigation that extends from bench to bedside has made Mount Sinai synonymous throughout the world with the study and treatment of liver disease. The foundations of its reputation in modern hepatology were laid in the thirty years between the creation of the Division of Liver Disease in the late 1950s, with Fenton Schaffner as its first chief, and his retirement in 1988. Some of the division's seminal contributions include: the identification of the clinical and pathophysiologic significance of cholestasis; recognition of the importance of fibrosis as the final pathway leading from different inciting injuries to the common end result of cirrhosis; elucidation of the nature of chronic viral infections of the liver; and delineation of the clinical spectrum and natural history of primary biliary cirrhosis. Fundamental though they were, these landmark contributions were made with little more than sharp bedside observation, a light microscope, and keen human intellect. The use of special stains to enhance the diagnostic power of light microscopy, or – on occasion – the application of transmission electron microscopy, were the principal inroads made at Mount Sinai by high technology during this period. This was a multidepartmental effort, involving hepatologists, surgeons, pathologists, anatomists, and clinical chemists. Few would dispute, however, that the driving force for more than 30 years came from Hans Popper and Fenton Schaffner, friends and colleagues Schaffner held joint professorships in both Medicine and Pathology. In a coincidence of almost poetic symmetry, Dr. Schaffner's death, on January 24, 2000, occurred on the very day that the January 2000 issue of *The Mount Sinai Journal of Medicine*, containing his last published article, "History of Liver Disease at the Mount Sinai Hospital" (1), was distributed, bringing to a close an extraordinary era.

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The Post-Schaffner Era

By the time of Dr. Popper's death in 1988, followed shortly thereafter by Dr. Schaffner's retirement as chief of the division, winds of change had already begun to transform Mount Sinai's liver disease program. The first liver transplant at this institution, performed by Dr. Charles Miller (Mount Sinai School of Medicine [MSSM] class of 1978) in September 1988, initiated a massive, clinical enterprise combining the talents and dedications of the Liver Transplant Surgery Team and the Division of Liver Disease. The appointment of Dr. Paul D. Berk, then chief of Hematology, to succeed Dr. Schaffner as Mount Sinai's second chief of Liver Disease initiated a strategy to complement the outstanding clinical research enterprise with a laboratory program exploring basic mechanisms of liver disease.

In 1988 the Division of Liver Disease had two faculty members, two small NIH grants, and clinical revenues of less than $150,000 annually (Figure). Its faculty roster now stands at sixteen, eleven M.D.s, an M.D./Ph.D., and four Ph.D.s, and its annual clinical faculty practice activity has increased more than ten-fold. The division now carries out diverse research projects supported by five grants from the NIH, extensive support from private, nonprofit foundations, and clinical trial funding from the pharmaceutical industry. The research budget has grown steadily since 1988, and is approaching $3 million annually.

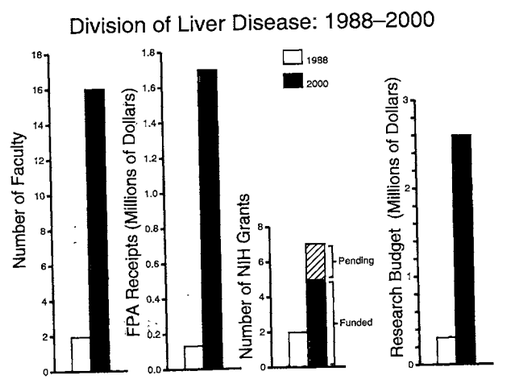

Figure. a. Number of faculty and clinical practice income in 1988 vs 2000. **b.** Number of NIH grants and total research expenditures in 1988 vs 2000.

Clinical Investigation

Over the past 12 years, the Division of Liver Disease has been a model of "translational research." Dr. Henry Bodenheimer, a Schaffner trainee, was recruited from Brown University to become the division's clinical director in 1992. A figure known nationally for his participation in important clinical trials, including those establishing a role for interferon in the treatment of chronic hepatitis C, he has spearheaded the development of a clinical research program that has kept Mount Sinai at the forefront of evolving medical therapies for chronic liver diseases. Most recently, he was named medical director of the Recanati-Miller Transplantation Institute. Dr. Bodenheimer has also played a critical role in the development of training programs in liver disease for both the medical house staff and fellows. This commitment to our training environment was recently highlighted by the awarding of three fellowships from the American Association of the Study of Liver Disease (AASLD)/Schering Advanced Hepatology to divisional trainees, the most of any institution in the country. In addition, Dr. Efsevia Albanis, a 1994 MSSM graduate and currently Senior Research Fellow in the laboratory of Dr. Scott Friedman, won the highly prestigious AASLD/AMGEN Physician Development Award.

In addition to Drs. Bodenheimer and Berk, the clinical staff of the division currently includes Drs. Nancy Bach, Scott Friedman, David Jaffe, Leona Kim-Schluger, Albert Min, Thomas Schiano, Michael Schilsky, and Samuel Sigal. All of them participate in a cooperative enterprise that combines the care of a large and challenging population of patients with liver disease, along with close collaboration with investigators in other departments, such as Drs. Swan Thung and Isabel Fiel from Pathology and Drs. Charles Miller, Myron Schwartz, Patricia Sheiner, Sucru Emre, and other members of the liver transplant surgical team. A selection of recent publications from this clinical program is included in the reference list of this article (2–17).

The investigative interests of the Liver Disease faculty reflect the breadth of Mount Sinai's patient population and the diverse venues in which these patients are seen, including the Faculty Practice suite, The Mount Sinai Hospital Liver Clinic, clinics associated with the liver transplant program, and a satellite office in New Jersey. Shared clinical research interests include: the diagnosis and management of chronic hepatitis, especially that resulting from infection with the hepatitis B and C viruses (2–4); other complications of these infections, including the development of hepatocellular carcinoma (5) and B-cell lymphomas (6); and the utility of various diagnostic studies used in screening for specific complications of liver disease (7). At the same time, faculty members have evolved their own areas of special expertise, on which they have focused both their patient care activities and their clinical investigative programs. Thus, Dr. Albert Min has a strong interest in hepatocellular carcinoma in the setting of chronic liver disease (5). In addition, Dr. Min is currently involved in various Phase II and III clinical trials of novel therapies for hepatitis B and C. Along with Dr. Henry Bodenheimer, he is involved in assessing the efficacy of long-acting interferon in combination with ribavirin for chronic hepatitis C, both in previously untreated patients and in those unresponsive to prior antiviral therapy. With his interest in pretransplant evaluation of patients with end-stage liver disease in the setting of a severe scarcity of donor livers, he has attempted, along with Dr. Thomas Schiano, to find additional prognostic factors for identifying the most suitable pretransplant candidates (7). He is currently analyzing the long-term outcomes of patients transplanted at Mount Sinai for various forms of chronic viral hepatitis.

Dr. Nancy Bach, another Schaffner trainee, supervises a productive office-based program focused on clinical investigation in primary biliary cirrhosis (8). Dr. Bach is also involved in a study assessing the efficacy of combination antiviral treatment in patients with chronic hepatitis C and normal liver enzymes.

Although all the physicians in the division are actively involved in the evaluation and preoperative care of liver transplant candidates, Drs. Leona Kim-Schluger and Thomas Schiano have primary responsibility for postoperative care of transplanted patients, and for identifying specific medical complications that arise in the post-transplant setting (9–11). Dr. Kim-Schluger is also participating in clinical trials of new immunosuppressive agents in liver transplant patients, and is spearheading a pilot study of the long-term efficacy of liver or kidney transplantation in patients infected with human immunodeficiency virus. Dr. Schiano has a particular clinical interest in the treatment of recurrent viral hepatitis after liver transplantation. In this regard, he is involved in studies of passive immunoprophylaxis to prevent recurrent disease in patients undergoing transplant for hepatitis C-related, end-stage liver disease. Having been trained in clinical nutrition, he is also exploring the association between nutrition and the health of the liver, and in the use of herbal and complementary medications for the treatment of liver disease.

Dr. David Jaffe, an outstanding biliary endoscopist, has become a regionally recognized authority on biliary tract disease. His interests include assessing the outcome of patients transplanted for primary sclerosing cholangitis, and screening these patients for possible development of cholangiocarcinoma. Dr. Samuel Sigal's long-standing interest in hepatic regeneration (12) translates into a clinical focus on managing complications of end-stage cirrhosis, such as ascites, electrolyte disturbances, hepatorenal syndrome, portal hypertension, and hepatic encephalopathy. Dr. Sigal's particular interests include managing and evaluating patients who have undergone transjugular intrahepatic portosystemic shunts (TIPS), and caring for patients with hepatocellular carcinoma, especially those who are candidates for percutaneous ethanol injection therapy (PEIT). Dr. Michael Schilsky, recruited from the Albert Einstein College of Medicine in 1999, is a recognized expert on disorders of metal metabolism, including hereditary hemochromatosis and Wilson's disease (13–17). Dr. Schilsky is currently participating in an FDA-sponsored pharmacologic trial with Dr. George Brewer of the University of Michigan, to determine the best initial therapy for the treatment of patients with Wilson's disease and neurologic symptoms. This study is being conducted in Mount Sinai's General Clinical Research Center in collaboration with the Department of Neurology. Dr. Schilsky is also a co-investigator in the National Hemochromatosis Transplant Registry, which is designed to determine the outcome of patients with hemochromatosis who undergo liver transplant. Along with staff from the surgical intensive care unit (SICU) and colleagues from the Transplant Institute, he is initiating a trial of an extracorporeal liver assistance device (ELAD) for patients with fulminant hepatic failure. Depending on the clinical situation, this device will be used either to provide a bridge to liver transplant or to support the patient during recovery of the native liver. Dr. Berk, an authority on jaundice and the hereditary hyperbilirubinemias (18), also has clinical and research interests in primary biliary cirrhosis, hemochromatosis, the porphyrias, and hepatitis C. Thus, the division has broadened both its clinical expertise and clinical research interests over the past twelve years. It is moving toward a goal of having virtually every patient participate in one of its multifaceted clinical research programs.

Bench Research

The last dozen years have witnessed an explosive growth in the discipline of hepatology, as measured by a tripling of attendance at major national and international meetings devoted to the liver, an increase in the number of books and journals devoted to the specialty, and increased emphasis on training in liver disease within the framework of fellowship programs in gastroenterology. The enormous growth in this field is largely a consequence of two major phenomena: the dramatic increase in liver transplantation and the worldwide epidemic of hepatitis C. What is sometimes overlooked is the equally dramatic growth in the application of such basic disciplines as cellular and molecular biology to the study of liver disease, and the increased basic science content of the entire field, as is clearly reflected both at its meetings and within its published literature. The prominence of basic science within the discipline of hepatology, both nationally and internationally, is reflected in parallel changes within the Division of Liver Disease at Mount Sinai. The division currently conducts four major basic science efforts.

Fatty Acid Transport

When the Berk laboratory moved from Hematology to Liver Disease in 1998, it brought with it a well-established program in hepatic metabolism and hepatic transport. While the focus had for many years been on bilirubin (18), the laboratory's interests were evolving, and by 1988 at least half of the effort was focused on the plasma membrane transport of long chain free fatty acids (LCFFA). LCFFAs are increasingly recognized as important intracellular modulators of gene expression, suggesting that control of their intracellular concentrations through regulation of their cellular uptake and efflux would be of great value. However, cellular uptake of LCFFA was long considered an entirely passive, and therefore unregulated, process of relatively little intrinsic interest. Over the past 15 years, studies in the Berk laboratory, which have included research assistant professors Drs. Michael Bradbury and Shengli Zhou, as well as Dr. Xinqing Fan; Decherd Stump, and Chih-Li Kiang, have established that LCFFA uptake under physiologic conditions is mainly a facilitated transport process (19). The laboratory also identified the first putative LCFFA transporter, initially designated "plasma membrane fatty acid binding protein" (FABPpm). Tissue-specific regulation of the expression of this protein and of facilitated LCFFA transport occurs in several cellular and animal models of human disease. In particular, LCFFA uptake is selectively up-regulated in adipocytes, but not in other critical tissues such as liver and cardiac muscle, in a variety of rodent models of obesity and non-insulin-dependent diabetes mellitus (20, 21). The net effect of this change is to divert LCFFA from skeletal and cardiac muscle, where they would be consumed for energy production, into adipose tissue, where they are stored as fat. Thus, the observed changes in LCFFA disposition contribute to perpetuation of the obese phenotype. Conversely, ethanol was found to up-regulate LCFFA uptake selectively in hepatocytes, contributing to alcohol-induced fatty liver (22). Somewhat surprisingly, FABPpm proved to be identical to mitochondrial aspartate aminotransferase (mAspAT) (reviewed in reference 19). Molecular modeling studies of mAspAT, carried out in collaboration with Dr. Frank Guarnieri of the Department of Physiology and Biophysics, have identified a previously unrecognized hydrophobic cleft of suitable size to be an LCFFA-binding site. His laboratory has shown that the plasma membrane and mitochondrial components of mAspAT are both derived from a single message; sorting of the protein to different sub-cellular sites does not involve alternative splicing of the mRNA (23). Ongoing cell biologic studies are elucidating the complex route by which mAspAT traffics to the plasma membrane and is exported from the cell.

Studies of the Hepatitis C Virus

The hepatitis C virus (HCV), now recognized as the principal causative agent of non-A,

non-B hepatitis, was first discovered in 1989. Its ~9 kb RNA genome encodes a single polyprotein that is subsequently cleaved by both host and virally encoded enzymes to the various recognized structural and nonstructural proteins characteristic of HCV. Of approximately 4 million Americans who have antibody evidence of having been infected with HCV, only some 15% appear to clear the virus spontaneously. The remainder experience chronic hepatitis of variable severity that persists for decades. Approximately 20% eventually develop cirrhosis and, ultimately, the complications of end-stage liver disease. Chronic HCV infection is now the most frequent indication for liver transplantation in the United States and Western Europe.

The biology of the virus remains poorly understood. Because of the division's growing clinical involvement with hepatitis C, Dr. Andrea Branch, an outstanding authority on plant viroids and on the delta agent (hepatitis D virus, HDV), was recruited from Rockefeller University in 1994 to develop a program of basic studies of the HCV virus. Her highly reasoned critical reviews of what is known about hepatitis C (e.g., reference 24), and of the potential strengths and weaknesses of conventional approaches to both antisense therapy (25–28) and gene therapy (29, 30), have very quickly established her as an important and creative contributor to the field. Recognizing that viral genomes often have overlapping genes, Dr. Branch and her associates, in particular Dr. Jose Walewski and Decherd Stump, developed software that has facilitated their comparative sequence analyses of published HCV isolates, in an effort to identify overlapping, dual-use regions. Their strategy for identifying such regions is based on the degeneracy of the genetic code. Thus, the code for a number of amino acids is fully specified by the first two bases of a codon. Since the third base in this situation is of no consequence for defining the encoded amino acid, it would be anticipated that, over time, random mutations would have resulted in the given amino acid being encoded by any of four sequences, with the same bases in positions 1 and 2, and A, T, G or C in position 3. This variability in position 3 would have no effect on the amino acid sequence of the encoded polypeptide. However, if there were an overlapping reading frame, an insignificant change in base position 3 in one reading frame could produce a significant alteration in the amino acid composition of a polypeptide encoded in an overlapping, alternative reading frame. Based on these theoretical considerations, diverse HCV sequences were obtained from GenBank (Bethesda, MD), and aligned. The proximal portion of the main open reading frame (ORF) was found to contain a region of highly constrained sequence, in which the third base in numerous codons was far more restricted than would be anticipated by chance. When read in the alternative 1+ reading frame, nearly 90% of the retrieved sequences contained at least 124 codons without a stop codon, representing a candidate second or alternate ORF. By contrast, within the same region of HCV RNA, the 2+ reading frame was riddled with stop codons. To determine if this alternate ORF (A-ORF) was biologically significant, two peptides, representing different regions of the encoded A-ORF polypeptide, were synthesized and used to develop assays to detect antibodies against the A-ORF protein. Analysis of sera from patients with chronic HCV demonstrated that an appreciable proportion of them contained antibodies to the A-ORF protein (31), indicating that the protein must be synthesized during chronic HCV infection. Efforts are now ongoing to identify the protein itself in liver samples from infected patients. The identified protein may be of value in improved HCV diagnostics. Moreover, the new protein, as well as the uniquely conserved region of the HCV genome that encodes it, are potential targets for a variety of new anti-HCV therapeutic strategies. It is likely that therapies developed on the basis of these observations will eventually undergo clinical evaluation within our program at Mount Sinai.

Mechanisms, Diagnosis and Treatment of Hepatic Fibrosis

Dr. Scott Friedman, a graduate of the MSSM (class of 1979), returned as a faculty member and director of research in the Division of Liver Disease in November 1997. His return followed an absence of 18 years, which included 15 years at the University of California San Francisco (UCSF), first as a gastroenterology fellow and then as a faculty member. During his tenure at UCSF, he did pioneering research into the underlying causes of scarring, or fibrosis, associated with chronic liver disease. Dr. Friedman was the first to isolate and characterize the hepatic stellate cell, which is the key cell type responsible for scar production in liver (32). This work has led to major insights into how the liver responds to injury, and points the way toward new treatments.

Dr. Friedman's interest in liver disease can be traced directly to Mount Sinai's founding fathers of hepatology, Drs. Schaffner and Popper, whose lectures planted the seeds of interest that led to his specialty. Remarkably, his experimental studies have followed directly from earlier observations by Drs. Popper and Schaffner, who emphasized the stellate cell's potential importance in liver disease. From this initial finding, Dr. Friedman's research has expanded into a comprehensive program exploring the cellular and molecular basis of liver fibrosis, which has spawned parallel efforts in dozens of laboratories and pharmaceutical companies throughout the world (33–38). Liver fibrosis, leading ultimately to cirrhosis, is a serious consequence of excessive alcohol consumption (39), and has assumed major importance as a potential treatment target for the millions of patients infected with hepatitis C (40). In addition to continuing an in-depth exploration of molecular mechanisms of hepatic fibrosis, he is collaborating with Dr. Frank Eng and several other colleagues, in the clinical realm, with the testing of novel diagnostic agents and therapies for hepatic fibrosis. Much of the current excitement about the potential benefits of anti-fibrotic therapy in these important liver diseases can be traced to Dr. Friedman's contributions.

The Pathobiology of Primary Biliary Cirrhosis

Mount Sinai has had a major and productive interest in primary biliary cirrhosis (PBC) for nearly 50 years, with important studies by Drs. Popper and Schaffner illuminating its clinical spectrum, natural history, and histopathologic evolution, as well as the nature and significance of cholestasis. This interest led to the accumulation of a large group of PBC patients, who have participated in numerous trials of medical therapies, and have provided many candidates for Mount Sinai's liver transplant program. Mount Sinai is currently following as many as 600 patients with this uncommon disease, including more than 100 who have received liver transplants and a similar number with advanced disease, who are currently being followed in the pretransplant clinic. The remainder, at earlier stages in their disease, are being followed in either the Liver Disease Associates FPA suite or the Liver Clinic.

As a result of this unique experience, the Artzt Family Foundation Trust recently provided the division with a three-year grant to initiate the Center for the Study of Primary Biliary Cirrhosis at Mount Sinai. The Center will support both clinical and basic science initiatives related to PBC. A major component of the clinical program is the development of a unique patient database, which will eventually contain patient data not only from Mount Sinai, but also from collaborating centers around the world. The database, under development with the assistance of Computer Associates (Islandia, NY), will incorporate *neugents*, a unique artificial intelligence tool capable of identifying previously unrecognized trends and correlations in very large data sets and using them for the formulation of new hypotheses. This database will also support future clinical trials, some of which, we anticipate, will be designed to test hypotheses developed with the *neugents* technology. A serum and tissue bank, linked to the database, will be an important resource for laboratory investigations. The Center is already supporting basic studies in several laboratories, including those of Drs. Berk, Branch, Friedman and Thung. For the most part, these studies represent an extension of ongoing work, such as studies of mitochondrial protein trafficking and hepatic fibrosis, as well as relevant aspects of PBC. A critical component of the program, however, is the creation of a new laboratory devoted specifically to the immunology of PBC. Dr. Joseph Odin, an alumnus of Mount Sinai's M.D./Ph.D. program, has been recruited back to his alma mater from the Johns Hopkins School of Medicine to create this new program. Dr. Odin has had a long interest in the immunology of PBC and most recently has been investigating the role of apoptosis of biliary epithelial cells in the generation of the antimitochondrial antibodies that are characteristic of this disease.

Hepatology in the New Millennium

The Mount Sinai Division of Liver Disease, by virtue of its long tradition and extraordinary recent development, is perfectly positioned to exploit the explosive growth in biomedical research now being witnessed worldwide. This era of science, driven in part by the impending completion of the sequencing of the human genome, is a "golden age of biology," much as the 1940s and 1950s were a golden age for physics, with the harnessing of nuclear energy. Moreover, the trajectory of anticipated divisional growth is aligned perfectly with the institutional commitment to translational research, as articulated in Dean Arthur Rubenstein's Strategic Plan.

What new advances can we expect in the field — at Mount Sinai and elsewhere? New computer technologies, such as the unique patient database described above, will allow investigators to gather and analyze data from patients with PBC and other liver diseases, with a level of sophistication not even dreamed of only 5 years ago. Laboratories within the Division of Liver Disease at Mount Sinai will make major contributions to improvements in molecular diagnostics and imaging for viral hepatitis and its fibrotic complications. This will reduce the need for invasive methods of assessing liver disease. Antiviral therapies for the treatment of hepatitis B and C will be continually refined, and will include new therapeutic tools such as ribozymes, in addition to improved versions of conventional antiviral drugs. Along with better characterization of genetic and host factors that influence prognosis and response to therapy, these will lead to improved outcomes for medical treatment of these serious illnesses. Improved understanding of the immunopathogenesis of PBC will permit the development of rational, successful medical therapy for this disorder as well. Basic studies of the membrane transport of fatty acids will provide insights that will foster specific therapies for steatohepatitis, as well as for disorders such as obesity and non-insulin-dependent diabetes mellitus, which are not primarily diseases of the liver. Antifibrotic therapies, already in early clinical trials, will be refined on the basis of still further understanding of the fibrotic process, and will delay the evolution of cirrhosis across a wide spectrum of liver diseases, even those for which the underlying pathogenesis is incompletely understood: These advances, in all of which Mount Sinai scientists will play a major role, will reduce the need for liver transplantation for many patients, thereby bringing into more reasonable balance patient needs and the limited supply of donor organs.

The progressive maturation of gene therapy will overcome current obstacles and achieve safe, targeted delivery and sustained function of a variety of genes. Isolated hepatocyte transplantation will also find a role in the treatment of genetic diseases of the liver and, perhaps, of some acquired forms of liver failure. These complementary modalities have the ability either to replace genetically deficient gene function or to augment acquired deficiencies of function, for a spectrum of disorders from fulminant liver failure to malignancy. These efforts will be informed by the knowledge of the human genome sequence in ways that cannot be predicted, and totally new paradigms of cellular and integrative biology are sure to emerge. Equally certain is that growth in biological understanding and therapy will dramatically enhance collaboration among Mount Sinai's programs in liver disease, neoplastic diseases, pediatrics, and genetics. Although these medical advances will decrease the need for liver transplantation, transplants will remain a crucial therapy of last resort. Transplantation biologists from the Immunobiology Center and the Transplantation and Gene Therapy Institutes, working in collaboration with the Division, will discover the optimal modes of immunosuppression that can prevent liver rejection and minimize complications. For desperately ill patients awaiting liver transplantation, new modalities will be developed as a bridge to liver transplantation, using either extracorporeal devices or molecular reconstitution of liver function. The Transplantation Institute will continue its pioneering role in creating new surgical options for patients requiring liver transplantation, as exemplified by the recent growth in living-related-donor transplantation surgery.

Underlying all these efforts will be the sustained growth in interdisciplinary science that is so vital to success in this golden age of biology, combining the expertise of basic scientists and clinicians in divisions and departments throughout the institution. This critical ingredient will create synergy in all aspects of science and clinical care. These activities, in turn, will continue to rely on the support of the NIH and other federal agencies, pharmaceutical partners, grateful patients and generous patrons. Now, as much as ever, the Mount Sinai Division of Liver Disease — together with its many institutional partners — is on course to maintain its role as a world leader in understanding and treating patients with liver diseases.

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The Mount Sinai Division of Gastroenterology at the Beginning of the 21st Century

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Abstract

The Mount Sinai Division of Gastroenterology has an international reputation for outstanding contributions to the study of digestive diseases, especially inflammatory bowel disease. A discussion of the current structure of the gastroenterology (GI) fellowship training program is provided, along with an overview of the GI Division at the turn of the 21st century.
Key Words: Gastroenterology, The Mount Sinai Hospital, twenty-first century.

Introduction

THE DAWN OF A NEW CENTURY is an appropriate time to survey the medical advances of the past one. The scientific community has just reported the sequencing of the human genome. The tremendous achievement of the Human Genome Project is a tribute to how rapidly scientific knowledge is advancing. Gene therapy may become a reality in the delivery of health care during this new century. It has been said that biological science's knowledge is doubling every 180 days (1). This exponential increase in scientific knowledge probably underlies the fact that half of the increase in the average life expectancy in recorded history occurred within the last century (2). Curiously though, most of this increase occurred in the first half of the old century. Advances in public hygiene and disease prevention, even more than medical interventions, account in large part for the rise in life expectancy from 47 years in 1900 to 78 years in 1995 (2). Preventive medicine has had a tremendous impact in some areas, such as infectious forms of diarrheal illness, although these remain a major cause of death in many underdeveloped countries.

The specialty of gastroenterology combats these and other diseases of the gastrointestinal system. Possibly its greatest single advance in the past century was the development of oral rehydration therapy for cholera, which was based on scientific understanding of the processes involved in intestinal absorption. The abundance of serious gastrointestinal diseases ensures a constant need for individuals trained in the specialty of gastroenterology and committed to advancing public health. This article will provide an overview of the current gastroenterology training program of The Mount Sinai School of Medicine.

Gastroenterology Fellowship Training

There are currently 250 gastroenterology (GI) residency (fellowship) programs in North America. In the mid-1990s, the duration of gastroenterology fellowships in the U.S. was extended from two to three years, in recognition of the growing complexity of the specialty and to provide sufficient time for fellows to pursue

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scholarly activity during their training. Reflecting the major scholarly disciplines within the specialty, the American Gastroenterological Association currently consists of 11 sections (Table 1). Although this structure was created partly for organizational purposes, it reflects the major areas of training and competence that are expected of modern gastroenterologists. Along these lines, the Gastroenterology Leadership Council (GLC) established a curriculum that attempts to standardize education of the gastroenterology trainee (3).

The three-year fellowship program at the Mount Sinai Division of Gastroenterology provides at least 18 months of clinical training. The remaining time is devoted to specialized research. The clinical training consists of consultative experience in both the in-patient and out-patient settings, learning how to perform endoscopic procedures, and training in hepatology (including the complexities of liver transplantation). The Mount Sinai GI Fellowship program presently includes experience on four campuses: The Mount Sinai Hospital, the Veterans Affairs Hospital in The Bronx, The Mount Sinai Services at the City Hospital Center at Elmhurst, and Queens Hospital Center. Thus, it exposes the GI fellow to a variety of patient populations and faculty expertise. There are currently 12 fellows in the program.

All fellows, as part of their training, are required to pursue either clinical or laboratory-based research (Table 2). The fellow selects a topic of interest and is paired with an appropriate faculty mentor, who helps to develop the line of investigation. In addition to personal mentoring, fellows attend institution-wide conferences and lectures that further develop their knowledge base. Fellows also have many opportunities to develop their public speaking skills at internal conferences, and by the end of their three-year fellowship, it is expected that all fellows will have presented their own work at local and national meetings.

TABLE 1
Sections of the American Gastroenterological Association

Biliary Disorders
Clinical Practice
Esophageal, Gastric, Duodenal Disorders
Gastrointestinal Oncology
Growth, Development and Aging *
Hormones, Transmitters, Growth Factors and their Receptors
Immunology, Microbiology and Inflammatory Disorders
Intestinal Disorders
Motility and Nerve Gut Interactions
Nutrition
Pancreatic Disorders

* As part of the Strategic Plan of the AGA to enhance research and education in nutrition, in the Year 2000 the Growth, Development and Nutrition section was renamed Growth, Development and Aging, and a new Nutrition section was established.

A particular strength of the Mount Sinai Division of Gastroenterology is in the field of inflammatory bowel diseases (IBD). Training in IBD is facilitated by the availability of a large patient population with these diseases, and considerable depth of faculty in this area. Research in the field of IBD at Mount Sinai includes a rather comprehensive variety of topics, including basic immunopathogenetic mechanisms, genetic susceptibility, experimental therapeutics, research on classification and natural history of IBD, new surgical therapies for IBD, outcome measures (such as quality of life) and treatment of complications following ileal pouch anal anastomosis procedures, and basic mechanisms and clinical management of colitis-associated neoplasia. Fellows participate in these projects under the guidance of faculty mentors. In addition, a special one-on-one IBD preceptorship has been in place for many years. Under the supervision of a master clinician, this rotation has each senior fellow spending time learning the art of the consultation and gaining experience with ambulatory and in-patient gastroenterology. This valuable training experience, initially under the skilled guidance of Dr. Henry Janowitz (4), has more recently been supervised by other master clinicians, including Dr. David Sachar and Dr. Daniel Present. In 1999, Dr. Present established a new training opportunity for fellows from outside institutions to spend an intensive year of research and patient care devoted to IBD, with the goal of having this fellow return to his or her home program to further enhance its IBD program.

As part of their learning experience in consultative gastroenterology, all fellows receive superb training in endoscopic procedures. The chief of Endoscopy, Dr. Jerome Waye, is a highly gifted teacher, who along with a staff of highly proficient endoscopy faculty, personally supervises fellows in the indications and techniques of endoscopy.

Mount Sinai also has a strong tradition in the study of liver diseases (5), which led to the creation of a separate Division of Liver Disease. All gastroenterology fellows at Mount Sinai obtain outstanding training in hepatology. During the rotation on the Liver Disease ser-

TABLE 2
Research Projects in the Division of Gastroenterology

Field	Topic	Principal Investigator(s)
	Basic Research	
Gastrointestinal Oncology	Pathobiology of mucins in GI cancer	Steven Itzkowitz
	Gene therapy of metastatic colon cancer	Steven Itzkowitz, Mark Babyatsky
	H. pylori in gastrointestinal lymphoma	Steven Itzkowitz, Lawrence Werther
Mucosal Immunity	Neuropeptides in IBD	Mark Babyatsky
	Epithelial cells in IBD	Lloyd Mayer
	Mucosal cytokines in IBD	Lloyd Mayer, Scott Plevy
	Genetic susceptibility to IBD	Scott Plevy, Lloyd Mayer
	Clinical Research	
Inflammatory Bowel Disease	Novel immunomodulatory agents/IBD	Daniel Present, David Sachar, Lloyd Mayer, Asher Kornbluth, James Marion, Ellen Scherl, Simon Lichtiger, Samuel Meyers, James George, Lisa Toy
	Ileal pouchitis — therapy, natural history	David Sachar, James Aisenberg
	Quality of life — outcomes research	Anthony Weiss
Gastrointestinal Oncology	Cancer in IBD	Steven Itzkowitz, David Sachar, Jerome Waye, Daniel Present, Peter Rubin, Thomas Ullman
	High-risk colon cancer registry	Steven Itzkowitz
	Neuroendocrine tumors	Richard Warner
Endoscopic Research	Colonoscopic tatooing	Jerome Waye
	Novel endoscopic cautery techniques	Jerome Waye
	Biliary endoscopy	David Jaffe
	Endoscopic ultrasound	Harry Snady, Thomas Riley, Anthony Borcich
	Ischemic bowel disease	James George
Motility Disorders	Spinal cord injury	Mark Korsten
	Gastric and small intestinal motility	Mark Korsten
	Collagen vascular diseases	Barry Jaffin
	Pelvic floor dysfunction; incontinence	Suzanne Rose
	Esophageal motility disorders	Lawrence Cohen
Irritable Bowel Syndrome	Combined medical/psychological therapy	Charles Gerson
	Novel probiotic therapies	Gerald Friedman

vice, they focus on the evaluation and treatment of patients with complex liver disease (pre- and post-transplant). The other three campuses feature unified GI/liver consultative experiences, affording additional training in liver disease. For the GI fellow with a particular interest in pursuing a career in hepatology, the third year of the three-year fellowship can be completely devoted to training in liver disease. In addition, the Division of Liver Disease offers a specialized fourth year of training.

As an integral part of fellowship education experience, the GI Division offers an extensive menu of teaching conferences (Table 3). In addition to these conferences, fellows rotating on the other campuses are exposed to separate pathology, radiology, and clinical conferences conducted on those campuses. While rotating on the Mount Sinai Liver Disease service, fellows attend conferences within the Division of Liver Disease, including liver pathology, ambulatory liver diseases, journal club and grand rounds. All GI and Liver fellows at Mount Sinai are expected to attend weekly Department of Medicine grand rounds, weekly GI/Liver Research Seminar and the bi-weekly Molecular Medicine/Dean's Lecture Series, which features outstanding scientists dis-

TABLE 3
Conferences in the Division of Gastroenterology

Conference	Description
1. GI Grand Rounds	
Summer Lecture Series:	This series of 10–12 weekly Friday morning conferences introduces fellows to basic and clinical pathophysiology and to fundamentals of managing the most common sites and categories of disease seen in GI practice.
Controversies in Gastroenterology:	Interdisciplinary panels discuss realistic cases of the commonest clinical problems in gastroenterology, exploring diverse viewpoints concerning the safest and most cost-effective approaches to prevention, diagnosis, and treatment.
Clinical Trends & Topics:	Clinical outcomes, complications, and quality assurance issues are discussed in depth, centering around real cases identified in quality review exercises. The Gastroenterology fellow prepares presentations of literature reviews and evidence-based conclusions in collaboration with the faculty moderator.
Fellow's Pathophysiology Seminar Series:	With a single thematic topic running throughout the academic year, each GI fellow chooses a particular aspect of the topic, researches it in depth, and presents a full and formal slide-illustrated lecture on it to the entire division. Fellows are supervised by a faculty mentor.
IBD Case Conference:	GI fellows present a patient with IBD who exemplifies a particular management problem. A multidiscipliinary panel discusses the medical, surgical, pathological, and radiological aspects of the case, followed by a literature review prepared by the fellow.
Invited Lectures:	Clinical and basic science topics are covered by speakers from inside and outside the Medical Center.
2. GI Endoscopy Conference	A weekly conference led by the chief of Endoscopy, highlighting interesting diagnostic or management problems. Videotapes are presented by gastroenterologists and laparoscopic surgeons.
3. GI Fellows' Endoscopy Conference	A weekly conference attended by GI fellows during which the chief of GI Endoscopy demonstrates lesion recognition, and discusses the latest innovative therapeutic endoscopic technologies and issues related to proper indications for performance of endoscopy.
4. GI Pathology Conference	A weekly conference at which fellows present their biopsies of the preceding week to the senior GI Pathology attending and other GI attendings for review and discussion regarding diagnostic and management decisions. Operative specimens and autopsy results are also presented and discussed.
5. Chief's Rounds	At this bi-weekly conference, fellows meet with the director or director emeritus of the division to present a noteworthy recent case. A strong emphasis is placed on the reading and interpretation of GI x-rays. Fellows are expected to provide literature that offers some insights into the clinical entity they are presenting.
6. GI Journal Club	A bi-weekly journal club is held, consisting of a topic-oriented approach to interpreting the medical literature and mastering the statistical methods. Statistical concepts and study design are addressed in detail through homework assignments at each session.
7. Ambulatory Care Conference	This bi-weekly conference immediately precedes Continuity Clinic. Fellows present one of their own clinic patients who manifests a particular management problem, and use an evidence-based medicine (EBM) approach to review the literature on the subject. A final management decision for the patient is then reached in conjunction with faculty.
8. Motility/Dysphagia Conference	A monthly conference that gives fellows an understanding of the indications and potential pitfalls in the performance of motility studies.
9. Pancreaticobiliary Conference	This monthly interdisciplinary conference brings together physicians and investigators from Gastroenterology, Liver Disease, Laparoscopic Surgery, Hepatobiliary and Transplant Surgery, and Diagnostic and Interventional Radiology to discuss interesting, problematic, and illustrative pancreatic and biliary cases.
10. GI/Liver Research Seminars	This weekly conference provides a forum for principal investigators from outside and within the institution to present research related to GI and liver disease.

cussing a broad range of clinical and basic science topics.

The GI Division is also responsible for undergraduate teaching programs. The first-year medical students are taught basic histology and anatomy of the GI tract by the Gastroenterology faculty in conjunction with faculty in the Department of Anatomy and Cell Biology. Second-year students receive an intensive, 6-week course on GI/liver pathophysiology, which integrates concepts of pathophysiology, diagnostic strategies, medical and surgical management, geriatrics, pediatrics, and bioethics. In addition to core lectures, case-based small group discussions are led by GI and Liver faculty. Medical students in third- and fourth-year clinical clerkships are expected to see and examine patients with gastrointestinal and liver diseases and interact with faculty preceptors, including those in Gastroenterology and Hepatology.

Leadership of the Gastroenterology Division of The Mount Sinai School of Medicine

In 1958, the Division of Gastroenterology was founded by Dr. Henry D. Janowitz, who served as its director until 1983. As a tribute to Dr. Janowitz's service to the GI Division and his international reputation, in 1992 the GI Division was officially endowed as the Dr. Henry D. Janowitz Division of Gastroenterology, becoming the first named GI division in the country.

In 1983, Dr. David B. Sachar became the second chief of Gastroenterology. Dr. Sachar was invested as the first Burrill B. Crohn Professor of Medicine in 1992.

Dr. Steven H. Itzkowitz assumed leadership of the Dr. Henry D. Janowitz Division of Gastroenterology on July 1, 1999, and was inducted as the second Dr. Burrill B. Crohn Professor of Medicine in September 1999. Dr. Itzkowitz, an alumnus of the Mount Sinai School of Medicine (Class of 1979) was recruited from the University of California at San Francisco, where he served as a GI fellow and subsequently as assistant professor of Medicine. He served as associate director of the division from 1993–1999, and is currently chair of the GI Oncology Section of the American Gastroenterological Association, and president of the New York Gastroenterological Association.

Faculty of the Division of Gastroenterology

The division's faculty currently consists of 50 physicians, including seven full-time gastroenterologists, representing a broad diversity of expertise. Faculty members contribute to the teaching program by mentoring GI fellows in research, supervising endoscopy, teaching fellows, medical residents and students on the consultation service and in the clinic, and participating in conferences.

Many of the currently active gastroenterologists have achieved international prominence and recognition for making major contributions in their area of expertise (see also Table 2). These include Jerome Waye (chief of Endoscopy; founder and developer of new endoscopic techniques), Daniel Present (developer of novel immunomodulatory therapies in IBD), J. Lawrence Werther (role of the gastric mucous barrier and *Helicobacter pylori* in acid peptic disease and gastric cancer), Mark Chapman (role of gastric acid secretion in peptic ulcer disease), Charles Lieber (alcoholic liver disease), Richard Warner (neuroendocrine tumors), Gerald Friedman (gastrointestinal pharmacotherapeutics and irritable bowel syndrome), Charles Gerson (physiology of the small intestine and irritable bowel syndrome), Samuel Meyers (medical therapy of IBD), Peter Rubin (endoscopic management of neoplasia in IBD), Simon Lichtiger (medical therapy of IBD), Mark Korsten (pancreatitis and gastrointestinal motility disorders), Blair Lewis (small bowel enteroscopy and endoscopic evaluation of gastrointestinal bleeding), Asher Kornbluth (medical therapy of IBD), Mark Babyatsky (role of neuropeptides in IBD and mucosal restitution), Lawrence Cohen (esophageal diseases), Barry Jaffin (gastrointestinal motility disorders) and Suzanne Rose (gastrointestinal motility disorders and medical education).

The Gastroenterology Service of The Mount Sinai Hospital

The Mount Sinai Hospital has more than 1200 beds, of which 600 are on teaching services. Two hundred of these are occupied by patients with gastrointestinal disease. The facilities include a new state-of-the-art pavilion designed by the famous architect, I.M. Pei, completed in 1992. In 1995, gastroenterology patients on both medical and surgical services were consolidated into an autonomous, integrated GI Care Center with its own dedicated teams of house staff and teaching attending physicians. Recently renamed the GI-Surgical Subspecialties Care Center (GISS-CC), it offers the benefit of centralized administration. Perhaps more important, it streamlines the delivery of nursing care and social service support by staff who are familiar with issues relevant to the GI patient (for example, adjusting to and caring for a new ileostomy). House staff in the Department of Internal Medicine rotate on the GI-Surgical Subspecialty Care Center for two months during their three years of internal medicine training and become familiar with the diagnosis and management of complex GI and liver diseases. During their rotation, they are supervised by a GI and a Liver attending whose primary purpose is to teach these residents. With teams of medical and surgical residents making rounds on the same ward(s), interaction between them is greatly facilitated. The Gastroenterology fellow assists the medical house staff with the management of GI patients, including any procedures that are indicated, and also functions as a liaison between the house staff and the Gastroenterology attending physician. To assure continuity of care, upon discharge from the hospital, any patient who does not have his/her own private doctor can be followed in the clinic by the Gastroenterology fellow who cared for him/her in the hospital.

In addition to caring for patients on the inpatient GISS-CC Teaching Service, Gastroenterology fellows are assigned to handle requests for consultations from other services in the hospital. Daily clinical records, consultations, and the performance of procedures during the three weekly endoscopy sessions are always under the supervision of an attending physician.

In the ambulatory GI clinic, new patients are seen by Gastroenterology fellows alone with those they have seen previously in the clinic or hospital. A separate Continuity Clinic is specifically designed for fellows to see their own cadre of patients, with whom they have established a relationship based on prior inpatient or outpatient care. The regular Mount Sinai GI clinics meet twice a week and are supervised by the same attending physicians throughout the entire year. The fellows have complete responsibility for their outpatients, who may call them for medical advice at any time.

Conclusion

Training in gastroenterology is becoming increasingly more complex and specialized, in keeping with rapid advances in medical knowledge and technology. We live in an exciting time, when sophisticated biotechnology can make a tremendous impact on how we treat, and even think about, disease. The application of new knowledge together with powerful molecular tools to treat and prevent digestive diseases should allow us to make an even greater impact on public health in the next century.

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Pediatric Gastroenterology at The Mount Sinai Hospital

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Abstract

The history of pediatric gastroenterology at Mount Sinai begins in 1960. Early publications by Drs. Korelitz and Gribetz on the management of inflammatory bowel disease in children served as the preface to forty years of progress in this important area. The history of pediatric gastroenterology includes important work by many individuals, including Horace Hodes, Lotte Strauss and Frederick Kopel. Early observations on the nature of inflammatory bowel disease (IBD), and its course, preceded work on nutritional therapies for IBD, mechanisms of gene-nutrient interactions, regulation of gene transcription, and molecular processes involved in bile transport in the liver and small intestine. Over the last twenty years, the division has grown in size and reputation. Today there are fourteen full-time faculty – 9 M.D.'s and 5 Ph.D.'s – who work in three funded research laboratories. There are also five advanced practice nurses (including three nurse practitioners), two social workers and two nutritionists, as well as several administrators and assistants. In addition to being recognized as a premier center for the treatment of children with general pediatric gastroenterological problems especially inflammatory bowel disease, the division is also known as one of the nation's largest pediatric liver and liver transplant centers, and it is rapidly becoming one of the largest pediatric short gut syndrome and small bowel transplant centers.

Key Words: Pediatric gastroenterology, inflammatory bowel disease, liver disease, short gut syndrome, liver transplant, small bowel transplant, Mount Sinai.

DR. FREDERICK KOPEL was probably the first "official" pediatric gastroenterologist at The Mount Sinai Hospital, specializing in cystic fibrosis. In the 1960s, Kopel was encouraged by Drs. Fenton Schaffner and Hans Popper to learn and adapt the techniques of liver biopsy to pediatrics. Dr. Lotte Strauss, together with Popper, studied neonatal hepatitis and attempted to correlate what was seen histologically through the microscope with what was seen clinically and biochemically. Kopel also joined Burton Korelitz and Donald Gribetz to publish a major report on granulomatous colitis (1). This work emphasized the importance of appropriate medical management for granulomatous disease, in contrast to the recommendations for surgery in ulcerative colitis.

Inflammatory Bowel Disease

Korelitz and Gribetz were struck by the devastation that resulted from inflammatory bowel disease (IBD) in children. They systematically examined the natural course of IBD in the pre-steroid era and mentored one of their residents, Dr. Irwin Danziger, as he sought answers to important questions in pediatric gastroenterology. Korelitz, Gribetz and Danziger reviewed the records of children with IBD followed at that time by Korelitz and seen at Mount Sinai (2). They noted that, in the era before anti-inflammatory drugs, most children seen in the hospital became very ill, and many died. Anecdotal reports relate many animated discussions between Dr. Horace Hodes, the then-chief of pediatrics, who staunchly advocated medical management, and the wellknown surgeon, Dr. John Garlock, chief of one of the surgical services. Drs. Garlock and Ginzburg usually favored surgical management. Danziger's review of the records suggested that if a child survived for two years after being hospitalized for severe colitis, not only was that child very fortunate, even remarkable, but that even after the two years the child might still become very ill. His review of patients with ulcerative colitis supported the surgical approach advocated by Garlock. Although this preemptive operative approach for these children was seriously criticized, Ehrenpreis concluded that a child with severe, acute colitis should be made as well as possible, and that the colon should be removed early in the course of the disease (3).

The work by Korelitz, Gribetz and Danziger reflects the highest level of pioneering work in pediatric gastroenterology. Their studies of the prognosis of ulcerative colitis with onset in childhood in the pre-steroid era are historic. To quote from their discussion (2), "the relentless morbidity menacing the child with ulcerative colitis is given somber testimony by this study of the history of the disease in the pre-steroid era." Korelitz, Gribetz and Danziger (2) also reported that 43% of the children who developed ulcerative colitis in the pre-antimicrobial era died as a result of their disease, the mean age of death occurring at 22 years. After the development of antibiotics, that mortality was cut in half, but was still 22%, with a mean age at death of 17 years. The article, which detailed the complications and long-term follow-up, is a landmark in the study of pediatric inflammatory bowel disease. The companion paper by Korelitz and Gribetz on the prognosis of ulcerative colitis with onset in childhood, in the steroid era (4), was also important. They reported that with the use of adrenocorticotrophic hormone (ACTH) and adrenal steroids, the number of complications from ulcerative colitis (inflammatory bowel disease) has "not been obviously reduced." The number of patients with ulcerative colitis treated by surgery increased during the early years of this period, and surgery seems to have been performed when the patients were less ill. This reduction in urgent surgery seems to have been accompanied by fewer operative stages and fewer operative complications in morbidity and mortality. After six years of disease, 30% of the patients had ileostomies, but almost 90% were alive and 40% were well without definitive surgery. The authors concluded that the response to steroids helped determine which children with inflammatory bowel disease would benefit from colectomy. They concluded that surgery should be performed early enough to avoid irreversible complications of the disease and to minimize surgical mortality.

The Mid-1970s

Events occurring in the mid-1970s (1973–1974), while Horace Hodes was Chairman of Pediatrics, confirmed the significance of some of his earlier findings from the 1940s. Hodes, while studying diarrhea in calves, had found a filterable (viral) agent that could not be identified with the existing technology; stool samples were frozen for future investigation. Years later, with the use of electron microscopy, it was discovered that the viruses he had isolated, but not identified, belonged to the same family of viruses that was found to cause infantile winter diarrheas, i.e., rotavirus (personal communication).

In 1975, Gribetz and Korelitz worked with another Mount Sinai pediatric resident, Dr. Michael Berger, to report their findings of growth retardation in children with ulcerative colitis, and the effects of medical and surgical therapy (5).

After Kopel's untimely death, in 1971, Dr. Richard Bonforte helped fill the void. He worked with the then-chief resident, Dr. Neal LeLeiko, to re-establish the sweat test as the procedure for diagnosis of cystic fibrosis. Bonforte established the Cystic Fibrosis Center and the Pediatric Pulmonary Center. LeLeiko went on to the Massachusetts Institute of Technology, where he earned his Ph.D. in nutritional biochemistry and metabolism in the laboratory of Dr. Hamish Munro. He then went to the Boston Children's Hospital to train in pediatric gastroenterology, following which he was recruited (in 1979) by Dr. Kurt Hirschorn, Chairman of Pediatrics, at Mount Sinai, to establish a major division of pediatric gastroenterology.

LeLeiko's expertise was in nutritional metabolism and the use of parenteral nutrition and special feeding regimens to treat children with a variety of diseases, especially inflammatory bowel disease and short gut syndrome. He rapidly established Mount Sinai as a major referral center for children with both ulcerative colitis and Crohn's disease, and his interest in nutritional metabolism led to published papers on energy expenditure in patients with Gaucher's disease (6), inflammatory bowel disease (7), and also in elderly Alzheimer patients (8). LeLeiko, along with Dr. Martin Walsh, studied the use and effects of 6-mercaptopurine on intestinal metabolism and found that often the effects of 6-mercaptopurine could be biochemically mimicked by the use of an elemental diet (9). LeLeiko trained many pediatric gastroenterologists, some of whom have remained at Mount Sinai. Dr. Keith Benkov, for example, became a recognized clinical consultant of the division's clinical practice in caring for children with inflammatory bowel disease. Benkov was invited to discuss the case of a child with inflammatory bowel disease for the case records of the Massachusetts General Hospital (10).

LeLeiko's interest in short gut syndrome and nutrition has continued to develop, and 1999 saw the successful inauguration of the region's first small bowel transplant program.

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Patients whom LeLeiko had been following, and who in past years had been sent to other centers, could now receive all of their care at Mount Sinai.

Of the 26 fellows trained in the division, 8 are now division chiefs and directors elsewhere, 8 are full-time academic pediatric gastroenterologists, 2 full-time laboratory researchers and 8 pediatric gastroenterologists in private practice. The members of the division, under LeLeiko's leadership, continue to see children with inflammatory bowel disease and attract a large number of children with nutritional problems, especially children with short gut syndrome and liver disease

In 1990, the existence of the division's significant liver program was instrumental in New York State authorizing the liver transplant program at Mount Sinai. The pediatric portion of the liver transplant program has developed into one of the major pediatric liver transplant programs in the country. Two of LeLeiko's fellows, Drs. Audrey Birnbaum and Joel Rosh, developed a particular interest in liver diseases and liver transplant, and they helped guide the program through its nascent years. In 1997, Dr. Birnbaum reported, with the rest of the group, on the recurrence of autoimmune hepatitis after liver transplantation (11), thus revising the then accepted view that the disease did not recur. In 1996, Dr. Frederick Suchy, a world-renowned pediatric hepatologist, was recruited as Chairman of Pediatrics. Dr. Benjamin Shneider was recruited from Yale to be director of the division's section for liver diseases.

Current Research

The division has had an active research program. The focus of the work by Walsh and LeLeiko has been on mechanisms of gene transcription in epithelial cells. Research has also focused on the study of gene regulation in the developing and differentiated epithelium and the special effects of nutrition on intestinal epithelium. The current goal of the laboratory is to understand the mechanisms of transcriptional control in epithelial cells. The division's studies have identified transcription factors and cofactors involved in the regulation of the cystic fibrosis transmembrane conductance regulator (CFTR) and N-myc genes. The studies have provided evidence for the function of transcription factors, mediated by protein kinase A and cyclic adenosine monophosphate (AMP), in the modification of chromatin structure and gene transcription. Discovery of a unique member, epithelial cell DNA binding factor-α (ECDFα), of the paired-homeobox class of transcriptional regulatory proteins encoding guanosine triphosphatase (GTPase) activity, has helped our understanding of the importance of these proteins in directing transcription through a GTPase-activated pathway. Analysis of these factors has also helped clarify the role of specific transcription factors in determining the fate of differentiating epithelial cells during development and oncogenesis. Many original research publications in prestigious scientific journals have resulted from this work (12–18). The group has also made significant contributions in this area, in the form of chapters in standard texts and reviews in specialty journals (19–22).

Suchy, working with Drs. M. Ananthanarayanan and An-Qiang Sun, focused on the ontogeny and regulation of bile formation, using the rat as an animal model. Since arriving at Mount Sinai they have focused on Na^+ taurocholate co-transporting polypeptide (ntcp) (NTCP in humans) gene, whose product is involved in the Na^+-dependent uptake of conjugated bile acids from sinusoidal blood into the hepatocyte across the basolateral membrane. They have successfully mapped and localized the chromosome in rat and mouse, and are working on mapping the human gene. In addition, they are in the process of generating transgenic mice that carry promoter regions for ntcp with a reporter gene whose activity can be assayed as an index of promoter activity. Effects of hormones, cytokines, or other agents on the activity of ntcp promoter are of great interest. Studies are in progress using the latest molecular techniques to create "knockout mice" in which the ntcp genes have been deleted. The laboratory also investigates a gene called "sister to p-glycoprotein (spgp) gene," which has been shown to be an adenosine triphosphate (ATP)-dependent bile acid transporter on the canalicular membrane of the hepatocyte, its human homolog has been found to be mutated in PFIC-2 (Progressive Familial Intrahepatic Cholestasis Type 2). The work at Mount Sinai has already resulted in several important contributions to the literature (25–29).

The primary focus of Shneider's research has been to elucidate the regulatory mechanism(s) associated with the ileal sodium-dependent bile acid transporter, including molecular events involved at the developmental and transcriptional levels. Descriptive studies of the response of this system to changes in bile acid homeostasis are also being undertaken in a variety of animal species, including rat, rabbit, and mouse. Other activities include analysis of bile acid transport proteins in acquired human liver disease and in previously poorly understood inherited pediatric liver diseases (28–32).

In 1998, more than 43 students and residents came from 10 medical centers and 6 medical schools to spend time at Mount Sinai. The Division of Pediatric Gastroenterology, with three funded laboratories, consists of 14 faculty (9 M.D.'s and 5 Ph.D.'s), three nurse practitioners, two social workers, three nurses, two medical assistants, and two nutritionists. Each year, approximately 4,000 patient visits are made to the doctors of the division.

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The Evolution of Gastrointestinal Endoscopy at The Mount Sinai Hospital

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Abstract

Gastrointestinal endoscopy came to The Mount Sinai Hospital in the 1950s, along with the Wolf-Schindler gastroscope. In 1961, it was supplemented by the Eder-Hufford semi-flexible esophagoscope and later by the Olympus gastrocamera and then the Hirschowitz fiberoptic instruments from ACMI and Olympus. A formal training program was started by Jerome Waye in 1966 for flexible gastroscopy and esophagoscopy. In 1969, endoscopic retrograde cholangiopancreatography (ERCP) was introduced. Colonoscopy was at first performed under x-ray control, and subsequently replaced by the nonfluoroscopic method of colonoscopic topography, which was developed by Dr. Waye. A full-time nurse who was in charge of the endoscopy unit founded the Society for Gastrointestinal Nurses and Assistants while working at The Mount Sinai Hospital.

Key Words: Endoscopy, esophagoscopy, gastroscopy, ERCP, colonoscopy, Mount Sinai Hospital.

GASTROINTESTINAL ENDOSCOPY came to The Mount Sinai Hospital in the 1950s, when Dr. Albert Cornell personally purchased the first Wolf- Schindler gastroscope (1). The instrument permitted gastric visualization via a series of lenses in the distal half; "flexibility" was achieved with a gentle curvature of 20% from a straight axis. Dr. Harry Yarness introduced the procedure to Mount Sinai after visiting Dr. Schindler and learning it from him. During residency training, Dr. J. Lawrence Werther, who was already interested in gastric physiology, extended his interest to upper intestinal endoscopy and became a teacher of gastroscopy along with Dr. Yarness.

At that time, rigid sigmoidoscopy and proctoscopy were being performed at Mount Sinai by surgeons and gastroenterologists, in a separate operating room (OR) within the ear, nose and throat (ENT) operating room suite. But gastroenterologists were not allowed to perform esophagoscopy, because the ENT service (whose OR was used by Gastroenterology) considered the esophagus to be within their domain. However, the ENT physicians permitted gastroenterologists to use the Wolf-Schindler gastroscope because its optics were fixed at a right angle to the long axis of the instrument, thus rendering it impossible to see the esophagus as the scope was passed through to the stomach.

In 1961 an Eder-Hufford (semi-flexible) esophagoscope was purchased by the Gastroenterology Division. The flexible portion consisted of a coil-spring obturator which passed through the long, rigid esophagoscope and protruded about 7 inches, thereby providing a short, flexible introducer to the otherwise inflexible instrument. The semi-flexible esophagoscope was introduced into the esophagus in a manner similar to that of the gastroscope, with the flexible portion advanced into the posterior pharynx by bending the coil spring with the fingers of the left hand, which had previously been inserted into the mouth. The right hand then swung the rigid portion around as the chin was extended to configure the mouth and esophagus in a straight line. During the procedure, the patient was supine on an examining table, with the head hanging over its edge, permitting the headholder assistant to swing the head down to allow a straight intubation passage. The operator sat on a stool facing the patient. At the proximal end of the esophagoscope was a small telescope which could be rotated into view after the "flexible" obturator was withdrawn. This telescope focused on and magnified the tissue at the distal end of the esophagoscope. Esophagoscopy without the telescope, as performed by ENT physicians, displayed a tiny patch of mucosa 12 mm in diameter, viewed by the naked eye through a hollow tube 50 cm long. Because of

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the constraints imposed by the ENT Department, it was not possible to use this new, semi-flexible esophagoscope in the ENT operating room suite, and its use was confined to the GI clinic. Despite the magnified field visualized with the newer instrument, the ENT Department continued to do standard rigid esophagoscopy.

Preparation for an upper endoscopy was a formidable task. The ENT physicians taught gastroenterologists how to use cocaine to swab the posterior pharynx, providing effective local anesthesia. The pledgets of cocaine-laden cotton balls would be placed on an L-shaped clamp which painted the tongue and soft palate, gradually advancing deeper and deeper into the pharynx, where the swab, continually refreshed in a container of cocaine, would finally come to rest in the vallecular spaces. When the patient no longer retched on having the pledget placed deep into the pharynx, he or she was considered to be adequately anesthetized. Topical anesthesia was applied in a room across the hall from the main operating rooms, and following pharyngeal anesthesia, patients would walk across to the operating theaters, where rigid gastroscopy was performed without sedation. The Schindler rigid gastroscope had a two-inch rubber finger at the tip of the instrument, which aided its passage through the posterior pharynx. Hyperextension of the neck was accomplished as the gastroscope was introduced, because it was fairly rigid and an absolute straight path was necessary to be able to pass the scope from the incisor teeth to the stomach. Once past the cricopharynx, the instrument was rapidly advanced into the stomach. If the esophagus needed to be inspected, the ENT department was requested to perform esophagoscopy.

Light from a tiny bulb at the end of the gastroscope was transmitted through a series of lenses to the operator's eye. Neither fiberoptic teaching attachments nor video monitors were available, and the only view that could be obtained was through the lens at the proximal end of the scope. Since everyone in the room wanted to see any lesion found by the examiner, and photography had not been adapted to these instruments, the endoscopic examination necessarily took a long time when an abnormality was seen. During training sessions, each observer had to line up and take a quick look through the eyepiece as it was being held by the endoscopist. When more time was needed to see the mucosa, to view a lesion or to inspect the stomach, the endoscopist would take a stance in front of the patient, holding the protruding portion of the instrument with both hands, while raising both elbows to ear level. This maneuver would keep others from grabbing the scope during the examination. Since patients were not medicated for the examination, it had to be done as quickly as possible to minimize the discomfort. While endophotographs were unknown, sketches were commonly made of any lesion seen. The duodenal bulb was never visualized, and a complete view of the stomach was rare. Atlases of endoscopy were not available, but attending physicians and students pored over the drawings from the Schindler book of endoscopy (2), which was considered the gold standard.

In 1975, the ENT Department left the operating theaters in the old administration building and moved to new quarters. The Gastroenterology Division was assigned to these vacated suites and was then able to perform both esophagoscopy and gastroscopy without supervision by the ENT Department. Soon, a new "system" was devised, with which esophagoscopy and gastroscopy could be performed sequentially. After completing the inspection of the esophagus with a standard Eder-Hufford esophagoscope, a slim-caliber lateral-viewing gastroscope could be passed through the esophagoscope to inspect the stomach. This modified system was the Eder-Palmer trans-esophagoscopic semi-flexible gastroscope.

The division later obtained a gastroscope with a channel for a small forceps, to allow for taking a biopsy. This was known as the Benedict operating gastroscope, manufactured by the American Cystoscope Makers, Inc. (ACMI), of New York City. When the forceps was extended beyond the gastroscope for only a few centimeters, it passed out of the field of view. In order to accomplish a biopsy, the forceps had to remain in the field of view while suction was applied to deflate the stomach. As the stomach collapsed and the lesion occluded the view, the biopsy forceps were closed and then withdrawn. Thus, adequate biopsies were obtained mainly by chance.

During both gastroscopy and esophagoscopy, air had to be continually insufflated by a hand-held bulb which was pumped throughout the examination. The operator would often hold the bulb in the palm of the hand, pumping it with three fingers while the thumb and forefinger held onto the shaft of the gastroscope to steady, advance, or rotate it.

It was during my fellowship, in 1963, that Hirschowitz's first flexible fiberoptic instrument became commercially available from ACMI. Dr. Gerald Friedman and I, co-fellows, carried this fiberscope from floor to floor, showing the house staff and attending physicians the

new instruments for performing upper intestinal endoscopic examinations. The first instruments were side-viewing scopes that did not permit a view of the esophagus, but a dedicated forward-viewing instrument soon followed. Focusing had to be done continually, and, as with rigid scopes, air was pumped in with a hand-held insufflator. The light source was actually a small incandescent bulb located at the tip of the instrument, causing the distal end of the gastroscope to become rather hot during prolonged examinations. The fiberoptic bundles, which transmitted the image, were fragile, and if the scope became kinked (or, worse yet, was bitten), the broken fiberoptic bundles were immediately seen as permanent black spots in the visual field.

Drs. Yarness and Werther, the previous teachers of rigid endoscopy, each held a training session one day a week. In 1963, when the flexible tools became available, they included them in the regular schedule of cases. When I finished my fellowship in 1963, I had performed flexible endoscopies twice weekly under supervision, and had twice the expertise with these instruments as the instructors, who only used the flexible scopes once per week. I was requested to stay on as a teacher of flexible endoscopy. Soon, Dr. Werther resumed his laboratory activities on gastric acid secretion and Dr. Yarness retired, leaving me as the only (very young) teacher in the endoscopy unit. Dr. Julius Wolf, who was chief of staff of The Medical Service at the Bronx Veteran's Affairs (VA) Hospital, was enlisted to come to Mount Sinai twice a week to be the official head of the endoscopy unit and lend an air of authority (and maturity) to endoscopy. Dr. Wolf came to Mount Sinai on a regular basis for three years and then on an irregular basis for another year, until 1972. At that time, I found myself the senior gastrointestinal flexible endoscopist. I was never officially appointed to the position of chief of GI endoscopy, since this program was always considered to be an integral part of the overall GI program.

Changes in techniques and instrumentation progressed at a dizzying pace. Just before the introduction of fiberoptics, miniaturized photographic capability was integrated onto the tip of a flexible endoscope. The first flexible gastroscopes were "blind," without visual capability, but had a camera on the tip. This gastrocamera took multiple pictures on a 5-mm film strip, which, upon development, showed the mucosal views taken during a prescribed sequence of instrument positions while moving the patient from supine to prone. Mount Sinai did not acquire the original 1962 gastrocamera, but did buy the next model, GTF V, manufactured by Olympus Optical Company, Japan, which provided both a fiberoptic view and a film strip. The tiny images were projected onto a small screen, and our weekly endoscopy conference was born, as the growing number of faculty and GI fellows met regularly to watch the showing of the week's work. When endoscopic retrograde cholangiopancreatography (ERCP) was introduced, I traveled to Japan, in 1969, to learn the various techniques. Upon returning to Mount Sinai, I asked a senior endoscopist from the Minneapolis VA hospital, Dr. Jack Vennes, to visit Mount Sinai and take me through ERCP procedures under his tutelage. There was no funding for this. I lined up a series of private patients and sent Dr. Vennes the full amount of the fees collected from each patient to provide an honorarium and travel expenses. Once adept at this procedure, I traveled to several hospitals in New York City to teach the technique to anyone who asked.

When colonoscopy began at The Mount Sinai Hospital, it was performed under radiologic guidance, so that the location of the endoscope tip and the direction in which the endoscope was heading could be determined. The colonoscopes of that time had only two-way tip deflection and were rather stiff and clumsy. The first colonoscopic examination at The Mount Sinai Hospital was performed, without sedation, in the Radiology Department. Dr. Bernard Wolf, the then-chief of Radiology, and the other senior radiologists, were wondering how the advent of colonoscopy might affect the future need for the barium enema. At the onset, the patient was dismayed because of the gallery of attending radiologists, radiology fellows, attending gastroenterologists, GI fellows, and many x-ray technicians. She was also audibly uncomfortable during most of the procedure. After the first hour, all the attending radiologists had left, happy in the knowledge that this technique would not replace barium. After the second hour, all the GI attendings and fellows in Gastroenterology and Radiology disappeared. After the third hour, there was not a technician left to help with the imaging. Throughout the entire prolonged procedure, the patient, although obviously uncomfortable, continually encouraged and prayed for all the doctors. The procedure was successfully concluded, to the relief of both the patient and her endoscopist.

The following day, Dr. Wolf called me into his office and told me that I would not be able to tie up an x-ray room for half a day trying to perform colonoscopy. Eager to continue developing my skills in this examination, I asked Dr. David

Dreiling, a surgeon with an abiding interest in pancreatic physiology, if I could use his fluoroscope (with which he positioned his "Dreiling tube" for pancreatic secretory studies). His laboratory was on the sixth floor of the old hospital building and was not air conditioned. It was accessible by a stairway from endoscopy on the fifth floor level; the patients and I walked up and down the stairs to use this facility, since it was easier and quicker to walk with the patient and instruments rather than wait for the old elevator. My colonoscopy career began in the heat of midsummer and with a fluoroscope which was old and inefficient. One needed to dark-adapt for twenty minutes with red glasses in order to visualize the faint image on the screen, and, even so, if a hand was waved under the fluoroscopic screen, one could not discern the skeletal structures. Also, the shape of the instrument could be seen, but the air column was not visible.

During these tedious sessions, where sedation was not used, I noticed that various areas in the colon had different appearances and shapes that could be correlated with the position of the instrument tip as noted on the fluoroscopic screen. After four sweat-soaked sessions in Dr. Dreiling's fluoroscopy room, I decided that there had to be a better way of doing colonoscopy than with x-ray imaging. This experience stimulated me to develop the nonfluoroscopic method of colonoscopic topography by noting various visual landmarks in the colon, which give a fairly accurate location of the tip of the endoscope. Over the next few sessions, I was able to further delineate these landmarks and they became universally adapted (3). Currently, with the use of these landmarks, abdominal pressure, and palpation, most colonoscopy is currently performed without x-ray imaging.

The original GI endoscopy service consisted of three (previous ENT) operating rooms and the operating room office. The fluoroscopic unit for ERCPs was borrowed from a nearby surgical intensive care unit (ICU), so that all ERCPs were performed in the surgical ICU area. The first full-time nurse for GI endoscopy was Marna Schirmer, who was instrumental in teaching everyone how to do endoscopy. She formed the Society for Gastrointestinal Nurses and Assistants (SGNA) while running The Mount Sinai Hospital endoscopy unit. This organization is now the largest and best-known organization of its type in the world.

In preparation for the new Guggenheim Pavilion, it was necessary to demolish the building in which the endoscopy unit was located. Endoscopy was moved into the Annenberg Building, in a space that was known to be inadequate. Since it was the only space available, we were asked to "squeeze in" for a period of "one to two years," until the new building was constructed. That was fifteen years ago. The entire endoscopy space (as of this writing) is still contained in a 1,000 square foot area, which includes a waiting area, a reception area, a recovery space, two small endoscopy rooms, an even smaller storage room that was converted into a third endoscopy room, and a cleaning area. ERCPs are performed at a remote location using a C arm portable fluoroscope and monitor without the capability for overhead x-ray films. The unit currently performs about 7,000 endoscopic examinations annually. Because of space constraints, the forty members of the voluntary staff of the Gastroenterology Division now perform endoscopy in their private offices outside the hospital, while the full-time staff physicians have their own endoscopy set-up in their faculty practice area.

Many instructors are present for each and every scheduled endoscopy session. There is a special "fellows' endoscopy teaching session" weekly, in addition to the weekly "endoscopy conference." The latter has become one of the hospital's favorite meetings, attended by adult and pediatric gastroenterologists, general, laparoscopic and transplant surgeons, pathologists, residents, and medical students. This conference evolved from the original weekly gathering of interested GI physicians who reviewed the week's film strips of gastroscopic photographs.

The endoscopy training program at Mount Sinai is one of the best in the country, supervised by many dedicated GI attendings who give their time and effort without recompense. At the end of their training, the GI fellows are highly focused on both the cognitive and procedural aspects of endoscopy.

Plans have again been drawn up for a new endoscopy suite in the future ambulatory surgical pavilion, with an interim expansion and renovation of some of the current space.

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Ileostomy and Colostomy Support Groups

ALBERT S. LYONS, M.D.

Abstract

The first organized ostomy support group in the world was formed at The Mount Sinai Hospital, in 1950, through the efforts of a surgeon and the patients themselves. Later, similar groups were set up in other locations and some even took the name of Mount Sinai's first such society (QT).

These groups had two major functions:

- Psychological: reassurance and understanding from other ostomates before and after the operation; advice on how to deal with oneself and others.
- Educational: instruction on the details of stoma management; information for surgeons on the proper location and other details of fashioning a stoma; information to the public on the existence and needs of ostomates.

In order to extend services to more people and with more individual attention, a special clinic was established at The Mount Sinai Hospital devoted entirely to patients with ileostomy and colostomy. It too was the first of its kind anywhere.

Years later, two surgeons arranged an all-day convention of the ostomy groups in the greater New York City, New Jersey, and Connecticut areas, at the New York Academy of Medicine. At the convention, the idea of a national society was conceived. In the following years – in Detroit, then Cleveland, and finally Los Angeles – the United Ostomy Association was developed, structured, and incorporated.

The educational uses of the ostomy groups were later supplemented and partly replaced by enterostomal therapists who originally were trained and practiced in Cleveland. Now the therapists, the societies, and the ostomates themselves are available to patients with various types of stomas, whether recent or longstanding, before and after surgery.

Key Words: Ileostomy, colostomy, patient groups.

IN 1949, FOUR PATIENTS with ostomies met at the Veterans' Hospital in Valley Forge, PA, as did others in 1949 and 1950, in New York City and elsewhere. But these were occasional, spontaneous, mainly social get-togethers of two, three, or four persons with ileostomies or colostomies. The first formal, organized ostomy support group in the world began at The Mount Sinai Hospital in 1950; in 1952 I reported the earliest meetings of this group (1). The monthly meetings were attended by patients who had had ileostomies for the treatment of ulcerative colitis on the ward surgical service and other services, and at other hospitals. The meetings had their origin in a small social gathering at the home of one of the eight women patients who had come to know each other as patients in the hospital. It became clear that these patients had a most valuable idea which needed some nurturing. Both Miss L.M. Neary, a social worker assigned to the surgical service, and I set out to encourage these efforts.

Since the patients were admitted to Wards Q and/or T, the new group called themselves "QT Alumni." The choice of the term "QT" avoided using the word "stomas." Elsewhere, other groups began to form. For instance, in recognition of the fact that the pioneering work was done in New York, the Boston group called themselves QT Boston and the Detroit group, QT Detroit. Years later, people no longer felt it necessary to use the term "QT" and groups became known as ileostomy, colostomy, or ostomy associations (2).

In a 1987 interview with Hall (2), I described how I helped supervise the early meetings. My chief, Dr. John Garlock, was most helpful and encouraging. Because of his influence in the hospital, I was able to get support that I might not have gotten otherwise. My colleagues and co-workers, and others in the institution, were also favorably impressed. Ultimately, the group became larger and began to function by itself.

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Shortly after we started the ileostomy group, I thought we ought to start doing the same for people with colostomies. The first colostomy meeting, however, was discouraging. In the ileostomy group, there were a couple of very enthusiastic and remarkable young women and men who took responsibility and helped make the group possible. Unfortunately, the colostomy group did not have enough members willing or able to do likewise. Therefore, I didn't have another meeting until some years later, when three patients with colostomies met with my surgical colleague, Dr. George Schreiber, and me. They said that they wanted to form a group which included people who were willing to become involved (2).

The benefits derived by the patients in The Mount Sinai Hospital groups and elsewhere may be classified as psychological and educational.

Psychological. Enormous reassurance and support was received by the interaction of individuals with the same conditions, when they had the chance to discuss their feelings and how they dealt with family, friends, fellow-workers, and society at large. Also, the experiences of ostomates were enlightening to each other, notably on sex, pregnancy, occupation, and leisure activities. Patients have frequently said that their entire attitude changed when they were visited in the hospital by a club member. Some who had been unable or reluctant to properly manage their own stomal care after leaving the hospital came to accept their involvement in their own care. Moreover, even the well-adjusted person of long-standing club membership found an added meaning to his or her life by serving as an "expert" to help the neophytes (1).

Among the most useful contributions were visits by an ostomate member to patients before and/or after operations. Patients often reported that these visits transformed uncertainty to optimism. Instead of fear of "abnormality" because of the stoma, patients cheerfully adapted to a procedure which restored their health.

Educational. Information and even instruction on the management of ileostomy, colostomy and urostomy were provided by fellow patients, as well as by doctors and nurses who came as guests or advisers. Details were also provided about the specific types of appliances available, and the advantages and requirements of each. Before the advent of enterostomal therapists (ET), this technical advice was sometimes the principal source on which the ostomate could depend, since many doctors and nurses had limited experience in the details of stoma care and control.

Both patients and surgeons learned much at these meetings. For instance, the patients' recital of difficulties often indicated to the professional how to plan the stoma and its location before the operation, by taking into account particular anatomical and functional requirements of each person. When the enterostomal therapists came upon the scene, the needs of particular people and the resolution of difficulties were highly instructive to all parties. Moreover, the local groups working together could educate and influence the public, whereas individual patients, concerned about their privacy, were less likely to "reach out."

The Intestinal Rehabilitation Clinic

The ostomy group at Mount Sinai originally met in the evening in a clinic waiting room. Various problems were discussed, and then I, or somebody else, would talk. At the end of the meeting, the people would line up, and I would discuss their particular problems, one by one. I was joined later in this enterprise by Dr. George Schreiber, who had been a resident at Mount Sinai and then an attending (2, 3).

Attendance at meetings of the ileostomy club was about 15 at first; then it increased to more than 50, and sometimes to well over 100. The colostomy group, which met separately, also grew rapidly, making it impossible to deal with the special problems of individual people. In the late 1950s, I appeared before a committee of the Board of Trustees, headed by the president, Joseph Klingenstein, to request a special clinic devoted entirely to persons with external intestinal stomas. Soon afterward, the Trustees agreed. This "Intestinal Rehabilitation Clinic" was the first of its kind in the world. It was staffed voluntarily by myself, Dr. George Schreiber, Dr. Bernard Robinson, and Dr. Robert Turrell, a proctologist who would later found the Society for Surgery of the Alimentary Tract (at first, it was named the Society for Colon Surgery). A registered nurse, Miriam Jacobson, who was Robinson's office nurse, acted as the clinic nurse.

At that time, there was no clinic other than the one at Mount Sinai devoted solely to the care of stomas. At the Massachusetts General Hospital in Boston, and at other sites, there were follow-up clinics used by the surgical staff just to keep track of the postoperative patients.

The United Ostomy Association

In 1956, QT New York invited the known existing ileostomy and colostomy groups to

share their experiences. Representatives from eight ostomy groups (six ileostomy and two ileostomy-colostomy) throughout the U.S. met there. Some attended with the idea of forming a national organization (4).

As a result of this meeting in New York, *Ileostomy Quarterly* and *Colostomy Quarterly* were created. The colostomy publication appeared only once, but the *Ileostomy Quarterly,* sponsored by QT Boston and edited by Edith Lennenberg, continued on a regular basis. In New York, Leon Berger put together a monthly bulletin, *QT New York,* which was mimeographed. Later, formally printed monthly bulletins were sent out by both the ileostomy group and the colostomy society.

In 1960, QT New York sponsored a workshop at the New York Academy of Medicine, to which all existing ostomy groups in the U.S. and Canada were invited (2, 4). There were presentations by patients and panel discussions by surgeons, internists, gastroenterologists, and psychologists. Afterwards, the people who came from the various clubs sat down with us and asked if it was possible to make something of this that extended beyond just the local area. We all thought it was a very good idea.

In 1961, a meeting was held in Detroit. I could not attend, but I was in touch by telephone with several people there, and learned that there was intense disagreement. I remember sending a telegram to one attendee, saying that if the thirteen colonies could get together and form a union, I hoped that people who had a common purpose could act together and forget geographic differences and other personal needs. I do not know whether the telegram had any effect at all, but I do know that the decision was made, at that meeting, to meet in Cleveland subsequently. During that interval, various working parties met to facilitate the founding of the new national organization (2).

At the Detroit meeting, a committee on a constitution and bylaws had been established. In 1962, delegates from 24 groups assembled in Cleveland, Ohio and set up the structure for the United Ostomy Association.

In Los Angeles, in 1963, the organization was officially and legally established and its first officers elected. *The Ostomy Quarterly* appeared in December 1963, under the editorship of Virginia Pearce — who introduced the term "ostomate" into the medical literature, taking it from Egon Orawan, an engineer at MIT who was interested in perfecting a superior ostomy appliance. He coined the word "ostomate" by combining the suffix "ostomy" with the term for a person, "mate" (2). Until then, various other terms had been used, such as "stoma person," "ostomite," and even "person with an ostomy," but "ostomate" became and remained the standard term thereafter. An international Ostomy Association was established in 1975, principally because of the dedicated work of Vinitsky (4).

Norma Gill (5), under the aegis of the surgeon Dr. Rupert Turnbull in Cleveland, developed the concept of specifically trained professional therapists for ostomates. Thus, she was the first enterostomal therapist. At Mount Sinai, Marlene Brockmeier, and then Sally Bishop, both registered nurses, followed this pioneering work of Gill and Turnbull.

Ever since these pioneering efforts, the technical knowledge and advice for ostomates have been provided by enterostomal therapists, most of whom are nurses, some of whom have had stomas themselves. They have been specifically trained as professionals to teach, care for, and advise patients and doctors on the management of stomas. ETs (as they are usually referred to) often give instruction and advice at the ileostomy and colostomy meetings. Indeed, they themselves still learn from the ostomate groups. But the psychological and educational functions of the ostomy groups continue as before.

Perhaps the most important result achieved by these support groups has been their demonstration, by living example, that a person with a stoma can lead a healthy, happy life filled with all the joys and activities of "normal" people (1). In 1987, at a convention of enterostomal therapists, in response to a question on the continued usefulness and effectiveness of the ostomy groups, I characterized the need felt by ostomates for the ostomy societies as follows:

> No land of birth nor right of name
> Shall claim my family line,
> But he and she who share my pain
> Are brother, sister mine.

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To Make a Difference:

The Founding of the Crohn's and Colitis Foundation of America

SUZANNE ROSENTHAL

Abstract

In 1965, with the help of Dr. Henry D. Janowitz, Irwin M. Rosenthal established the Foundation for Research in Ileitis, Inc., now known as the Crohn's and Colitis Foundation of America, Inc. He was joined shortly thereafter by William D. Modell. At that time, the entire annual NIH budget for research on inflammatory bowel disease was only $25,000. Successful fund raising made it possible to recruit a research fellow at The Mount Sinai Hospital in the Division of Gastroenterology to study ileitis. Thereafter, the efforts of the foundation expanded nationwide. It supported a nationally coordinated research program and sponsored education for physicians, patients and the public. In addition, it established support groups to help patients and their families cope with Crohn's disease and ulcerative colitis. With the energy and philanthropy of the foundation's many lay leaders, tens of millions of dollars have been raised for research and education in inflammatory bowel disease.

Key Words: Ileitis, ulcerative colitis, colitis, regional enteritis, Crohn's disease, Crohn's and Colitis Foundation of America.

IN 1965 HENRY D. JANOWITZ, M.D. and Irwin M. Rosenthal took the first steps in creating what was to become the world's largest public, nonprofit inflammatory bowel disease (IBD) research, education and support organization: the Crohn's and Colitis Foundation of America, Inc. (CCFA). Each brought to their partnership a unique set of abilities and a deep commitment to the major goal of the foundation: to find the cause and cure for Crohn's disease and ulcerative colitis. Dr. Janowitz provided the expertise of a skilled clinician and scientist who, as chief of the Division of Gastroenterology of The Mount Sinai Hospital, had the authority to determine the direction of research and clinical care. Irwin Rosenthal, an attorney, provided the organization legal and leadership skills. The establishment of the foundation was completed shortly thereafter when Bill Modell, Chairman of the Board of the Modell's Sporting Goods chain, joined as a co-founder, providing the fund-raising, organizational and networking capabilities of one of the city's leading merchants.

Irwin was to remain president of the foundation for 10 years, and Henry, the founding chairman of the National Scientific Advisory Committee (NSAC) for 8 years. The third founding partner, Bill Modell, served as Chairman of the Board for 10 years. All three were critical to the financial success of the foundation as it grew over the years, changing its name from the Foundation for Research in Ileitis, to the National Foundation for Ileitis and Colitis (NFIC), and finally to the Crohn's and Colitis Foundation of America.

Henry D. Janowitz, MD, the physician member of this unique partnership, started his medical career at The Mount Sinai Hospital, concentrating on basic research in pancreatic inflammatory disease. In 1952, Dr. Janowitz moved into clinical medicine and, with the influence of Drs. Crohn and Ginzburg, together with the sheer number of IBD patients that he saw at Mount Sinai, was drawn into research on inflammatory bowel disease, publishing a number of important papers that advanced the knowledge of IBD clinical manifestations.

In 1958, Dr. Janowitz was asked by Dr. Alexander Gutman, the chief of Medicine at Mount Sinai, to form a division of gastroenterology. From the start, he knew that the division would have to engage physicians to combine classical practice with the intellectual rigor and academic curiosity of a laboratory scientist or clinical investigator. This philosophy prevailed, as he went on to train more than 125 fellows including Drs. Burton I. Korelitz, Daniel H. Present, Peter Banks, David Sachar, Lloyd Mayer, Jerome Waye, Lawrence Brandt, Eugene Strauss and dozens of others who, in time, would make their own contributions to the field. Dr. Janowitz's enthusiasm and expertise would soon play a major role in the founding of the Crohn's and Colitis Foundation of America.

In August 1956, Suzanne and Irwin Rosenthal were finally married C after several postponements because of Suzanne's painful and mysterious intestinal illness. Some three years later, the problem was diagnosed by Dr. Janowitz as ileitis. At that time, there were few

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medical and surgical treatments for this disease of unknown etiology.

Irwin, a young Yale Law School graduate and attorney with one of New York's leading corporate securities law firms, had been an activist in a number of civic and political organizations. So it was not unusual for him to challenge Dr. Janowitz, demanding of him a response to a question formed in the heat of his and Suzanne's deep frustration and anger, "Why doesn't someone do something about it?" Dr. Janowitz responded by challenging Irwin to fund a gastroenterology fellow to concentrate on ileitis research. It would cost at least $25,000 annually, which Dr. Janowitz informed Irwin was the amount of ileitis research then funded by the National Institutes of Health. Irwin accepted the challenge.

By early 1963, they were planning the establishment of an organizational effort to start "doing something about it." On December 17, 1965, the Foundation for Research in Ileitis, Inc. was officially incorporated in New York State, with Dr. Janowitz as its director of research and Irwin as its president. They now had the legal authorization to start raising money in New York State to support research. Together, they formulated the lay and medical partnership philosophy of the foundation; many of its principal medical research and research training concepts and programs are still in force today. They also determined that the NIH grant review system would be utilized to protect the quality of the research and the credibility of the foundation. All research monies, no matter where they came from, would flow into a single research fund, to be appropriated as determined by the grant reviewers and the Board of Trustees.

In January 1966, the very first meeting of the Board of Trustees of this new foundation was held at The Mount Sinai Hospital. The principles espoused by Dr. Janowitz and Irwin were unanimously approved. Irwin and Henry particularly had recruited Drs. Burrill Crohn, Leon Ginzburg and Gordon Oppenheimer, the three scientist-clinicians who discovered ileitis, as honorary co-chairmen of its scientific advisory board. Also recruited were Dr. Arthur H. Aufses, Jr., Suzanne's surgeon; Dr. Arthur Ludwig, her internist; Dr. Samuel K. Elster; Dr. Richard Marshak, the leading abdominal radiologist; and others who cared deeply about helping this young couple and Henry to find the cause and cure of ileitis. Friends and clients of Irwin's completed the lay portion of the foundation Board.

In 1966, with the foundation's legal basis in place, the research program officially began. Daniel H. Present, one of Henry's gastroenterology fellows, was recruited to organize a comprehensive research program, by compiling a list of existing and planned research projects. Mount Sinai gastroenterologists, surgeons, radiologists, nutritionists and immunologists were recruited to work either individually or jointly on a multidisciplined approach to "A Comprehensive Study of Regional Enteritis," including the effects of diet on motility, the mechanisms that cause kidney stones in ileitis patients, and the immunologic status of ileitis. The studies were conducted from 1966 to 1974, by Burton I. Korelitz, Robert Taub, Shelly Brown, Gerald Friedman and Charles Gerson, doctors then at Mount Sinai. One summer, a Mr. Barry Coller, then a medical student at New York University, was recruited to assist Dr. Present. Dr. Coller would later become the Murray M. Rosenberg Professor and chairman of the Department of Medicine at the Mount Sinai School of Medicine.

To conduct these studies, a small space in an unused apartment at 19 East 98th Street, provided by Mount Sinai, became the "research center." The bathtub was used to store pharmaceutical supplies, including those provided by Pharmacia, an early supporter of the foundation, to study the effects of Azulfidine suppositories on the treatment of proctitis. Beds for research patients were promised, and a group of patients was admitted to the Clinical Research Center, supported by a grant from the NIH. These patients were evaluated for various motility disturbances and symptomatology. Some patients remained under observation for as long as three weeks.

In 1966, with the Rosenthals' dining room table used as the foundation's "administrative office," Irwin began the fund-raising efforts which resulted in $25,000 for the first year's research. He accomplished this by letters of appeal concerning Suzanne's battle with ileitis. He sent them to family and friends, and to more than 1,000 members of his synagogue, with the blessing and permission of Rabbi Israel Mowshowitz. He urged them to help him raise funds to support ileitis research at Mount Sinai, and raised several thousand dollars. Each time Suzanne was hospitalized that year, and in future years, Irwin would prowl the halls of Mount Sinai to recruit the fathers, husbands and wives of other ileitis patients on the medical and surgical floors, to help raise money. Suzanne and Jane Present were recruited to prepare letters to send to Dr. Crohn's ileitis patients, asking for their assistance.

In the spring of 1966, Irwin asked Irving Rubin, from Detroit, Michigan, whose daughter

was hospitalized at Mount Sinai, to help. Irving recruited his family and business associates, and he himself contributed funds for a very significant research effort. He was asked to underwrite an important conference with eminent gastroenterologists, on designing clinical trials, including a review of Drs. Present and Korelitz's proposed research protocol. Invited to attend were Dr. Joseph B. Kirsner of the University of Chicago, Dr. Fred Kern of the University of Denver, and Dr. Thomas Chalmers, a world renowned expert in the design of clinical trials. Dr. Chalmers, who was then serving at the NIH, would become the President/Dean of Mount Sinai in 1973.

While planning the research program of this new organization, Dr. Janowitz and his associates saw that clinical trials on the use of pharmaceuticals for ileitis were to be a major element. Dr. Daniel H. Present was awarded the first grant from the Foundation for Research in Ileitis, to prospectively study the pharmacological and therapeutic properties and side effects of 6-mercaptopurine (6-MP) in a controlled, double-blind study. Collaborators in the study included Drs. Burton I. Korelitz, David Sachar, and Nathaniel Wisch. The primary therapeutic effect to be studied was improvement of bowel function, fistulae and steroid sparing. There was careful monitoring of blood count to avoid marrow depression. The controlled trial ultimately took eight years to complete and was published in the *New England Journal of Medicine* in 1980 (N Engl J Med 1980; 302:981–987). An update on the history of drug treatment of inflammatory bowel disease can be found in chapter 23.

This first Foundation for Research in Ileitis grant award and other Mount Sinai studies were to have an immense impact on today's scientific knowledge concerning inflammatory bowel disease. It was Burton I. Korelitz, one of Suzanne's original physicians at Mount Sinai, who had published a number of articles concerning ulcerative colitis (particularly with regard to the use of 6-MP in children and adults), who suggested to Irwin that the foundation include the study of ulcerative colitis in its research program. Dr. Janowitz concurred, and ulcerative colitis studies were added to the foundation's research portfolio. In 1967, the name of the foundation was changed to the National Foundation for Ileitis and Colitis (NFIC).

Bill Modell and his dynamic and talented wife, Shelby, joined the foundation efforts when their son Michael, then 14 years old, was diagnosed with ileitis by Dr. Burrill Crohn. They were referred to Irwin and Suzanne to learn how they could help find the cause and cure of the disease afflicting their son. With Michael as their inspiration, they provided the strong financial support for the foundation that was critical to its success, as well as to the progress of the ileitis and colitis research programs of the Division of Gastroenterology at Mount Sinai.

The Modells, experienced fund-raisers with strong business connections from their sporting goods stores in New York State, and with legions of caring family and friends, offered to chair the foundation's first major fund-raising event. In December 1967, a dinner dance at the glamorous nightclub of the Americana Hotel was arranged. With the Modells' huge and devoted following, Irwin and Suzanne's friends and clients, and members of the Board, the commitment to the hotel was met. The gala featured entertainment by Ella Fitzgerald, as well as a brief ceremony to honor Drs. Crohn, Ginzburg, and Oppenheimer.

Subsequently, with each passing year, with Shelby and Bill Modell as dinner chairpersons, the size of the banquet room increased to accommodate the burgeoning crowds of generous contributors. In addition to funds raised from the dinner, there were funds raised from journal ads for a journal book dedicated to the honorees. In the early years, Jane Present edited these successful journals. The list of honorees through the years has included people from the world of merchandising, politics, banking, government, medicine, pharmaceuticals and entertainment. The honorees also added to the excitement and glamour of the dinner dances, helping make them successful events. The net proceeds from the journal and the dinner, which came to be known as the Greater New York Chapter Annual Dinner, for many years contributed one-third of the national organization's gross revenue.

Today, the dinner, the largest single fund-raising event, still provides more than $1 million annually to the budget of the national foundation, now called the Crohn's and Colitis Foundation of America (CCFA). Bill Modell and Shelby co-chaired this dinner for 25 consecutive years until 1993, when they turned the dinner chairmanship over to their son Michael and his wife Abby, who continue in this role. Through the years, Shelby and Bill, and the Modell family have been responsible for raising more than $40 million for research and education. Bill Modell is still chairman of the board, emeritus, and Shelby is national vice-president of the Board. They have been instrumental in the founding and development of the foundation's

Long Island chapter and the Gold Coast chapter of Boca Raton, Florida, contributing to the great financial success of each of these chapters.

Suzanne Rosenthal was the original inspiration for the founding of the CCFA and for Mount Sinai's intensified research efforts in the field of ileitis. She brought to the organization the management skills she learned at her college's business school and the wide knowledge she acquired about ileitis and colitis, and their treatment. These were of great value when she established the ladies auxiliary of the Board, with officers including Shelby Modell, Jane Present, Toby Fuchs, Dee Hollander and other women dedicated to building the foundation. Suzanne served as president and created committees for fund-raising, membership and patient education. Anticipating the growth of chapters, she wrote the operating manuals for chapter governance, membership, and education, as well as for chapter scientific advisory committees. Suzanne was well enough between hospitalizations to travel to many cities to help develop NFIC chapters along the East Coast, starting with the New York City boroughs and Long Island, then New Jersey, Westchester, Rhode Island, Boston, Philadelphia, Washington, D.C. and Greater Miami. In addition, Suzanne formed the government advocacy committee to help increase the NIH – National Institute for Diabetes, Digestive and Kidney Diseases' (NIDDK) inflammatory bowel disease research portfolio. Suzanne later became national president and remains chairman of the Board, emeritus.

In New York City, open education meetings for the public, with panels of ileitis and colitis medical experts (often Mount Sinai gastroenterologists), were held monthly. Upwards of one hundred patients and their families turned out for each meeting. In addition to the foundation's top priority of finding the cause and cure of inflammatory bowel diseases, patient and professional education became important goals. Eventually, mutual-help support groups would appear, first in New York City. This important program also became a major priority of the foundation.

During its first decade, the foundation was viewed as a Mount Sinai Hospital project, even though grants had been awarded to many researchers at other hospitals. In order to alter that perception, chairmanship of the National Scientific Advisory Board was to be rotated nationally among the leading IBD clinicians and scientists. NFIC President Irwin Rosenthal recruited Dr. Joseph B. Kirsner from the University of Chicago Medical Center as National Scientific Advisory Board chairman, and Dr. Kurt Isselbacher from Massachusetts General Hospital as Grant Review Committee chairman. He was to succeed Dr. Kirsner as NSAC chairman. Dr. Burton I. Korelitz, then chairman of Gastroenterology at Lenox Hill Hospital in New York, succeeded Dr. Isselbacher and formed subcommittees of the NSAC to address research training, professional education and patient education. He encouraged IBD clinical research investigators to participate more actively on committees, and organized conferences with research scientists and clinicians to exchange ideas. Word was widely circulated that funds were available to investigators from all over the United States and abroad.

Today, the CCFA has a large suite of offices at 386 Park Avenue South at 27th Street in New York City, to appropriately service an organization with a $21 million budget. The CCFA has 60,000 lay and physician members. Its 55 chapters across the country offer more than 350 support groups. It has published four books for patients and distributes annually more than one million educational IBD brochures, newsletters, etc. CCFA publishes *Inflammatory Bowel Disease*, its own medical journal, which is now listed in the Index Medicus. The CCFA is a partner with the NIH in research conferences and workshops that significantly advance IBD research. Through its strong Congressional advocacy efforts, it has helped two NIH institutes to progressively expand their funding for IBD research portfolios. Today, the NIDDK funds more than $21 million in IBD research grants. The National Institute for Allergy and Infectious Diseases (NIAID) funds close to $3 million for IBD immunology research.

More than 75% of the research investigators funded by the NIH in the last five years were first funded with CCFA seed money to help them develop and refine their projects. This was the vision of its founders. Irwin and William remain active with the foundation to this day. The CCFA continues to provide seed money for the development of IBD research to enable investigators to compete more successfully for the highly competitive NIH grant awards that provide considerably more funds for research projects.

As CCFA enters a new millennium in which many questions about IBD remain to be answered, clinicians and scientists at Mount Sinai and around the world are increasingly more hopeful that the cause and cure of these diseases will be found within the next decade. When this happens, CCFA members will know that they have played an important part in this success — that they have made a difference.

Gastroenterology and Hepatology at the Mount Sinai Hospital, 1852–2000

Edited by Jeremy Hugh Baron, honorary professorial lecturer, and Henry D. Janowitz, clinical professor emeritus, The Dr. Henry D. Janowitz Division of Gastroenterology, Mount Sinai School of Medicine, New York, NY.

This book celebrates the 150th anniversary of The Mount Sinai Hospital by describing the past, present, and future of its divisions of gastroenterology and hepatology, with their national and international reputations. Each chapter is written by an expert, many of whom have made significant contributions to the progress of their specialties. The book covers the whole alimentary tract from the esophagus to the colon, as well as the pancreas and liver, and describes the important clinical and research contributions leading to advances in scientific understanding and thus in patient care.

Many of the chapters are devoted to Inflammatory Bowel Disease, *the* Mount Sinai gastroenterological disorder, par excellence. The history of these diseases, ulcerative colitis and Crohn's disease are described in detail both before and after 1932, the critical year of the publication of both Ginzburg and Oppenheimer's and Crohn, Ginzburg and Oppenheimer's key papers which are here reprinted in full.

Distinguished chiefs such as Burrill B. Crohn, Asher Winkelstein, Franklin Hollander and Fenton Schaffner are commemorated in Brief Lives.

Recommended to medical and surgical gastroenterologists and hepatologists and those with an interest in the history of medicine.

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