

The Pancreas

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

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)

From the Dr. Henry D. Janowitz Division of Gastroenterology, Mount Sinai School of Medicine, New York, NY.

Address correspondence to Dr. J.H. Baron, Division of Gastroenterology, Box 1069, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029-6574.

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

normal ranges for the various constituents of the duodenal aspirate from samples of aspirate obtained 2¹/₂ 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, $\text{HCO}_3^- > 90$ 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 accu-

racy 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.

References

- Boyle JD. The American Gastroenterological Association. History of its first seventy-five years. *Gastroenterology* 1973; 65(6 Pt2):1019–1106.
- Crohn BB. *Gastroenterology at The Mount Sinai Hospital*. *J Mt Sinai Hosp* 1945; 12:129–136.
- Rudisch J, Strauss I. Two cases of acute yellow atrophy of the liver. *Mt Sinai Hosp Rec* 1903; 3:15–25.
- Crohn BB. Notes on the evolution of a medical specialist. 1907–1965. New York: Burrill B. Crohn Foundation; 1984.
- Brill NE. Primary carcinoma of the duodenum. *Am J Med Sci* 1904; 128:824–837.
- Crohn BB. The diagnosis of the functional activity of the pancreatic gland by means of ferment analyses of the duodenal contents and of the stools. *Am J Med Sci* 1913; 145:393–405.
- Koplik H, Crohn BB. Fat and nitrogen metabolism in a case of congenital absence of the bile ducts with a study of ferments of the pancreatic secretion and the feces. *Am J Dis Child* 1913; 5:36–42.
- Crohn BB. New growths involving the terminal bile and pancreatic ducts: Their early recognition by means of duodenal contents analyses. *Am J Med Sci* 1914; 148:839–856.
- Crohn BB. The chemical examination of duodenal contents as a means of diagnosis in conditions of jaundice. *J Am Med Ass* 1915; 64:565–569.
- Crohn BB. Studies in pancreatic disease. *Arch Intern Med* 1915; 15:581–607.
- Crohn BB, Reiss J, Radin MJ. Experiences with the Lyon test (magnesium sulphate lavage of the duodenum). *J Am Med Ass* 1921; 76:1567–1571.
- Auster LS, Crohn BB. Notes on studies in the physiology of the gall bladder. *Am J Med Sci* 1922; 164:345–360.
- Hollander E. Experiences with non-surgical biliary drainage (Meltzer-Lyon test). *Am J Med Sci* 1923; 165:497–512.
- Epstein AA. Observations on pancreatic rennet. *Proc Soc Exp Biol Med* 1921; 19:3–6.
- Epstein AA, Rosenthal N. The effect of pancreatic rennet on blood coagulation. *Proc Soc Exp Biol Med* 1921; 19:79–84.
- Hollander E, Marcus JM. Pancreatic function. I. The quantitative determination of pancreatic enzymes. *Arch Intern Med* 1925; 36:585–591.
- Kahn J, Klein HM. Human pancreatic secretion studied from a case of pancreatic cyst with fistula. *Am J Med Sci* 1932; 184:503–511.
- Hammarsten E. The secretin of Bayliss and Starling. *J Mt Sinai Hosp* 1938; 6:59–67.
- Diamond JS, Siegel SA, Gall MB, Karlen S. The use of secretin as a clinical test of pancreatic function. *Am J Dig Dis* 1939; 6:366–372.
- Simon B. In memoriam: Ralph Colp, M.D. *Mt Sinai J Med* 1975; 42:95–98.
- Dreiling DA, Hollander F. Studies in pancreatic function. I. Preliminary series of clinical studies with the secretin test. *Gastroenterology* 1948; 11:714–729.
- Dreiling DA, Hollander F. Studies in pancreatic function. II. A statistical study of pancreatic secretion following secretin in patients without pancreatic disease. *Gastroenterology* 1950; 15:620–627.
- Dreiling DA. Studies in pancreatic function. III. The use of the secretin test in the diagnosis of patients with the post-cholecystectomy syndrome. *Gastroenterology* 1950; 16:162–171.
- Dreiling DA, Lipsay JL. The use of the secretin test in the diagnosis of biliary tract disease. A report of 327 case studies. *Gastroenterology* 1951; 17:242–259.
- Dreiling DA. Studies in pancreatic function. IV. The use of the secretin test in the diagnosis of tumours in and about the pancreas. *Gastroenterology* 1951; 18:184–196.
- Dreiling DA. Studies in pancreatic function. V. The use of the secretin test in the diagnosis of pancreatitis and in the demonstration of pancreatic insufficiencies in gastro-intestinal disorders. *Gastroenterology* 1953; 24:540–555.
- Dreiling DA. The technique of the secretin test: Normal ranges. *J Mt Sinai Hosp* 1955; 21:363–372.
- Rosenberg IR, Friedland N, Janowitz HD, Dreiling DA. The effect of age and sex upon human pancreatic secretion of fluid and bicarbonate. *Gastroenterology* 1966; 50:191–194.
- Dreiling DA, Janowitz HD. The measurement of pancreatic secretory function. In: de Reuck AVS, Cameron MP, editors. *Ciba Foundation Symposium on the Exocrine Pancreas*. London: Churchill; 1962. pp. 225–258.
- Dreiling DA, Nieburgs HE, Janowitz HD. The combined secretin and cytology test in the diagnosis of pancreatic and biliary tract cancer. *Med Clin North Am* 1960; 44:801–815.
- Dreiling DA, Richman A. Evaluation of provocative blood enzyme tests employed in diagnosis of pancreatic disease. *Arch Intern Med* 1954; 94:197–212.
- Dreiling DA. Pancreatic secretory testing in 1974. *Gut* 1975; 16:653–657.
- Dreiling DA, Messer J. The secretin story: A saga in clinical medicine and gastrointestinal physiology. *Am J Gastroenterol* 1978; 70:455–479.
- Dreiling DA, Wolfson P. New insights into pancreatic disease revealed by the secretin test. In: Berk JE, editor. *Developments in digestive diseases*. Philadelphia: Lea & Febiger; 1979. pp.155–170.
- Dreiling DA. The early diagnosis of pancreatic cancer. *Scand J Gastroenterol* 1970; 5(Suppl 6):115–122.
- Dreiling DA, Druckerman LJ, Hollander F. The effect of complete vagisection and vagal stimulation on pancreatic secretion in man. *Gastroenterology* 1952; 20:578–586.
- Dreiling DA. Effect of histamine and histalog (gastramine) in pancreatic secretion. *Gastroenterology* 1954; 27:334–346.
- Dreiling DA, Janowitz HD, Haemmerli UP, Marshall D. The effect of glucagon on the exocrine pancreatic secretion of man. *J Mt Sinai Hosp* 1958; 25:240–243.
- Birnbaum D, Hollander F. Inhibition of pancreatic secretion by the anhydrase inhibitor 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide, Diamox (#6063). *Am J Physiol* 1953; 174:191–195.
- Dreiling DA, Janowitz HD, Halpern M. The effect of a carbonic anhydrase inhibitor, Diamox, in human pancreatic secretion: Implications on the mechanism of pancreatic secretion. *Gastroenterology* 1955; 29:262–279.
- Waitman AM, Dyck WP, Janowitz HD. Effect of secretin and acetazolamide on the volume and electrolyte composition of hepatic bile in man. *Gastroenterology* 1969; 56:286–294.
- Dreiling DA, Janowitz HD. The secretion of electrolytes by the human pancreas. *Gastroenterology* 1956; 30:382–390.

43. Dreiling DA, Janowitz HD. The electrolyte secretion of the pancreas: A new hypothesis of the mechanisms of secretion by the pancreas. In: *Proceedings of the World Congress on Gastroenterology*, Vol. 2; 1958; Washington (DC). Baltimore (MD): Williams & Wilkins; 1959. pp. 243–247.
44. Dreiling DA, Janowitz HD. Inhibitory effect of new anticholinergics on the basal and secretin-stimulated pancreatic secretion in patients with and without pancreatic disease: Therapeutic and theoretic implications. *Am J Dig Dis* 1960; 5:639–654.
45. Janowitz HD, Dreiling DA. The pancreatic secretion of fluid and electrolytes. In: de Reuck AVS, Cameron MP, editors. *Ciba Foundation Symposium on The Exocrine Pancreas*. London: Churchill; 1962. pp. 115–133.
46. Lester LJ, Birnbaum D, Hollander F. Studies in external pancreatic secretion, surgical and experimental procedures used in these investigations. *J Mt Sinai Hosp* 1960; 27:382–386.
47. Tankel H, Hollander F. Effect of vagotomy on pancreatic secretion. *Am J Physiol* 1958; 193:393–399.
48. Baron JH. Studies of basal and peak acid output with an augmented histamine test. *Gut* 1963; 4:136–144.
49. Baron JH. An assessment of the augmented histamine test in the diagnosis of peptic ulcer. *Gut* 1963; 4:243–253.
50. Kay AW. Effect of large doses of histamine on gastric secretion of HCl. *Br Med J* 1953; 2:77–80.
51. Baron JH, Perrier CV, Janowitz HD, Dreiling DA. Maximum alkaline (bicarbonate) output of the dog pancreas. *Am J Physiol* 1963; 204:251–256.
52. Perrier CV, Baron JH, Dreiling DA, Janowitz HD. Relationship between maximum bicarbonate and maximum acid outputs in the dog. *Proc Soc Exp Biol Med* 1967; 124:312–314.
53. Hansky J, Tiscornia OM, Dreiling DA, Janowitz HD. Relationship between maximal secretory output and weight of the pancreas in the dog. *Proc Soc Exp Biol Med* 1963; 114:654–656.
54. Hansky J, Tiscornia OM, Dreiling DA, Janowitz HD. Maximal secretory capacity of the canine pancreas in response to pancreozymin and secretin. *Am J Physiol* 1964; 206:351–356.
55. Agren G, Lagerlof H. The pancreatic secretion in man after intravenous administration of secretin. *Acta Med Scand* 1936; 90:1–29.
56. Dreiling DA. Comparison of standard and augmented secretin test responses in patients with and without pancreatic disease. *Am J Gastroenterol* 1974; 61:433–442.
57. Wormsley KG. Tests of pancreatic function. *Proc R Soc Med* 1970; 63:431–433.
58. Wormsley K. Pancreatic function tests. *Clin Gastroenterol* 1972; 1:27–51.
59. Gutierrez LV, Baron JH. A comparison of Boots and GIH secretin as stimuli of pancreatic secretion in humans with or without chronic pancreatitis. *Gut* 1972; 13:721–725.
60. Petersen H, Myren J. Secretin dose-response in the diagnosis of chronic pancreatitis [abstract]. *Scand J Gastroenterol* 1974; 9(Suppl 27):33.
61. Baron JH. The relationship between basal and maximum acid output in normal subjects and patients with duodenal ulcer. *Clin Sci* 1963; 24:357–370.
62. Preshaw RM, Grossman MI. Stimulation of pancreatic secretion by extracts of the pyloric gland area of the stomach. *Gastroenterology* 1965; 48:36–44.
63. Gutierrez LV, Baron JH. A comparison of basal and stimulated gastric acid and duodenal bicarbonate in patients with and without duodenal ulcer disease. *Am J Gastroenterol* 1976; 66:270–276.
64. Dreiling DA, Bordalo O. Secretory patterns in minimal pancreatic inflammatory pathologies. *Am J Gastroenterol* 1973; 60:60–69.
65. Manges M. Acute pancreatitis — disseminated fat necrosis of peritoneum — laparotomy recovery. *Philadelphia Med J* 1899; 3:724–728.
66. Dreiling DA, Janowitz HD, Perrier CV. *Pancreatic inflammatory disease*. New York: Harper and Row; 1964.
67. Paulino-Netto A, Dreiling DA, Baronowsky ID. The relationship between pancreatic calcification and cancer of the pancreas. *Ann Surg* 1960; 151:530–537.
68. Zimmerman MJ, Dreiling DA, Rosenberg IR, Janowitz HD. Secretion of calcium by the canine pancreas. *Gastroenterology* 1967; 52:865–870.
69. Bayer M, Rudick J, Lieber CS, Janowitz HD. Inhibitory effect of ethanol on canine exocrine pancreatic secretion. *Gastroenterology* 1972; 63:619–626.
70. Dreiling DA, Bordalo O. Secretory patterns in minimal pancreatic inflammatory pathologies. *Am J Gastroenterol* 1974; 60:60–69.
71. Tiscornia OM, Jacobson JH, Dreiling DA. Microsurgery of the canine pancreatic duct: experimental study and review of previous approaches to the management of pancreatic duct pathology. *Surgery* 1965; 58:58–72.
72. Tiscornia OM, Dreiling DA. Recovery of pancreatic exocrine secretory capacity following prolonged ductal obstruction: Bicarbonate and amylase response to hormonal stimulation. *Ann Surg* 1966; 44:267–270.
73. Tiscornia OM, Janowitz HD, Dreiling DA. The effect of alloxan upon canine exocrine pancreatic secretion. *Am J Gastroenterol* 1968; 49:328–340.
74. Feldman M, Dreiling DA, Paulino-Netto A, et al. Effect of d-lithionine on electrolyte secretion of the dog pancreas. *Am J Physiol* 1963; 205:878–884.
75. Tiscornia OM, Dreiling DA. Does the pancreatic gland regenerate? *Gastroenterology* 1966; 51:267–271.
76. Perrier CV, Dreiling DA, Janowitz HD. A stop-flow analysis of pancreatic secretion. *Gastroenterology* 1964; 46:700–705.
77. Wastall C, Rudick J, Dreiling DA. Bicarbonate-chloride exchange across pancreatic duct epithelium in dogs. *Am J Gastroenterol* 1969; 52:99–110.
78. Banks PA, Janowitz HD. Some metabolic aspects of exocrine pancreatic disease. *Gastroenterology* 1969; 56:601–617.
79. Salen S, Kessler JI, Janowitz HD. The development of pancreatic secretory insufficiency in a patient with recurrent pancreatitis and type V hyperlipoproteinemia. *Mt Sinai J Med* 1970; 37:103–106.
80. Tiscornia OM, Dreiling DA. The effect of hypophysectomy on canine pancreatic function. *Surgery* 1966; 60:883–890.
81. Tiscornia OM, Hansky J, Janowitz HD, Dreiling DA. The adrenal cortex and external pancreatic secretion in the dog. *J Mt Sinai Hosp* 1965; 32:551–561.
82. Cohen N, Mazure P, Dreiling DA, Janowitz HD. Desoxyribonuclease I activity in the duodenal juice and serum of man. *J Mt Sinai Hosp* 1961; 28:537–542.
83. Dreiling DA, Janowitz HD, Josephberg LJ. Serum iso-amylases: An electrophoretic study of the blood amylase and the patterns observed in pancreatic disease. *Ann Intern Med* 1963; 58:235–244.
84. Dreiling DA, Leichtling JJ, Janowitz HD. The amylase-creatinine clearance ratio: Diagnostic parameter or physiologic phenomenon? *Am J Gastroenterol* 1974; 61:290–296.
85. Kessler JI, Finkel M, Dreiling DA, Janowitz HD. Lipoprotein lipase activity in the dog pancreas and pancreatic juice. *Proc Soc Exp Biol Med* 1963; 113:127–132.