

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 Uffelmann'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 gastrodiphane 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 pepsin. 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 non-absorbed 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 penta-gastrin-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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