

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 alkalized 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 H₂ 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 taka-diastase (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 NaHCO₃/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, Winkelstein (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, endobenzyl 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 treat-

ment 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.



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 become 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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