The History of Acid Inhibition

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I review here the history of inhibition of gastric acid. References are limited to books and reviews in which detailed citations can be found.

ANTACIDS

In ancient times, acids were not understood in the modern chemical sense but merely as bitter sour liquids [1]. Some foods were thought acidic, and if the stomach had an ulcer, everything acid was to be avoided and soothing remedies such as starch and milk used. Antacids neutralize, rather than inhibit, acid secretion but could not be rationally prescribed until acids were understood in the modern chemical sense. Hydrochloric acid has been known since the early fifteenth century, thought to be in the stomach by Paracelsus in the sixteenth and by Van Helmont in the seventeenth century, but it was not until 1823 that Prout definitively identified free hydrochloric acid in the gastric juice of man and animals and made quantitative measurements of its concentration.

Antacids became widely used only this century, especially in association with Sippy-type diets for ulcers [2]. As recently as the 1960s, orthodox gastroenterologists believed that gastric acidity was reduced by minimizing the amount of acid-stimulating foods such as protein and increasing the amount of acid-inhibiting foods such as fats. It was thought that gastrin release was limited by limiting meals to 150 ml to prevent antral distension and by forbidding secretagogues such as meat juices, coffee, caffeine-containing beverages and alcohol. Moreover, since the patient on such a diet might become frustrated and then hypersecrete acid if he saw normal meals that were forbidden, patients were not allowed to join the family at meal times [2].

Certainly doctors have used antacids for thousands of years to treat patients’ symptoms, and both doctors and patients have generally been satisfied with this treatment. Half the adults in the United States have used antacids, and a quarter have taken two or more doses per month. Doctors are even more convinced than patients of the helpfulness of antacids in relieving symptoms. Nevertheless, there is little evidence in the double-blind, randomized controlled trials that antacids do relieve ulcer symptoms, and in the conventional doses, they are probably no more than a logical placebo [3]. By contrast, antacids have now been shown repeatedly to be more effective than placebo in healing duodenal ulcers, in the range of efficacy of H2 blockade. Although the classical study used over a 1000 mmol/day, lower doses have been tried and in further trials were found effective down to around 200 mmol/day [3, 4].

INHIBITION

Inhibition. The term inhibition is all too often used loosely and without making clear the precise extent of the inhibition: of what function, from what level, to what level, by

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what percentage, with what inhibitor, for what purpose. Rational use of inhibitors could occur only when one had a clear pathophysiological model of duodenal ulcer and its hypersecretory state, when there were dose-response data in patients before and after the inhibitor and with assessments of ulcer healing and/or follow-up with or without maintenance treatment. It is convenient to begin with Schwartz, who in 1910 postulated the battle between the autodigestive power of gastric juice versus mucosal resistance: ulcer formation was likely if the acid was increased, and ulcer healing could be achieved by decreasing the acid [5].

Test meals. In 1912, Moynihan claimed that 70 percent of patients with duodenal ulcers had hyperchlorhydria or hyperacidity, a claim based on test meals in 20 patients with duodenal ulcer by Adams (1911). However, there are now ample data that the ranges of maximum acidity in normal subjects and in patients with duodenal ulcer overlap completely, whether after test meals, food, alcohol, caffeine or submaximal histamine [5]. In the absence of a threshold of acidity, there was no appropriate target figure to which inhibitors could be directed, and patients with duodenal ulcer could not be managed successfully.

Basal secretion. The first careful data on basal interdigestive secretion were produced by Carlson in 1912, allowing Galambos in 1926 to demonstrate basal hypersecretion in duodenal ulcer disease [5]. Overnight secretion was first measured by Chalfen in 1928, and by 1935, Winklestein had confirmed nocturnal hypersecretion in duodenal ulcer disease [5].

Although early studies claimed that patients with duodenal ulcer always produced some acid at rest, it is now clear that basal anacidity does not exclude duodenal ulcer disease. Measurements of 12-hr overnight secretion are more difficult than in a one-hr morning basal collection, and both show poor repeatability [5]. However, about one in four patients with duodenal ulcer do secrete more than the upper limit of normal, so that basal acid output has been used as a criterion for measuring the acid-lowering efficacy of an inhibitor [5]. Indeed, one of the earliest modalities of acid inhibition was neither pharmacological nor surgical but rather was physical with radiotherapy, as used in Chicago from 1937. The acid criterion compared with recurrence was achlorhydria after a submaximal agonist. If achlorhydria was induced, then ulcers healed and did not recur unless acid returned. Only four percent of 1485 patients developed achlorhydria for two years or longer; their peptic ulcers invariably healed and remained healed [2]. Similarly, in the only controlled trial of radiation (Levin, 1969), patients whose ulcers recurred were those with continuous basal acid secretion, whereas those who after a period of basal achlorhydria showed acid secretion only intermittently did not develop recurrence of their ulcers [2]. A different physical acid-lowering treatment was gastric freezing, which had to be abandoned because sustained acid inhibition could be achieved only with marked damage to the gastric mucosa.

Maximal acid output. After the introduction by Kay in 1953 of his augmented histamine test measuring maximum histamine-stimulated acid, it was soon possible to show that measurements of peak acid output in response to maximal doses of histamine (or histalog or pentagastrin) were about twice normal in patients with duodenal ulcer and that the proportion of patients with duodenal ulcer in the diagnostic hypersecretory range was now about a third [5]. It was also then possible 30 years ago to demonstrate a threshold of peak acid output of about 15 mmol/hr, below which duodenal ulcers were not found (Figure 1) [6]. This functional discrimination paralleled the morphology of the stomach [5].

It was already known that the number of parietal cells in patients with duodenal ulcer was twice normal, that half the stomachs attached to duodenum with ulcer had parietal
cell numbers above the upper limit of normal and that the threshold parietal cell mass was $1 \times 10^9$, below which duodenal ulcers were not seen post-mortem [5]. With this new threshold model, it was clear that any inhibitor, whether physical, surgical or pharmacological, that lowered acid output appropriately to below 15 mmol/hr, would induce healing of a duodenal ulcer. The ulcer would stay healed if acid remained below this threshold but might recur if acid returned to the previous higher level [5]. This model has been tested and supported world-wide with one notable exception (Figure 2) [7].

**ACID-LOWERING OPERATIONS**

Vagotomy. When Dragstedt was appointed Associate Professor of Surgery in the new University of Chicago School of Medicine, he had spent the whole of his undergraduate, postgraduate and professional life as a physiologist and had never been a surgeon even at a resident or intern level [8, 9]. His scientific approaches to a surgical solution to the problems of duodenal ulcer have been discussed elsewhere [8, 9], but it is important to point out that his human patients were studied before and after vagotomy and at follow-up with as precise measurements of gastric acid as were available to him at that time and had been used by him in the necessary preliminary animal experiments. Thus in 1950, Dragstedt published [10] the 12-hour overnight secretions of 19 patients who had been followed up for two to seven years and compared these with their pre- and post-operative studies. Data were given for each patient for volume, free acidity and acid output. Dragstedt [11] used as his main criterion for completeness of vagotomy a reduction of overnight acid output of greater than 60 percent and a negative secretory response to insulin hypoglycemia. None of the 142 patient who met these criteria had persistent or recurrent ulcer symptoms, but five of the 18 whose tests showed incomplete vagal section did have persistent or recurrent ulcer symptoms.

It is not surprising that 50 years later we use other criteria of completeness of vagotomy. We know that nocturnal gastric acid is a poor discriminant between patients with
duodenal ulcer and healthy volunteers and that it is poorly reproducible [12]. Today we would also look at maximal acid output and insulin or sham-feed stimulated acid output.

Probably the most complete data are those from Copenhagen, where Kronborg followed 99 percent of 500 patients who had duodenal acid treated by truncal vagotomy and drainage six to eight years before. He used the many previously published criteria but also performed discriminative analysis to place the highest possible proportion of recurrence and non-recurrence in relationship to a critical level of secretion. One of his key findings was that those patients who were left 10 days after operation with peak acid output after histamine greater than 21 mmol/hr had a 25 percent recurrent ulcer rate compared with only five percent if they produced less than 21 mmol/hr. Clearly, there are only two reasons why patients should have high residual maximal acid output. Either they were hypersecretors before the operation or the operation had achieved inadequate reduction in acid output. Kronborg’s data showed that those who were secreting greater than 46 mmol/hr before the operation had a 21 percent recurrent ulcer rate compared with five percent in those who secreted less than this output. Most interesting of all are those patients where the vagotomist achieved greater than 68 percent reduction in maximal acid output; they had only a two percent recurrence rate compared with 16 percent with less than 68 percent acid reduction [5, 13, 14].

Insulin tests. Dragstedt used the Hollander insulin test routinely [10], but both his criteria and his interpretation were based on the then current all-or-none judgments. Studies since then, both in healthy volunteers and in patients with duodenal ulcer, suggested that the acid response to insulin is both dose-dependent and hypoglycemia-dependent and not all-or-none [5]. Moreover, not only does insulin hypoglycemia provide a
quantitative glycopenic stimulus, but it also produces a quantitative vagal response that can be expressed as peak acid output after insulin in mmol/hr and not merely as a positive or negative result assessed by the peak or rise in acidity in mmol/l [5].

The second problem is also all-or-none. Dragstedt accepted the then current view that "in man, apparently, the persistence of a small vagus fibre after section of two of the larger vagal trunks permits the continued excessive night secretion characteristic of the ulcer patient. The remaining vagus fibre appears to be able to activate the entire glandular apparatus, acting presumably through the submucus plexus of Meissner" [10]. However, subsequent animal studies have suggested instead that after vagotomy, the fall in peak acid output after insulin is related to the extent of acid-secreting mucosa denervated, and the residual acid output after insulin or sham-feed is an expression of residual vagal innervation [5].

Using this now standardized methodology of quantitative interpretation, and corrections of juice volume (V_G) for pyloric loss and duodenal reflux, it was possible for Hobsley's group [15] to show that patients with duodenal ulcer always had V_G greater than 140 ml/hr before operation. All patients who after vagotomy had V_G less than 140 ml/hr remained symptom free, but of those men with V_G greater than 140 ml/hr (that is, within the preoperative range), half developed recurrent ulcers.

The use of acid secretion tests (basal, maximal, insulin or its safer successor sham-feed) has elucidated the nature of acid inhibition achieved by the various vagotomies. It has also improved the technique of the surgeon by comparing trained surgeons with trainees, trainees' improvement during their training, the learning phase when a surgical department first uses a new vagotomy, as well as comparisons between the acid inhibition achieved by general surgeons and by specialists in gastric surgery [5, 16]. It was thus possible to assess the efficacy of the latest approach to vagotomy, by laparoscopy, showing inhibitions of 79 percent of basal acid output and 83 percent of peak acid output after insulin [17].

Resection. The percentage reduction in basal and maximum acid outputs after the various gastric resections, with or without vagotomy are, like vagotomy alone, directly correlated with non-recurrence of the ulcer. (Figure 3) [13, 14].

![Figure 3. Non-recurrence of duodenal ulcer and percentage reduction of maximal acid output after gastric operations. Data of Baron (1973 and 1974) [13, 14].](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAgAAAAAbgAIAAADXaWqQAAAABJRU5ErkJggg==)
Operations for Zollinger-Ellison syndrome. When it became clear that the Zollinger-Ellison syndrome of intractable peptic ulcer, basal hypersecretion and pancreatic tumor was usually due to a gastrinoma, then it became possible in some patients to avoid the previous usual procedure of total gastrectomy and instead cure the patient’s ulcer disease from acid and gastrin hypersecretion by removal of the gastrinoma alone.

ACID-INHIBITOR DRUGS

It is now clear that the ulcer-healing properties of an acid-inhibiting drug is a strict function of the reduction of acid and acidity achieved, whether the drug blocks the acetylcholine M₁ or the histamine H₂ receptor on the surface of the parietal cell, or the intracellular enzyme responsible for acid production. In the last 30 years, there have been many double-blind, placebo-controlled trials of acid inhibitors in healing ulcers and preventing relapse. Many of these studies were done in countries with low placebo healing rates of 30 percent, so that large numbers of patients were not needed in these trials.

Anti-receptor acid inhibitors

Anticholinergics. Acetylcholine receptors are classified as nicotinic and muscarinic (with several subtypes). The old, classical anti-muscarinics (such as atropine) are not selective, because even if atropine is a potent and specific muscarinic antagonist, it is not subtype specific. Many non-subtype muscarinic receptor-antagonists have been synthesized since 1950 as acid inhibitors. Few have been effective in duodenal ulcer disease, partly because of the difficulty in finding an optimum effective dose, defined as just less than the dose in a particular patient that produces side effects [2-4]. Nevertheless, there were two convincing studies. The first by Sun in 1964 [18] was a double-blind, 18-month maintenance study with glycopyrronium, 1 mg, four times a day. The second by Walan in 1970 was a two-year maintenance therapy with L-hyoscyamine: data were provided for basal and maximal acid output before, during and after treatment [19]. Patients varied in the reduction of acid output that could be achieved by a maximum tolerable optimum effective dose of amitriptyline; ulcer recurrence was associated with non-reduction of acid secretion (less than 23 percent); prevention of ulcer recurrence was associated with adequate reduction of acid secretion (greater than 32 percent).

Pirenzipine was the first selective anti-muscarinic drug to be marketed, and it binds with higher affinity to M₁ than to other muscarinic receptors. Pirenzipine’s acid inhibitory power allows it to heal peptic ulcer significantly more effectively than placebo in a dose-dependent fashion and has a maintenance effect, but these properties are less powerful than those of H₂ blockade. Nevertheless, combination of an H₂ receptor blocker and antimuscarinic possess both theoretically and experimentally a greater anti-secretory effect than either alone. This combination has been used clinically, but rarely since the availability of omeprazole (see below).

H₂ receptor blockers. There is little need here to do more than point out that H₂-receptor blockers such as cimetidine and ranitidine will heal about 80 percent of duodenal ulcers in four to six weeks and almost 100 percent if continued for three months; maintenance therapy will keep about 80 percent of duodenal ulcers in remission for a year, and their clinical efficacy parallel their acid inhibitory property [3, 4].

Intracellular enzyme inhibitors. The enzyme carbonic anhydrase catalyzes the removal of bicarbonate from the cell and was once thought to be responsible for H⁺ production from H₂O in the parietal cell. The first carbonic anhydrase inhibitor to be identified was sulphanilamide in 1940. Acetazolamide was synthesized in 1950 but reduced acid only slightly, and there have been few reports of any ulcer-healing efficacy.
Once it became clear that H⁺/K⁺-ATPase was the enzyme regulating the production of hydrochloric acid at the secretory surface of the parietal cell, it was possible to synthesize gastric proton pump inhibitors such as omeprazole, a substituted benzimidazole. Omeprazole gives a dose-dependent inhibition of acid secretion of about 20-95 percent, and a four-week duodenal ulcer healing ranging from 50-97 percent with doses of 10-80 mg daily [4].

**ULCER HEALING BY APPROPRIATE ACID SUPPRESSION**

The threshold model has been tested not only with various acid-lowering operations and radiotherapy but also with antisecretagogues. If basal pH was greater than 3 both before and one week after starting pirenzipine 100 mg daily, three of seven patients with duodenal ulcer relapsed in 12 months; with pH greater than 3 only after one week, one of eleven relapsed; and with pH greater than 3 both before and after pirenzipine, none relapsed [20]. With cimetidine, five patients whose ulcers failed to heal after six weeks of 1500 mg daily had pre-treatment basal acid output (11.2 mmol/hr), thrice that of healers (3.4 mmol/hr) [21]. For peak acid output, the one-week healing was significantly higher (33 percent) with peak acid output less than 36 mmol/hr compared with 14 percent with peak acid output greater than 36 mmol/hr [22]. Overall, the proportion of duodenal ulcers that heal after two or four weeks of any acid suppressant treatment is strictly correlated with the percentage reduction of 24-hr gastric acidity [23] (Figure 4), and further meta-analyses yielded clear postulates such as that all duodenal ulcers would heal in four weeks if intragastric pH was kept above three for more than 18 hr a day (Figure 4) [24].

Total inhibition of acid and pepsin by operation drugs does not apparently interfere with normal digestion in the intestine but will lead to failure of the body to kill ingested...
bacteria with acid and, therefore, increase the risk of infective enteritis. However, removal of the parietal cells by total gastrectomy will remove intrinsic factor and inevitably produce B₁₂ deficiency when the body stores are exhausted: B₁₂ deficiency has not yet been seen with long-term acid inhibitor drugs. Powerful acid inhibitors will lead to increased gastrin release, which in animals has been associated with enterochromaffin cell hyperplasia and carcinoid tumors, but such tumors have not been seen in humans on long-term antisecretagogues.

**ACID INHIBITION OR HELICOBACTER PYLORI ERADICATION**

A century of acid-lowering operations and a half century of acid inhibitors have clearly shown that appropriate inhibition of acid, bringing it below a certain threshold, will heal duodenal ulcers, and if the acid inhibition is maintained by indefinite continuation of acid-lowering tablets, or by continued adequacy of the vagotomy, then ulcers will not recur. After ulcer healing, acid hypersecretors remain hypersecretors and at risk of recurrent ulceration, so maintenance tablets or an operation may be indicated.

The clear success of these acid-lowering treatments eventually convinced clinicians that excess acid was a necessary factor for the production of duodenal ulcers. However this, was not the end of the story for ulcerologists because there was no adequate explanation for the duodenal changes produced by excess acid, or indeed the cause of the excess acid.

Duodenal ulcer develops from duodenitis, which develops especially in abnormal mucosa in the duodenum. This abnormality has long been recognized as a mucosa containing not the normal cell types of duodenum but showing gastric metaplastic cells, which can be produced experimentally by increasing duodenal acidity [25]. Gastric heterotopia was never found in duodenal mucosa from gastric resection if the preoperative maximal acid output was less than 10 mmol/hr, was rare at less than 20 and became increasingly common the higher the acid output [26, 27]; it has also been correlated with fasting gastric pH and not seen unless the pH was below 2.5 [28].

Not long after the original isolation in 1983 by Warren and Marshall of *Helicobacter pylori*, this bacterium was held to be the prime cause of non-autoimmune gastritis, and indeed, Marshall produced gastritis in himself by swallowing *H. pylori*.

Antral gastritis was long known to be associated with duodenal ulcer disease, and it was therefore inevitable that antral *H. pylori* infection has been found in almost every patient with duodenal ulcer. Acute infection with *H. pylori* may lead to transient reduction in acid output, which can become permanent if gastric atrophy develops in the body of the stomach. It is still unclear whether mild inflammation of the antrum, which decreases D cell release of somatostatin and thus increases gastrin and histamine release, is a cause of gastric acid hypersecretion.

Marshall’s group found *H. pylori* in areas of focal metaplasia in the duodenum, and our current model of duodenal ulcer disease has two components: acid-induced duodenal gastric metaplasia infected with *H. pylori*. This model, that *H. pylori* is responsible for about 95 percent of duodenal ulcers, which can develop only if there is acid-induced gastric metaplasia in the duodenum, can be tested by the efficacy of eradication of *H. pylori*, which not only leads to healing of almost every duodenal ulcer but also prevents relapse of the ulceration.

Acid inhibition, whether medical or surgical, whether for healing or for maintenance, is no longer the treatment of first choice for most duodenal ulcers. However, acid suppression is now part of many regimes for eradicating *H. pylori*. Although acid inhibitors by themselves do not eradicate *H. pylori*, one of them (omeprazole) does have the property of suppressing (but not eradicating) *H. pylori*. Moreover, omeprazole’s chief role in an
H. pylori eradication scheme is to raise the intragastric pH and increase the bactericidal effect of antibiotics such as amoxycillin and clarithromycin, which show considerable pH sensitivity in their minimum inhibitory concentrations for killing H. pylori both in vitro and in vivo [29]. Clearly, acid inhibitors will remain the treatment of choice to heal and maintain in remission that five percent of duodenal ulcers that are not related to H. pylori and those peptic ulcers that are induced by non-steroidal anti-inflammatory drugs, quite apart from their continued role in the treatment of gastro-esophageal reflux disease. Naturally, there are other non-acid aggressive factors than H. pylori and non-steroidal anti-inflammatory drugs, such as smoking and stress (burns, polytrauma, organ failure). There are also ulcer-healing treatments that are neither anti-secretory nor lethal to H. pylori, for example carbenoxolone, prostaglandins and sucralfate.

FINALE

In New Orleans, on April 26, 1975, Dragstedt delivered his last paper. In his address, published posthumously [30], he reviewed his truncal vagotomy and welcomed the newer vagotomies as the likely best routine treatment of duodenal ulcer, which by lowering acid would reduce the morbidity and mortality of the disease. Indeed, his very last words were “Death is the worst thing that can happen to an ulcer patient. The game then is over.” As a physiologist turned surgeon, he would, I hope, have welcomed the replacement of elective vagotomy by acid-lowering drugs. But I wonder if he would have recalled his first paper, 60 years before, in 1917, when he grew bacteria from ulcers, which were caused, therefore, not by acid but by an infection [31].

Dragstedt’s acid-lowering vagotomy (a surgical triumph of applied physiology) led to acid-lowering drugs (medical triumphs of applied pharmacology) [32], and these two treatments have been effective in healing peptic ulcers over this last half century. By some bizarre fate, these acid-lowering treatments (which healed but did not cure the underlying ulcer disease) have been largely superseded by the vindication of Dragstedt’s first ulcer model, constructed in his early twenties, that these ulcers are caused by bacteria (now identified on culture as H. pylori) and, therefore, are curable by eradication with anti-bacterials.

We now know that both acid hypersecretion and these bacteria are needed for duodenal ulcer formation. Dragstedt’s bacterial model [31] was not capable of proof in 1917 in the absence of today’s culture techniques and antibacterials, but his later (acid hypersecretion) model was both testable and treatable. Few scientists are right twice and differently in their life work. Dragstedt was, and we rightly commemorate him.

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