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# Historical Perspective of Gastric Acid Inhibition

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## Abstract

The inhibition of gastric secretion has been a therapeutic objective for decades. A variety of pharmacologic and non-pharmacologic approaches have been proposed throughout history. Among the non-pharmacologic proposals, gastric surgery was widely used until effective drugs were available. Initially antacids and later anticholinergics, $H_2$ blockers and proton pump inhibitors took the predominant position. Finally, *Helicobacter pylori* eradication has been the milestone for the cure of peptic ulcers.

## 1. Introduction

The gastric and oesophageal diseases related to acid secretion (acid-related upper gastrointestinal conditions) have been, since ancient times, subjects for study and control. Over centuries they have caused considerable morbidity and mortality, while the physician could do comparatively little, not only to achieve a cure, but even to achieve palliation of symptoms. Throughout the 19th century and most particularly during the last one-third of the 20th century, significant advances have occurred that have profoundly changed our concepts and understanding regarding these diseases. In this paper, we will present a succinct review of the changes that have occurred over the past 100 years and the various therapeutic alternatives to which both physicians and patients have had access (figure 1). Other papers, drawing on evidence-based medicine, will carry out in-depth reviews of the details related to modern therapeutic management of acid-related diseases.

## 2. The Stomach

It was not until 1892, when Heinrich Irenäus Quincke proposed the term '*ulkus pepticus*' (peptic ulcer), that gastric acid secretion was correlated to gastric diseases and, more specifically, to ulcerations in the gastroduodenal mucosa. However, gastric ulcer disease had been known since long before then – more precisely since its description by Jean Cruveilhier under the name of '*ulcére ronde*' (round ulcer).[1] It was not until the end of the 19th and beginning of the 20th centuries that pathophysiological and experimental medicine came to the fore and an endless series of studies and experiments began, the results of which served only to demonstrate and confirm what some had already surmised: the significance of hydrochloric acid/peptic secretion in the pathogenesis of the disease.[2,3]

By the beginning of the 20th century, most of the better-informed physicians already believed that 'hyperchlorhydria' was the main and major cause

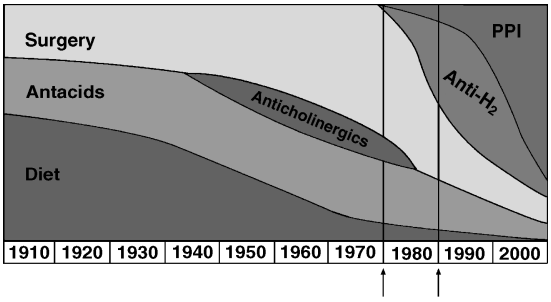


**Fig. 1.** Approximate schematic representation of the strategies used during the 20th century for counteracting the action of gastric acid. An inflexion occurs during the 1980s, with the introduction of drugs that inhibit acid secretion.

of ulcer disease, although, even then, others also defended the possible role that pepsin might have in the 'digestion' of the patient's own gastric mucosa. Despite some lines of thought that considered that ulcer disease was caused by a weakening of the defences (meaning the mucosal barrier), slowly the fact became established and recognised that, almost constantly, hyperchlorhydria constituted the basis of the disease. At that time, more thought was given to pathophysiological facts than to aetiological ones, as nothing could be identified that might be considered to be directly and causally responsible for the disease. It is noteworthy, however, that by the end of the 19th and the beginning of the 20th centuries thought was already being given to the theory of a possible infective cause (this period was the acme or the 'microbiological era'). This theory was soon set aside, however, as no responsible microorganism could be identified. The early years of the past century saw the first studies on gastric chemistry and chemical action, which showed that over 90% of patients with ulcer disease had hyperchlorhydria.

Ulcer therapy, in those days, was based on a number of different substances: belladonna, atropine, aluminium silicate and even bismuth subnitrate were used. Most patients suffered severe symptoms; some of them improved under treatment, but most of them, after a more or less protracted period of improvement, relapsed. The surgeons of the time advocated gastrectomy as the only way to put an end to the patients' sufferings and thus to eliminate the acid, if indeed it was the cause.

The years that followed brought about more profound and more detailed pathophysiological studies. It was confirmed that these patients had both nocturnal and fasting hyperchlorhydria, and that gastric stimulation via the *nervus vagus* or through the action of certain hormones was responsible for the disease. Experimental studies performed in dogs demonstrated that truncal vagotomy improved the condition by reducing gastric secretion, and the technique was added to the treatment strategies for human ulcer disease. Dragstedt and Owens, in 1943, performed the first therapeutic truncal vagotomy in a human patient; although the technique initially caused complications, it paved the way for new alternatives, such as gastrojejunostomy or pyloroplasty.[1]

Further new studies on gastric acid secretion were being undertaken in parallel. The various phases of gastric secretion (cephalic, gastric and duodenal) were studied in detail, and the role of gastrin began to be understood, opening new lines of research that would lead to improved understanding of other processes, such as the Zollinger-Ellison syndrome. Other pathways of research addressed the gastric mucosal barrier, but there was nothing to predict that gastric acid might be toppled from its pedestal as the pathophysiological culprit of the lesions observed.

## 3. The Oesophagus

Winkelstein[4], in 1934, was the first to report the presence of a peptic ulcer in the oesophagus. This opened the road towards recognition of a new pathological condition that had until then been unknown and unsuspected. As early as the 1940s, and through roentgenological studies, 'reflux oesophagitis' began to be considered and discussed. Under certain conditions, the acid gastric contents might flow back ('reflux') into the oesophagus and cause lesions, which were sometimes severe. Studies published at that time concluded that the cause of such a backflow, or

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reflux, was none other than a diaphragmatic hiatus hernia, and a number of papers were published discussing various types and concepts, explaining why there would be symptoms and lesions in some cases, but not in others.[5] The supporting evidence was minimal, as roentgenological studies could go only so far, and digestive endoscopy (at that time, with rigid endoscopes) was performed at only a handful of centres, so that available experience was limited.

Years later, and with improvements such as the introduction of the semi-rigid endoscope already available, Barrett[6] described a new clinical condition characterised by the presence of oesophageal ulcers. This is not the place to describe the discussions and debates that took place between Barrett and Allison[7], which are described elsewhere; suffice it to say that great importance began to be ascribed to the newly described 'reflux oesophagitis', regardless of the lesions it might cause and what relation it might bear to a number of (anatomical) types or variants of the oesophagus (short oesophagus). At that time the problems were strictly anatomical because, on the basis of roentgenology, it was quite difficult to define exactly where the oesophagus ended and the stomach began; the accompanying change in the mucosal lining would not be detectable in everyday clinical practice until the introduction of present-day endoscopes. Furthermore, the interpretation of the symptoms was not correct, as they were attributed more to the presence of a diaphragmatic hiatus hernia than to the reflux itself, even though some voices advocated the opposite. In any case, there was one and only one fact that was and remained completely clear and evident: hydrochloric acid/peptic secretion did have a significant, even a major role, in the lesions occurring in the oesophagus. The medical treatments used at that time provided few positive effects, and they were based on postural measures rather than on pharmacological intervention; only later, in the 1950s, was aluminium hydroxide incorporated into treatment – an inspired alternative.[8] Faced with this situation of therapeutic failure, it was again the surgeons (as we have seen, there were no alternative possibilities) who came to the forefront and advocated corrective surgery of the diaphragmatic hiatus hernia as the curative solution.

As before, the following years demonstrated and confirmed the clear relationship between acid and oesophageal disease; the diagnostic techniques were refined and improved, the oesophageal symptoms were reproduced with acid instillations, and more modern techniques of pH measurement in the stomach and oesophagus were developed, among them, in the 1960s, the *Heidelberg capsule*, with which we have had the opportunity to work.[9] The later introduction of oesophagoscopy and of 24-hour manometry and pH-metry finally afforded us detailed and profound knowledge of what we today know by the name of 'gastro-oesophageal reflux disease'.[10–12]

## 4. The Aim: To Neutralise Acid

It is evident that, once it had been demonstrated and confirmed that the gastric acid was the cause of the lesions occurring in the oesophagus and stomach, and regardless of other pathophysiological considerations, the strategy was quite clear: What can we do so that the acid may not be corrosive? Might some form of diet be effective? How can we neutralise the acid? Rather a lot of questions, and rather few really useful answers.

The first approach was recourse to a number of different diets that might be able to maintain the patient's stomach at a higher pH for as much of the day as was possible. Diets were thus recommended that involved smaller meals more often throughout the day, or consuming as alkaline a diet as possible. Observation had led to the knowledge that milk acted as an alkaline substance, and patients took milk either on prescription or on their own account. The famous 'Sippy diet' came into fashion: this involved the administration, every 2 or 3 hours, of 125 or 150 ml of milk together with its cream. This diet had to continue until the patient was symptom free, and then the variety of foodstuffs could be slowly increased, with limitations and restrictions.

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The second aspect to be considered was the neutralisation of the acid through the use of alkaline substances.[8] The mainstay of alkaline therapy was – and still is, for a number of elderly patients – sodium bicarbonate (or sodium hydrogen carbonate). Other substances used were bismuth subnitrate and the 'Sippy powders' (calcium carbonate and sodium bicarbonate at varying ratios ranging from 1:1 to 1:4). Later came aluminium hydroxide (better tolerated), magnesium trisilicate, magnesium carbonate and magnesium oxide. All had positive effects, but they had to be taken very often and were not devoid of side effects. In the 1950s and 1960s, a number of mucopolysaccharide sulphate-rich preparations were also recommended, with the aim of counteracting the action of pepsin. A fruitless effort! The patients still suffered; those who improved did so episodically in the best of cases, and for the remainder the quality of life was pitiful. They became embittered, and some authors even described an 'ulcerous personality' (Type 'B' personality).

We now know that gastric acid was not the cause, but the consequence, of ulcer disease.

The evolution of knowledge and treatments was similar in the case of gastro-oesophageal reflux disease, or GORD, as we now know it. There were any number of treatments, ranging from diets, diverse postural treatments (always favouring or taking advantage of gravity, never lying down after a meal) and massive use of antacids of various sorts.

## 5. The Aim: Surgery

What could be done under such circumstances? The clinicians could do no more. The patients began losing hope, and there were few solutions that could be offered to them. One of those solutions was gastric surgery, which experienced its golden age during the past century and well into the 1970s, when the first antisecretory drugs appeared. As already pointed out, the most radical approach, at the beginning of that golden age, advocated complete removal of the stomach; this not only eliminated the ulcer, but also the possibility of secreting acid. Total gastrectomy was then superseded by partial gastrectomy, and the latter by partial gastrectomy in association with vagotomy. In order to prevent gastroparesia, first gastrojejunostomy and then pyloroplasty were proposed. Even though many patients improved with these interventions, in about as many, surgery was not sufficient or the complications prompted the development of new techniques. First selective vagotomy, then supraselective vagotomy and finally all sorts of variants were proposed, with sometimes spectacular results, but they were far from being the ideal treatment.

In the field of acid-induced oesophageal disease the approach was similar, and failure of hygiene, dietetic measures and antacids was the rule. Again, the surgeons came into the breach and proposed a number of surgical procedures and techniques, among them fundoplication, a procedure that aimed at – insofar as was possible – reconstructing the gastro-oesophageal junction.

## 6. The Aim: Inhibiting Acid Production

This was the major – no, the prime – challenge: to achieve a drug that would inhibit acid production. The 1970s began with a flood of studies and trials in this field. Although the so-called anticholinergics, drugs that acted simultaneously on the preganglionic and postganglionic fibres (methantheline, banthine, propantheline, probanthine) had been known for years, and doubtlessly led, in combination with antacids, to improved and sometimes spectacular results, it was increasingly clear that these drugs inhibited acid secretion hardly at all.

It was already known that histamine was a common mediator of acid production; on the basis of this knowledge, the search began for drugs that might block the histamine type 2 receptors (the so-called $H_2$ receptor blockers or antagonists). The first publication by Black and co-workers[13] opened a door that never again would close.[14] Working at the Smith Kline & French company, they began their studies and, after examining other

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$H_2$ receptor antagonists such as burimamide and metiamide, they came to the conclusion that cimetidine exhibited an adequate pharmacological profile, with a clear antisecretory action and almost no side effects. This drug specifically blocked the $H_2$ receptors, so that the production of acid decreased dramatically. Ulcers healed within a few weeks, and the patients' pain disappeared within a couple of days. A true revolution! Beyond any reasonable doubt, James Black had entered into medical history. He had discovered two drugs that profoundly transformed modern pharmacotherapy: an adrenergic β-receptor blocker, propranolol, and an $H_2$ receptor antagonist, cimetidine. In 1988 his work was honoured with the Nobel Prize for Medicine or Physiology.

Nevertheless, the problem and the struggle to solve it were far from over. After medication was suspended, the patient relapsed: the ulcer was indeed healed, but not so the *ulcer disease*. A similar phenomenon was seen with reflux oesophagitis. New ways to use the drug had to be found, and this led to maintenance therapy. Although it did not modify the natural history of either disease, maintenance therapy kept the patient in a healed condition in most cases, provided the drug treatment was not interrupted.[15,16] Nevertheless, the studies by the pharmaceutical laboratories continued, and soon led to the development of further $H_2$ receptor antagonists (oxymetidine, mifentidine, etintidine, thiotidine and many others) that did not yield good results. However, some other drugs such as ranitidine, famotidine and nizatidine passed the stringent tests and appeared on the market with evident success – particularly ranitidine, which eventually developed into one of the most-prescribed, most-sold drugs world-wide.

Still the physicians were not wholly satisfied. There were many patients whose ulcers did not heal, or healed only partially, or who simply developed frequent relapses. Furthermore, in the case of reflux oesophagitis, the $H_2$ receptor antagonists were clearly insufficient, not only for achieving healing of the lesions but, much more importantly, for maintaining them in a healed condition. The doses were increased, but the response showed almost no variation. It was evident that a great step forward had been made, but that it was not the definitive one. One significant advantage of these drugs, however, was that gastric surgery began diminishing at an astounding rate.[17]

There was, however, another line of research under way, a much more ambitious one. What was searched for was a drug that acted in a completely different way: as the $H_2$ receptor antagonists only blocked the stimuli to the gastric parietal cell, this new drug should be able to prevent any stimulus from allowing or inducing further acid secretion. How, though, does a stimulus to the parietal cell lead to acid secretion? In 1973, Ganser and Forte[18] began their studies working on frog oxyntic cells, and they soon demonstrated the presence of a single enzyme in the parietal cell. This enzyme was a potassium-dependent proton-exchanging adenosine triphosphatase ($H^+/K^+$-ATPase),[18,19] and it acted as an 'exchange pump' that traded one proton (a $H^+$ nucleus) for a potassium ion ($K^+$). The studies continued in humans, and confirmed that this enzyme was also present in the human gastric parietal cell. The target had been found and was quite clear. Could a drug be developed that would block this enzyme, this 'proton pump'? Studies in search of such a drug lasted for some years, and after the discovery and assessment of picoprazole in 1976 they led, in 1979, to the development of omeprazole. This drug was much superior to the $H_2$ receptor antagonists in the treatment of both gastroduodenal ulcer disease and gastro-oesophageal reflux disease. The most recent meta-analyses, which will be discussed elsewhere in this Supplement, underscore the clear benefit of these 'proton pump inhibitor' drugs (PPIs) as compared with $H_2$ receptor antagonists. The following years were full of studies and trials for the development of new PPIs, some of which ended in success, whereas others failed. Among the successful PPIs we have, at present, esomeprazole, lansoprazole, rabeprazole and pantoprazole. A veritable revolution had occurred in the management of acid-related disorders, which has radically changed our approach to our patients and has at the

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same time even changed those patients' lives, affording a life of better quality, with fewer side effects from drug treatments and with fewer disease complications.

We still have much to learn about the use of these drugs, but it is beyond any doubt that we have entered an epoch that, when we finished our Medicine studies (oh, so long ago!), would have seemed to be the matter of purest science fiction.

Finally, further to the developments described above, and beyond, but interconnected with, this historical description of gastric acid inhibition, there has been the discovery of *Helicobacter pylori*. This is a completely new story in itself, and one that has fundamentally changed the natural history of gastroduodenal ulcer disease.

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