

# Pharmacological Management of Peptic Ulcer: A Century of Expert Opinions in *Cecil Textbook of Medicine*

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**Background:** Advances in drug therapy for peptic ulcer have had a significant impact on quality of life and work potential of many millions of affected persons and have contributed to a remarkable decrease in the prevalence of the disease, frequency and severity of complications, hospitalizations, and mortality.

**Study Question:** What are the milestones of the changes in the expert approach to the pharmacological management of peptic ulcer in the past century?

**Study Design:** To determine the changes in the experts' approach to the management of peptic ulcer, as presented in a widely used textbook in the United States.

**Data Sources:** The chapters presenting the management of peptic ulcer in the 26 editions of *Cecil Textbook of Medicine* published from 1927 through 2020.

**Results:** *Acid neutralization* with alkalis was the only pharmacological intervention recommended in the textbooks published from 1927 to 1975. Atropine and other antimuscarinic agents were mainly used to relieve pain and acid secretion according to the paradigm "no acid no ulcer." The shift to the *acid suppression* paradigm started with the introduction of the histamine-2 receptor antagonist cimetidine in 1979, the proton-pump inhibitor omeprazole in 1988, and the prostaglandin agonist misoprostol in 1992. Finally, the *eradication of Helicobacter pylori* was codified in 1996.

**Conclusions:** The pharmacological management of peptic ulcer has remained archaic well into the 20th century. Fundamental progress occurred in a very short period (1979–1996) and was due to paradigm shifts from acid neutralization to acid suppression and later the recognition of the role of *H. pylori* infection.

**Keywords:** peptic ulcer, pharmacological management, Cecil textbook of medicine

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## INTRODUCTION

Peptic ulcer disease is a classical and common condition, characterized by a mucosal break in the stomach or duodenum, of at least 3–5 mm, and deep enough to be visible by endoscopy.<sup>1</sup> In the past century, the condition has shown significant changes in prevalence, clinical presentation, and therapeutic options.<sup>2–5</sup>

The aim of this article is to review the evolution of pharmacological interventions for peptic in the close to a century old *Cecil's Textbook of Medicine*. The expert

contributors to the authoritative textbook have indicated to transition to an approach based solely on acid neutralization with alkalis to the revolutionary paradigm shift brought about by not only the discovery of the role of *Helicobacter pylori* in the pathogenesis of peptic ulcer disease but also the progress in the synthesis of pharmaceuticals and the changes in lifestyle and nutrition of the population.

For more than a century, the main pathogenic factor for peptic ulcer disease was considered to be the effect of hydrochloric acid on the gastric mucosa, before the mechanisms of this secretion was correctly identified. The famous Schwarz paradigm “no acid, no ulcer” dominated the medical approach to peptic ulcer disease for the most of the 20th century.<sup>6</sup> The advent of the infectious etiology of peptic ulcer disease changed this paradigm.

## METHODS

### Data sources

The primary data sources for this work were the chapters on the management of peptic ulcer in the 26 consecutive editions of *Cecil Textbook of Medicine*. The first edition of the textbook was published in 1927, whereas the latest became available in 2020. The expert authors were Thomas Brown from Johns Hopkins University (4 editions, 1927–1937), Walter Palmer from the University of Chicago (6 editions, 1942–1959), Joseph Kirsner from the

University of Chicago (3 editions, 1963–1971), Jon Isenberg from the University of California at Los Angeles (3 editions, 1975–1982), Walter Peterson from the University of Texas Southwestern Medical School at Dallas (3 editions, 1985–1992), David Graham from Baylor College of Medicine (3 editions, 1996–2004), Juan Malagelada from the Universidad Autonoma de Barcelona, Spain (1 edition, 2008), Martin Blazer from New York University (3 editions, 2008–2016), and Ernst Kuipers from Erasmus University, Rotterdam, the Netherlands (4 editions, 2008–2020) and secondary sources were publications retrieved from MEDLINE that clarified technical issues related to the development, regulatory approval, and utilization of the drugs mentioned in the *Cecil Textbook of Medicine*.

### Data collection and analysis

We started by identifying the pharmacological interventions proposed in the first edition of the textbook, after which we recorded the changes in subsequent editions. We also noted the year in which previously endorsed interventions were no longer recommended. Finally, we assessed the duration of latency periods during which the management was not changed.

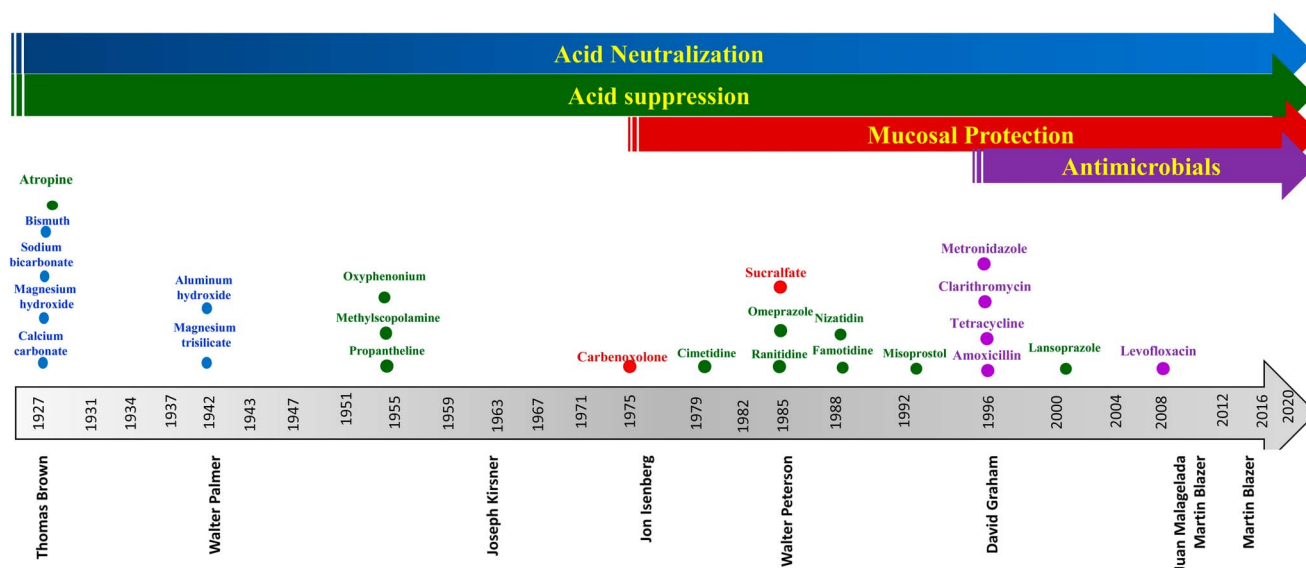
## RESULTS

### Main findings

The pharmacological management of peptic ulcer disease, as reflected in the expert opinions published in

**Table 1.** Pharmacological advance in management of peptic ulcer therapy 1927–2020.

Drugs		1927	1931	1934	1937	1942	1943	1947	1951	1955	1959	1963	1967	1971	1975	1979	1982	1985	1988	1992	1996	2000	2004	2008	2012	2016	2020	
Acid Neutralization	Calcium carbonate	█																										
	Magnesium hydroxide	█																										
	Sodium bicarbonate	█																										
	Bismuth																											
	Magnesium trisilicate					█																						
	Aluminum hydroxide					█																						
Acid suppression	Antimuscarinics	Atropine	█																									
		Propantheline																										
		Methyscopolamine																										
		Oxyphenonium																										
	H2-receptor Antagonists	Cimetidine															█											
		Ranitidine																										
		Famotidine																										
		Nizatidine																										
	Proton-Pump Inhibitors	Omeprazole																										
		Lansoprazole																										
Prostaglandin Agonists	Misoprostol																											
Mucosal Protection	Carbenoxolone																											
	Sucralfate																											
Antimicrobials	Amoxicillin																											
	Tetracycline																											
	Clarithromycin																											
	Metronidazole																											
	Levofloxacin																											



**FIGURE 1.** Pharmacological advance in management of peptic ulcer 1927–2020.

the *Cecil Textbook of Medicine* since 1927, is characterized by a half century of therapeutic inertia followed by 2 decades of major advances. The research community and pharmaceutical industry have not produced any new drug therapies in the past 25 years (Table 1).

*Acid neutralization* with alkalis (calcium carbonate, sodium bicarbonate, magnesium hydroxide, bismuth subcarbonate, and aluminum hydroxide) was the only pharmacological intervention recommended in the textbooks published from 1927 to 1975. Atropine and other antimuscarinic agents were mainly used to relieve pylorospasm. The shift to the *acid suppression* paradigm started with the introduction of the histamine-2 receptor antagonist cimetidine in 1979, the proton-pump inhibitor omeprazole in 1985, and the prostaglandin agonist misoprostol in 1992. *Mucosal protection* advanced with the apparition of carbenoxolone in 1979 and sucralfate in 1985. Finally, the *antimicrobial therapy* for *H. pylori* was codified in 1996 (Figure 1).

### Treatment of peptic ulcer in 1927

In the first edition of *Cecil's Textbook of Medicine*, the gastric and duodenal ulcers were considered to start with a mucosal lesion produced by a necrotic process, an abscess, or a hemorrhage followed by the digestion of the affected area. Lesions (presumably obstructive) in the celiac axis and an imbalance between the vagus and the sympathetic system were considered major contributing factors to the pathogenic process. The type of alcohol beverage intake had a role, as the condition was believed to be more prevalent in the schnapps drinking area of Northern Germany than

in the beer drinking south of that country. In the expert's opinion, hyperacidity and hypersecretion were the effect and not the cause of the ulcers.<sup>7</sup> The therapeutic recommendations did not change in the following 3 editions (1931–1937).

The treatment relied on changing eating habits and diet, allowing the stomach to rest by avoiding physical exertion and cognitive strain, eliminating pylorospasm, and counteracting gastric hypersecretion, in this order.<sup>7</sup> Dietary recommendations highlighted olive oil, gelatin, salt-free butter, and egg whites, which were believed to have no impact on gastric secretion. If these aliments were not available or not tolerated, the patient was advised to have 6 meals a day of cereal and a half and half mixture of cream and milk.

For acid neutralization, Brown<sup>7</sup> used equal parts of bismuth subcarbonate or subnitrate and sodium bicarbonate, of which 5 g (one teaspoon) was administered 1–2 hours after each of the 6 feedings and once or twice during the night. Bismuth subcarbonate was relatively inexpensive because it was obtained from the mineral bismutite. Calcinated magnesia (magnesium oxide), milk of magnesia (magnesium hydroxide), and calcium carbonate were other alkalis with similar effect. Calcium carbonate was indicated for patients with diarrhea, whereas magnesium hydroxide was a useful addition for patients with constipation.

Naturally occurring antimuscarinic agents were used to relieve pylorospasm. Tincture obtained through alcohol extraction of atropine, scopolamine, and hyoscyamine from the foliage and berries of *Atropa belladonna* was started at a dose of 5 drops before the

3 principal meals and increased 1 drop/d as tolerated. For “very nervous” patients, the preferred antimuscarinic was tincture of *Hyoscyamus niger*, in combination with strontium bromide.

### Acid neutralization

Walter Palmer and Joseph Kirsner, from the University of Chicago, were legendary gastroenterologists who presented their therapeutic approach to peptic ulcer in the 9 editions of *Cecil's Textbook of Medicine* published from 1942 to 1971. Palmer had founded the first academic gastroenterology division in the United States in 1927, and Kirsner joined his group in 1935 and worked with him for a decade on studies of gastric acid secretion.

Peptic ulcer, wrote Palmer<sup>8</sup> in 1942, was produced by the failure of the gastric mucosa “to withstand the digestive action of the acid gastric juice,” keeping in mind that “the acid is more destructive than pepsin.” The main factor was the continual and excessive secretion of acid, rather than decreased production of protecting mucus. This was an unshakably firm position and contrasted strongly with the paradigm used by Thomas Brown in the first 4 editions of the textbook.

The paradigm shift did not lead to a different therapeutic approach. As before, mental and physical rest had utmost importance. They were to be accomplished at home or in the hospital for 2–6 weeks but could also be obtained by going on vacation or on a tiresome fishing or hunting trip. No matter how, the patient was kept away from work until the ulcer was completely healed, as demonstrated by barium-enhanced radiological imaging or gastroscopy. All other interventions were directed toward neutralizing the hydrochloric acid anytime gastric secretions or food was in the stomach, but in the end, Palmer<sup>9</sup> believed that “nature heals the ulcer.”

Food protein continued to be used as a neutralizing agent, but the intensity of the intervention was increased to hourly intake of 90 mL of equal parts milk and 18% cream from 7 AM to 7 PM Magnesium trisilicate or aluminum hydroxide was also given hourly during the same interval. The patients were taught to aspirate all gastric content before going to bed in the evening, and the treatment was considered effective only if the pH was above 4.<sup>8</sup> Control of nocturnal secretion required atropine sulfate, 0.5–1.0 mg orally at 6 PM and after the gastric aspiration. For refractory cases, a continuous gastric drip through a nasogastric tube of 1 L milk mixed with 5 g of sodium bicarbonate was administered every 8 hours. As in the past, pylorospasm continued to be a therapeutic target for atropine administration, to which later editions of this era

added propantheline bromide, methscopolamine, oxyphenonium,<sup>10</sup> glycopyrrolate, and tricyclamine.<sup>11</sup> The antimuscarinic effect on the acid production was mentioned, but not considered to have a significant contribution. Proposed innovations included undefined extracts of pregnant urine or posterior pituitary<sup>8</sup> and enterogastrone, a prepartate of animal duodenal mucosa.<sup>12</sup>

### Acid suppression

The acid suppression represented a major progress in the pharmacological management of peptic ulcer and the histamine (H<sub>2</sub>) receptor antagonists and proton-pump inhibitors have been and still are widely used.<sup>13–15</sup> The emergence of these drug classes was no doubt linked to the post-World War II advances in molecular tweaking performed in industry-funded organic chemistry laboratories but also to the insights of a handful of great scientists working in Europe or Asia.

### Histamine (H<sub>2</sub>) receptor antagonists

Histamine (beta-imidazolyl ethylamine) was synthesized in 1907 by decarboxylation of histidine through bacterial decomposition animal pancreatic tissue.<sup>16</sup> Over the next 2 decades, physiologists described in detail the crucial role of this biogenic amine in the pathophysiology of anaphylactic reactions, as well as its effects on the skin, lungs, heart, and gastrointestinal tract. Histamine was known by 1918 to stimulate the gastric acid secretion, and its value as a test for gastric function was validated in the United States in 1927.<sup>17</sup> The first antihistamine molecules of the ethanolamine class were used in animal experiments in 1933 and then in clinical settings in 1942, to be followed in 1945 by the introduction of diphenhydramine, which is still widely prescribed today.<sup>16</sup> Within a few years, research on animal models and clinical studies indicated that antihistaminic drugs were capable to neutralize all histamine effects except the stimulation of gastric secretion.<sup>18</sup>

Among those publishing in the 1950s work demonstrating that antihistamines did not block the histamine-mediated effect on gastric parietal cells leading to acid secretion was James Black.<sup>19</sup> More than a decade later, after discovering the first selective beta-adrenergic blocker, Black was the first to ask a simple, yet fundamental question, “Might histamine, like adrenaline, have its own ‘beta’ receptors?” Collaborating chemists in the United Kingdom created a series of new molecules by substituting a methyl group for every available H atom of the histamine molecule, and one of these compounds, 4-methylhistamine, was shown to be much more potent with regard to

antihistamine-resistant gastric acid secretion than to the antihistamine-responsive ileal contraction. The work continued by replacing the side-chain moiety of 4-methylhistamine with guanidine, which enhanced the histamine blocking effect on the stomach.<sup>19</sup> Further modifications of the side chain led to the synthesis of burimamide, metiamide, and finally cimetidine<sup>20</sup> in work completed by Black and his group in 1972.<sup>21</sup>

Cimetidine was first mentioned in the 1979 edition of the textbook.<sup>21</sup> A dose of 300 mg administered orally was deemed sufficient to decrease by 75% the meal-stimulated acid secretion or to abolish the basal secretion for at least 4 hours.<sup>21</sup> The main indication was duodenal ulcer, for which a total daily dose of 1200 mg for a month was known to heal 70%–80% of the cases. The drug was also recommended for patients with “massive acid gastric hypersecretion” encountered in rare conditions, such as systemic mastocytosis and Zollinger–Ellison syndrome. By 1982, the textbook promoted cimetidine as first-line therapy for peptic ulcer<sup>22</sup> and in 1985 mentioned the availability of ranitidine, in which the presence of a furan ring increased the histamine (H<sub>2</sub>) blocking potency 5–10 times greater than that of cimetidine.<sup>23</sup> The other histamine (H<sub>2</sub>) blockers recommended later in the textbook were famotidine, which added a thiazole ring,<sup>24</sup> and nizatidine.<sup>25</sup>

### Proton-pump inhibitors

Omeprazole, a substituted benzoimidazole, is described in the edition published in 1988 as a drug that inhibits the H<sup>+</sup>/K<sup>+</sup> adenosine triphosphatase, the enzyme that makes possible the parietal cell transmembrane extrusion of protons (hydrogen ions) into the gastric lumen, through exchange with potassium ions.<sup>24</sup> The drug was considered more potent<sup>26–28</sup> for acid suppression than the H<sub>2</sub> blocking agents, but it was much more expensive at that time, and therefore, it was indicated only for ulcer refractory to other pharmacological interventions.

The discovery of omeprazole and of its congener, lansoprazole, is fascinating because the molecules were synthesized at about the same time, and using the same starting point, by researchers working independently in Sweden and Japan.<sup>29</sup> The initial compound was 2-pyridylthioacetamide, which had been patented as an antisecretory drug in Japan in 1969 but never used in clinical trials because of toxic effects observed in animal experiments. In a second step, conceptualized in Sweden, a benzoimidazole group was introduced (substituted) and the resulting compound, named timoprazole, was found to inhibit the proton pump of the gastric parietal cell. Further changes led to the synthesis of picoprazole

and later omeprazole in Sweden and to lansoprazole in Japan.<sup>29</sup>

The prostaglandin agonists enprostil and misoprostol were first mentioned in 1988<sup>24</sup> when they had not been approved for use in the United States. These methylated analogs of prostaglandins E<sub>1</sub> and E<sub>2</sub> were known to decrease acid production of the parietal cells. The mechanism was unknown but suspected to involve the production of cyclic adenosine monophosphate. In 1992, Peterson indicated that only misoprostol was available to American physicians and that its ulcer-healing effect was inferior to the H<sub>2</sub> blocking drugs. Overall, he felt that “the prostaglandin story is one of unfulfilled promises” and that the use of the drug should be restricted to preventing Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)-associated gastric lesions.<sup>25</sup>

### *Helicobacter pylori* eradication

The tectonic paradigm shift represented by the identification of *H. pylori* infection as the cause of an overwhelming majority of peptic ulcers made its debut in 2 low-key letters to the editors of *Lancet* and published back to back in the June 4, 1983, issue.

The first, written by Warren<sup>30</sup> described “unidentified curved bacilli” on the gastric epithelium in active chronic gastritis. The author, a pathologist at Royal Perth Hospital in Perth, Western Australia, had observed small, S-shaped or curved bacilli in 135 gastric biopsy samples. The bacterial distribution on the surface epithelium was focal, patchy, or continuous. Bacteria were observed between and within the gastric pits and better seen with a silver stain than with the routine hematoxylin and eosin stain. The bacterial presence was significantly greater in the presence of inflammatory changes than in biopsies diagnosed as chronic gastritis. Bacteria were not seen near focal lesions, such as peptic ulcers or carcinomas.

The second letter was signed by Marshall,<sup>31</sup> a gastroenterologist at the same institution. He acknowledged the fact that gastric spirochetes had been identified on autopsies in the 1930s and shortly afterward in partial gastrectomy specimens. These bacteria were known to colonize other mammals’ stomachs and appeared to multiply well in an acidic environment. However, the microorganisms discovered by Warren were morphologically closer to *Campylobacter* species than to spirochetes. Their significance, wrote Marshall in 1983, was unknown, but their presence in areas affected by antral gastritis suggested a possible pathogenetic contribution to gastritis-associated disease, including peptic ulcers. A double-blind prospective trial of 100 patients with duodenal ulcer and biopsy-proven *C. pylori* infection, published in 1988,

indicated a bacterial eradication rate of 70% using a 2-drug treatment with tinidazole and colloidal bismuth subcitrate.<sup>32</sup> After eradication, 92% of ulcers healed within 8 weeks and the 12-month recurrence rate was 21%.

The *H. pylori* infection was first mentioned in *Cecil's Textbook of Medicine* in 1988.<sup>24</sup> Describing the role of bismuth preparations in the management of peptic ulcer, Peterson wrote that these compounds may be bactericidal for *C. pyloridis*, a microorganism that "may play a role in some patients with peptic ulcer disease." In 1992, the same expert believed that "if *H. pylori* is proven to have a role in the pathogenesis of peptic ulcer, its eradication may become the goal of treatment."<sup>25</sup> The issue seems to have been settled by 1996, when Graham<sup>33</sup> indicated that the *H. pylori* infection was responsible for 60%–90% of gastric ulcers and for 90% of duodenal ulcers. In the same edition, the first choice among available therapeutic interventions was concomitant administration of tetracycline, metronidazole, bismuth subsalicylate, and an antisecretory drug for a 14-day course. The alternative for tetracycline plus metronidazole was the combination of amoxicillin plus clarithromycin. Acid suppression was necessary, in the expert's opinion, because the antibiotic regimen was most effective if the gastric content pH was 7.4.<sup>33</sup> The expert advised that using doxycycline instead of tetracycline or erythromycin in lieu of clarithromycin was not likely to lead to eradication and that proton-pump inhibitors were to be the preferred acid-suppressing drugs.<sup>34</sup> Later editions added only several "salvage" antibiotics, such as levofloxacin, rifabutin, and furazolidone.<sup>35</sup>

## DISCUSSIONS

The *Cecil Textbook of Medicine* provides important information not only for understanding how therapeutic opinion was involved in the evolution of treatment for different diseases<sup>36,37</sup> but also a series of useful lessons in the formation of medical thinking, based on education, clinical practice, and ethical experience.<sup>38,39</sup> The textbook is also a valuable source, a real model in the training of future professionals in the field of medicine, in approaching the different medication not only for a clinical perspective but also for a public health one, a bridge between past and future of medicine.

The therapy of peptic ulcer has witnessed many changes, from the empirical dietary recommendation in the premodern era to the discovery and widespread use of very potent drugs such as antisecretory drugs or antibiotics for *H. pylori* infection.<sup>40–44</sup> At the

same time, many illusions vanished, such as those related to the usefulness of pirenzepine and carbenoxolone.

Besides fighting acidity and infection, increasing the resistance was another strategy of management. In this respect, mucosal protection was important. The protection provided by the mucous layer and the trophism of the epithelial coating ensure the integrity of the gastrointestinal tract in the face of aggression of harmful factors. Observations accumulated over time led to the establishment of integrative constructs of defensive organization of digestive epithelial surfaces. In this defense system, the essential role was attributed to prostaglandins, with decisive interventions in mucus secretion, mobilizing growth factors, maintaining microcirculation in the mucosa, and controlling gastric secretion, prostaglandins E, prostacyclin, and to a lesser extent prostaglandins A. The organization of defense in the mucous membranes centered on prostaglandins is conceptually constituted in the gastric cytoprotection system.<sup>45</sup>

New hope arose with the attempts to use probiotics (eg, *Lactobacillus reuteri*), enhance acid suppression with vonoprazan (a potassium-competitive acid blocker), or improve mucosal protection with the quinolinone derivative rebamipide. However we should keep in mind that as peptic ulcer disease changed its presentation across the last one and half century,<sup>46</sup> it may change again its face in the future because of further lifestyle and eating changes, the advent of new risk factors, or resistance to antibiotics.

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