

GOODMAN & GILMAN'S The
PHARMACOLOGICAL
BASIS OF
THERAPEUTICS

Ninth Edition

Joel G. Hardman
Lee E. Limbird

EDITORS-IN-CHIEF

Perry B. Molinoff
Raymond W. Ruddon

EDITORS

Alfred Goodman Gilman

CONSULTING EDITOR

CFAD EXHIBIT 1016



Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 9/e

Copyright © 1996, 1990, 1985, 1980, 1975, 1970, 1965, 1955, 1941 by *The McGraw-Hill Companies*, Inc. All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without the prior written permission of the publisher.

1234567890 DOWDOW 98765

ISBN 0-07-026266-7

This book was set in Times Roman by York Graphic Services, Inc. The editors were Martin J. Wonsiewicz and Peter McCurdy; the production supervisors were Robert Laffler and Clare Stanley, and the cover designer was Marsha Cohen/Paralellogram. The index was prepared by Irving Condé Tullar.

R.R. Donnelley and Sons Company was printer and binder.

This book is printed on acid-free paper.

Library of Congress Cataloging-in-Publication Data

Goodman & Gilman's *The Pharmacological Basis of Therapeutics*. —9th ed. / Joel G. Hardman, Alfred Goodman Gilman, Lee E. Limbird.

p. cm.

Includes bibliographical references and index.

ISBN 0-07-026266-7 (hardcover)

1. Pharmacology. 2. Chemotherapy. I. Goodman, Louis Sanford. II. Gilman, Alfred. III. Hardman, Joel G. IV. Gilman, Alfred Goodman. V. Limbird, Lee E.

[DNLM: 1. Pharmacology. 2. Drug Therapy. QV 4 G6532 1995]

RM300.G644 1995

615'.7—dc20

DNLM/DLC

for Library of Congress

95-36658

AGENTS FOR CONTROL OF GASTRIC ACIDITY AND TREATMENT OF PEPTIC ULCERS

Laurence L. Brunton

The lifetime prevalence of peptic (gastric and duodenal) ulcer disease is approximately 10%, and some physicians estimate that 50% of healthy individuals experience heartburn on a daily basis. The goals of therapy for ulcers are relief from pain, promotion of healing, and prevention of recurrence. Therapeutic strategies are aimed at balancing aggressive factors (gastric acid secretion, pepsin, Helicobacter pylori infection) against defensive or cytoprotective factors (bicarbonate secretion, mucus secretion, prostaglandin production). Drugs that reduce gastric acid secretion (H_2 histamine receptor antagonists and covalent inhibitors of the H^+, K^+ -ATPase of the parietal cell) effectively promote healing. Cytoprotective agents (sucralfate, colloidal bismuth, and the prostaglandin agonist misoprostol) and antacids also are effective. Recurrence of ulcers is common, prompting long-term prophylactic use of H_2 receptor antagonists and proton pump inhibitors. In patients who test positive for Helicobacter pylori, eradication of this bacterium with antibiotics promotes healing and reduces the likelihood of recurrence (see also Chapter 47). Inhibitors of the H^+, K^+ -ATPase also are effective for gastroesophageal reflux disease and are preferred for erosive esophagitis. H_2 receptor antagonists are used extensively for maintenance therapy in reflux. Minimizing use of nonsteroidal antiinflammatory drugs (Chapter 27), alcohol, and tobacco are important adjuncts to drug therapies of both peptic ulcer and acid reflux disease.

Dyspepsia, in its many forms, has been mankind's companion since the advent of bad cooking, overindulgence, and anxiety. Since one "is not altogether fit for the battle of life who is in perpetual contention with his dinner" (Meredith, 1859), considerable energy has gone into relieving the symptoms of gastric upset and peptic ulcer disease.

For centuries, neutralization of gastric acid with antacids provided the only relief from the pain of ulcers. Studies of the physiological control of acid secretion demonstrated that anticholinergic agents would blunt this process. The development by Black and colleagues of antagonists that act at H_2 -histaminergic receptors provided a more specific class of inhibitors of gastric acid secretion. More recently, the substituted benzimidazole inhibitors of H^+, K^+ -ATPase offer a very effective means of selectively blocking the proton pump that is responsible for acid secretion by the parietal cell. Although gastric acid has dom-

inated thinking about peptic ulcer disease, appreciation of the means by which the gastric mucosa normally protects itself from damage has suggested additional therapeutic approaches, including the use of a variety of cytoprotective agents. The recognition of the role of *Helicobacter pylori* in causing gastritis and in contributing to ulcerative processes in the stomach and duodenum provided the therapeutic insight that eliminating this bacterium would be a useful strategy for promoting the healing of ulcers and preventing their recurrence.

The pathophysiology of acid-peptic disease may be thought of as an imbalance between aggressive factors (acid, pepsin, *H. pylori* infection) and local mucosal defenses—the secretion of bicarbonate, mucus, and prostaglandins. Although treatment most often is directed at the reduction of aggressive factors, it can be directed at strengthening mucosal defenses of the stomach and the duodenum with so-called cytoprotective agents.

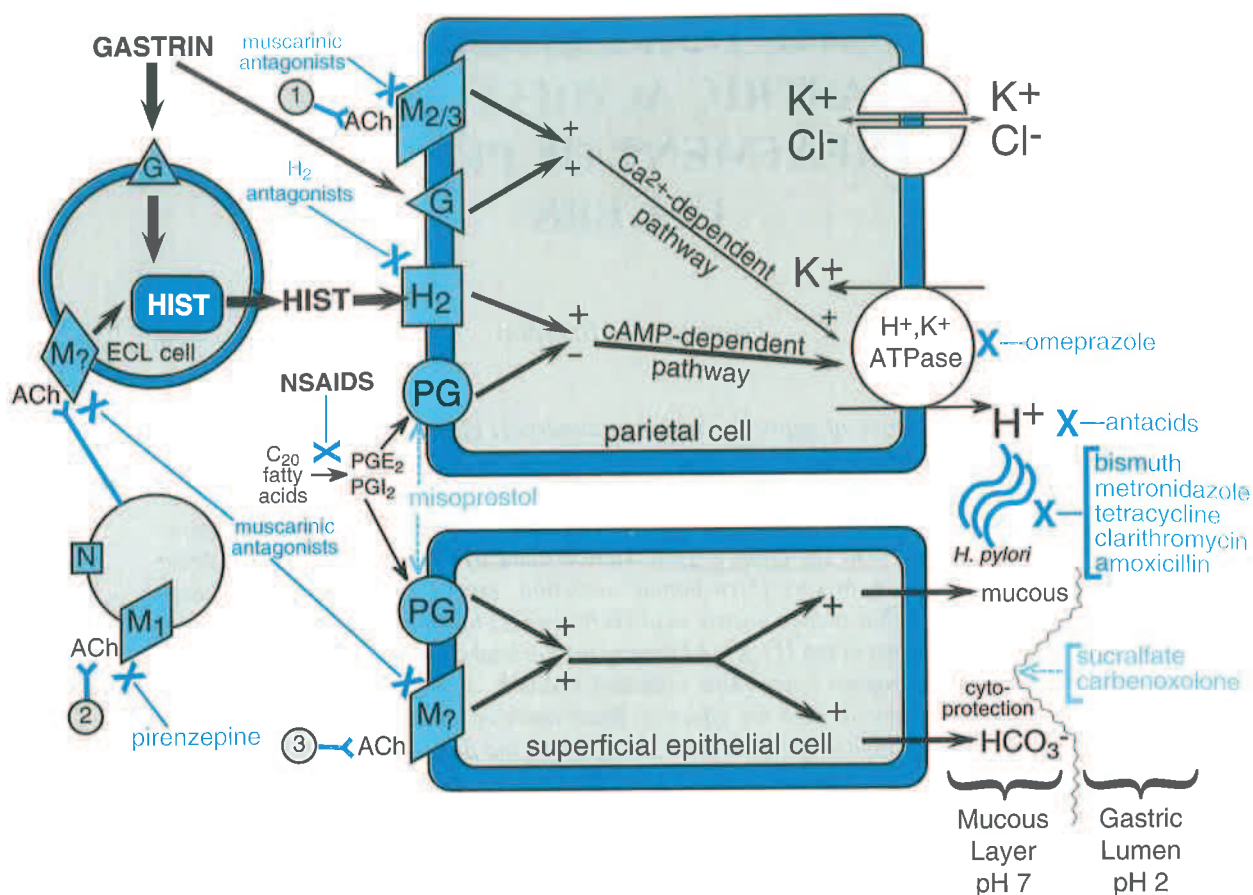


Figure 37-1. Physiological and pharmacological regulation of gastric secretions: the basis for therapy of peptic ulcer disease.

This schematic shows the interactions among an endocrine cell that secretes histamine (enterochromaffin-like [ECL] cell), an acid-secreting cell (parietal cell), and a cell that secretes the cytoprotective factors mucus and bicarbonate (superficial epithelial cell). Physiological pathways are in solid black and may be stimulated (+) or inhibited (-). Physiological agonists stimulate transmembrane receptors: muscarinic (M) and nicotinic (N) receptors for acetylcholine (ACh); G, gastrin receptor; H₂, histamine (HIST) receptor; PG, prostaglandin E₂ receptor. Actions of drugs are indicated by dashed lines. A blue X indicates a point of pharmacological antagonism. A light blue dashed line and arrow indicate a drug action that mimics or enhances a physiological pathway. Drugs currently used in treating peptic ulcer disease and discussed in this chapter are shown in dark blue. NSAIDs are nonsteroidal antiinflammatory drugs such as aspirin and are ulcerogenic. ① and ③ indicate possible input by cholinergic postganglionic fibers. ② shows neural input from the vagus nerve. See the text for detailed descriptions of these pathways and of therapeutic interventions.

Cellular Pharmacology of Gastric Secretion. The rationale for the use of agents that reduce gastric acidity is best understood in terms of the physiological regulation of acid secretion by the parietal cell. The three major pathways regulating parietal acid secretion include (1) neural stimulation via the vagus nerve, (2) endocrine stimulation via gastrin released from antral G cells, and (3) paracrine stimulation by local release of histamine from enterochromaffin-like (ECL) cells.

The major features of the regulation of gastric acid secretion as they pertain to pharmacological regulation are summarized schematically in Figure 37-1.

Vagal stimulation and the action of gastrin (from duodenal and antral G cells) stimulate release of histamine from paracrine ECL cells or mast cells. The histamine in turn activates parietal cell H₂ receptors that are linked to the stimulation of adenylyl cyclase, causing activation of

the cyclic AMP pathway. Gastrin and muscarinic stimuli also may act directly on the parietal cell to activate Ca^{2+} -sensitive pathways. H_2 receptor antagonists not only block the effects of histamine but also blunt responses to acetylcholine and gastrin, thus contributing to the remarkable clinical efficacy of these agents. These findings are consistent with the view that acetylcholine and gastrin may stimulate parietal cells indirectly by causing the release of histamine from paracrine cells (see Figure 37-1). Activation of either the cyclic AMP- or Ca^{2+} -dependent pathway, or both, stimulates activation of H^+, K^+ -ATPase on parietal cells, with its insertion into the apical membrane and leading to the formation of secretory canaliculi, with a consequent secretion of H^+ at rates between 20 and 40 mEq per hour. The result is an accumulation in the gastric lumen of H^+ to a concentration of about 0.1 N. An increase in the permeability of the apical membrane to K^+ and Cl^- accompanies activation of the proton pump.

This scheme (Figure 37-1) provides a rationale for the modest inhibitory effects of anticholinergic agents, the impressive inhibition of acid secretion by H_2 receptor antagonists, and the effects of neutralizing gastric HCl with antacids on production and maintenance of gastric acidity. Clearly, covalent inhibitors of the H^+, K^+ -ATPase, such as omeprazole, inhibit acid secretion, the final common pathway in gastric acid secretion. Prostaglandins, by inhibiting histamine-stimulated adenylyl cyclase activity in the parietal cell, reduce activity through the histamine-evoked cyclic AMP-dependent pathway and thereby reduce acid secretion. Prostaglandins also stimulate the secretion of mucus and bicarbonate by adjacent superficial epithelial cells, contributing to the cytoprotective effects of endogenous prostaglandins of the E series and to the protective effects of stable analogs of prostaglandins E_1 , such as misoprostol. The importance of the tonic role of prostaglandins in cytoprotection is manifest by the ulcerogenic effects of nonsteroidal anti-inflammatory drugs (NSAIDs; see Chapter 27) that inhibit prostaglandin synthesis. Bismuth, sucralfate, and carbenoxolone also enhance the cytoprotection afforded by the mucus layer.

Since *H. pylori* may contribute to the defect in mucosal defenses in some cases of peptic ulcer, the eradication of the bacterium constitutes yet another avenue of therapy. The details of acid, pepsin, and mucus secretion in health and disease and the etiology of gastric ulcers have recently been reviewed (see Goldschmiedt and Feldman, 1993; and Soll, 1993).

Therapeutic Strategies for Treatment of Peptic Ulcers and Gastroesophageal Reflux Disease. As indicated

earlier, peptic ulcers arise due to an imbalance of acid secretory mechanisms (so-called aggressive factors) and mucosal protective factors, and their rational treatment is aimed at restoring that balance. The loss of balance between acid secretion and mucosal protective factors varies among peptic ulcer types. Type I ulcers, which occur high in the stomach, are associated with less or no acid hypersecretion, suggesting the importance of impaired mucosal protective factors in this clinical setting. Type II ulcers, in contrast, include gastric ulcers and distal antral (prepyloric) and duodenal ulcers and are associated with acid hypersecretion and impaired negative feedback effects of acidification on gastrin release and on continued acid secretion.

The causes of gastric ulcers include *H. pylori* infection, NSAIDs, and malignancy. If malignancy is identified on endoscopy and confirmed cytologically, surgical removal is undertaken. If *H. pylori* infection is confirmed by culturing or by detection of circulating antibodies, appropriate combination antimicrobial therapy is instituted (see below). Otherwise, H_2 receptor antagonists or H^+, K^+ -ATPase inhibitors are administered. Duodenal ulcers also can be caused by *H. pylori* or by NSAIDs, but rarely by malignancy. The possible role of *H. pylori* in ulcer development is determined, and therapeutic agents are selected, as for gastric ulcers. However, as mentioned above, duodenal ulcers also can result from hypersecretion of gastrin, which can be assessed by evaluating fasting gastrin levels in patients unresponsive to other therapies for duodenal ulcers.

Based on the understanding of the mechanisms contributing to ulcer development and particularly to gastric acid secretion, a variety of therapeutic strategies exist, including suppressing the aggressive factors contributing to acidification with the use of antacids, H_2 receptor antagonists, and H^+, K^+ -ATPase pump inhibitors, and fostering defensive factors, with the use of cytoprotective and prokinetic agents. These overall strategies are discussed below in terms of specific therapeutic agents.

Gastroesophageal reflux disease (GERD) has been estimated to affect 10% of the population of the United States. Often it is treated by over-the-counter antacid preparations, as individuals with this condition frequently do not seek medical assistance. The therapeutic approach is based on reduction of gastric acidity, increase of lower esophageal sphincter tone, and enhancement of esophageal clearance of refluxed material. Recommended lifestyle changes include elevating the head of the individual's bed by at least 6 inches, which reduces esophageal exposure to acid; cessation of smoking; consumption of a bland diet devoid of citrus juices, coffee, and spicy food, which are direct irritants promoting GERD; avoiding bedtime meals; and avoiding certain medications, including theophylline, classic anticholinergic agents, and progesterone, all of which delay gastric emptying and decrease lower esophageal sphincter tone. Should GERD persist, H_2 receptor antagonists and proton pump inhibitors are the preferred therapies (see below).

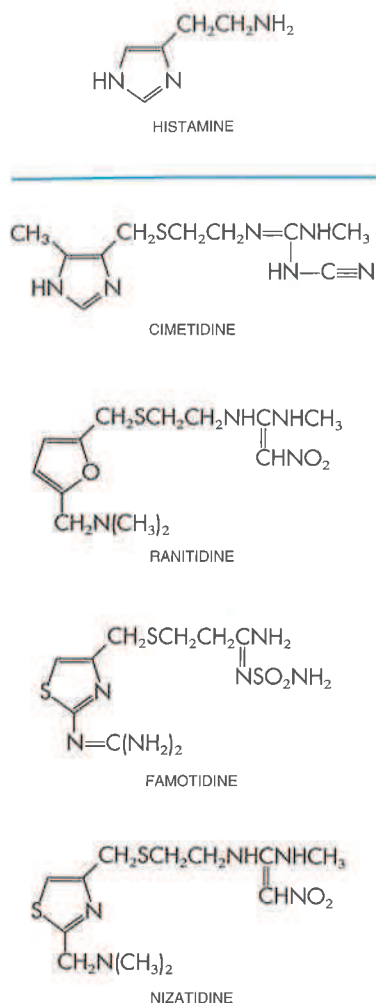


Figure 37-2. Structures of histamine and H_2 receptor antagonists.

H_2 HISTAMINE RECEPTOR ANTAGONISTS

H_1 histamine receptor antagonists do not inhibit gastric acid secretion. The development in the 1970s of H_2 receptor antagonists provided incontrovertible evidence for the importance of endogenous histamine in the physiological control of gastric secretion (see Figure 37-1; see also Chapter 25) and transformed the treatment of peptic ulcer disease. The recent availability of H_2 receptor antagonists as over-the-counter medicines likely will increase both their popularity and the necessity for physicians to understand the therapeutic and adverse effects of these agents.

Chemistry. The H_2 receptor antagonists in clinical use are histamine congeners that contain a bulky side chain in place of the ethylamine moiety. Early representatives of the group, such as burimamide (Black, 1993) and *cimetidine* (the first compound released for gen-

eral use) retain the imidazole ring of histamine. This ring is replaced in more recently developed compounds by a furan (*ranitidine*) or a thiazole (*famotidine*, *nizatidine*). Structures of the currently available H_2 antagonists are presented in Figure 37-2. As a group, these drugs are more hydrophilic than are the H_1 antagonists, and they reach the central nervous system (CNS) to only a limited extent. Highly lipophilic H_2 antagonists such as *zolentidine* are under study for their potential ability to antagonize histamine in the CNS. These compounds have little or no effect on acid secretion (see Black, 1993).

Pharmacological Properties. H_2 receptor antagonists competitively inhibit the interaction of histamine with H_2 receptors. They are highly selective and have little or no effect on H_1 receptors or other receptors. Although H_2 receptors are present in numerous tissues, including vascular and bronchial smooth muscle, H_2 receptor antagonists interfere remarkably little with physiological functions other than gastric acid secretion.

Gastric Secretion. H_2 receptor antagonists inhibit gastric acid secretion elicited by histamine and other H_2 agonists in a dose-dependent, competitive manner; the degree of inhibition parallels the concentration of the drug in plasma over a wide range (Figure 37-3). The H_2 receptor antag-

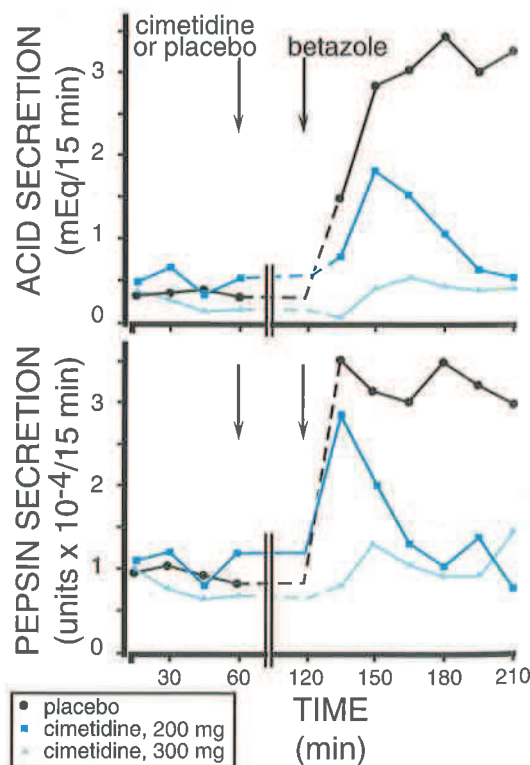


Figure 37-3. Effect of cimetidine on betazole-stimulated secretion of acid (upper panel) and of pepsin (lower panel) in human beings. (Adapted from Binder and Donaldson, 1978 with permission.)

onists also inhibit acid secretion elicited by gastrin and, to a lesser extent, by muscarinic agonists. It is important to note that H_2 receptor antagonists inhibit basal (fasting) and nocturnal acid secretion, and this effect contributes in a major way to their clinical efficacy. H_2 receptor antagonists also reduce acid secretion stimulated by food, sham feeding, fundic distention, and various pharmacological agents; this property, although not clinically significant, nonetheless reflects the vital role of histamine in mediating the effects of diverse stimuli (see Figure 37-1). The H_2 antagonists reduce both the volume of gastric juice secreted and its H^+ concentration. The output of pepsin, which is secreted by the chief cells of the gastric glands, generally falls in parallel with the reduction in volume of gastric juice (see Figure 37-3). Secretion of intrinsic factor also is reduced; however, since this protein normally is secreted in great excess, absorption of vitamin B_{12} usually is adequate even during long-term therapy with H_2 antagonists. The concentration of gastrin in plasma is not significantly altered under fasting conditions, although the normal prandial elevation may be augmented, apparently as a consequence of a reduction of the feedback inhibition of gastrin secretion that is normally provided by H^+ .

H_2 antagonists protect experimental animals from gastric ulceration induced by stress, pyloric ligation, aspirin, H_2 receptor agonists, or cholinomimetics. H_2 antagonists also counter peptic ulceration in human beings, as described below. They have no consistent effect on the rate of gastric emptying, the pressure of the lower esophageal sphincter, or pancreatic secretion.

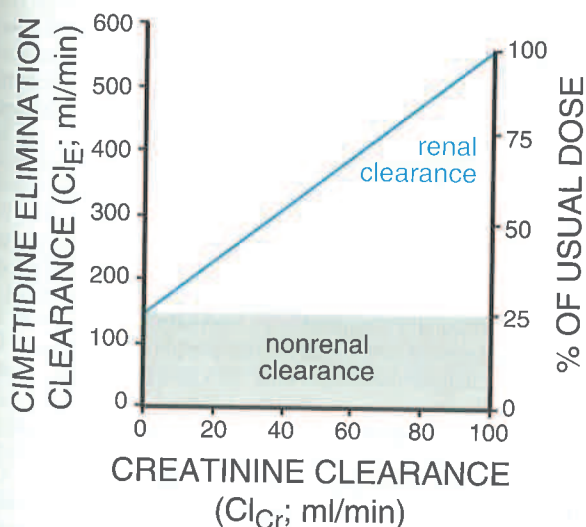


Figure 37-4. Relationship between creatinine clearance (Cl_{Cr}), cimetidine elimination clearance (Cl_E), and appropriate cimetidine dose reduction for patients with impaired renal function. (Adapted from Atkinson and Craig, 1990, with permission.)

Absorption, Fate, and Excretion. H_2 receptor antagonists are rapidly and well absorbed after oral administration; peak concentrations in plasma are attained within 1 or 2 hours. The oral bioavailability of nizatidine is approximately 90%, whereas first-pass hepatic metabolism limits the bioavailability of the other compounds to about 50%. The half-time for elimination of cimetidine, ranitidine, and famotidine is 2 to 3 hours, while that of nizatidine is somewhat shorter—about 1.3 hours. Although subject to hepatic metabolism, these drugs are excreted in large part in the urine without being metabolized. Thus, renal impairment requires a reduction in dosage of these agents. However, hepatic metabolism contributes sufficiently to the clearance of ranitidine that the half-life of this agent is significantly prolonged in patients with hepatic dysfunction.

Renal tubular secretion of H_2 receptor antagonists can be inferred from the fact that their renal clearance ($Cl_E \times$ percent renal excretion; see Chapter 1) exceeds the glomerular filtration rate. Because these agents are excreted from the kidney, their dosage should be reduced when treating patients with impaired renal function. Impaired renal function sometimes is difficult to assess in elderly patients, where a decreased skeletal muscle mass may result in normal serum creatinine levels despite markedly impaired renal function. The Cockcroft and Garret equation can be used to estimate creatinine (Cr) clearance for calculating appropriate reductions in dosage:

$$Cl_{Cr} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times (\text{serum Cr in mg/dl})} \quad (37-1)$$

This estimate is appropriate for men, but it should be reduced by 15% for women. Figure 37-4 provides a useful nomogram to guide the dosage choice for cimetidine when renal clearance is impaired. This nomogram is useful even in functionally anephric patients, since the nonrenal clearance is unimpaired in these individuals (Atkinson and Craig, 1990).

Adverse Effects. A variety of adverse reactions have been ascribed to cimetidine and ranitidine, reflecting, in part, the very large number of patients who have been treated with these drugs. The incidence of reactions is low, and the reactions generally are minor. The low incidence is attributable in part to the limited function of H_2 receptors in organs other than the stomach and to the poor penetration of these agents across the normal blood-brain barrier.

The incidence of adverse effects with cimetidine is less than 3%; reactions are usually less intense and less frequent (<1%) or absent with normal clinical doses of the other H_2 receptor antagonists. In many clinical studies, the incidence of side effects with H_2 receptor antagonists is not greater than that for patients treated with placebo. The most common side effects of cimetidine are altered lactation, headache, dizziness and nausea, myalgia, skin rashes,

and itching. The incidence of symptoms related to the CNS (somnolence, confusion) appears to be higher in the elderly and in patients with impaired renal function. Loss of libido, impotence, and gynecomastia sometimes are observed in patients who receive long-term therapy with high doses of cimetidine. These effects are presumed to be related to the ability of the drug to enhance the secretion of prolactin and to bind to androgen receptors, but they are rarely observed except following the high doses used to treat Zollinger-Ellison syndrome (*see below*). In addition, cimetidine inhibits the cytochrome P450-catalyzed hydroxylation of estradiol and increases the plasma concentration of estradiol in men, effects not shared by the other agents. Case reports suggest that cimetidine occasionally causes hematologic effects (various cytopenias) and altered function of the immune system. Rarely, the use of cimetidine has been associated with reversible bone marrow depression, hepatitis, or anaphylaxis. Cimetidine appears to inhibit competitively the renal tubular secretion of creatinine and causes a small increase in its plasma concentration. Rapid intravenous infusion of H₂ antagonists has caused bradycardia and release of histamine, responses common to many basic drugs. For recent reviews of the pharmacology and adverse effects of H₂ antagonists, *see* Deakin and Williams, 1992; and Wormsley, 1993.

Drug Interactions. All agents that inhibit gastric acid secretion may alter the bioavailability and rate of absorption of certain drugs secondary to changes in gastric pH (*see* "Antacids," below, and Chapter 1).

Cimetidine (but not the other H₂ blockers) inhibits the activity of cytochrome P450, thereby slowing the metabolism of many drugs that are substrates for hepatic mixed-function oxidases. Ranitidine, although it interacts weakly with cytochrome P450 *in vitro*, famotidine, and nizatidine do not inhibit the hepatic cytochrome P450 system. The concurrent administration of cimetidine will prolong the half-life of a host of drugs, including phenytoin, theophylline, phenobarbital, cyclosporine, benzodiazepines not metabolized by glucuronidation, carbamazepine, propranolol, Ca²⁺ channel blockers, quinidine, mexiletine, sulfonyleureas, warfarin and tricyclic antidepressants such as imipramine. Cimetidine can inhibit tubular secretion of procainamide, increasing the plasma concentration of the drug and its cardioactive metabolite, N-acetylprocainamide. Such interactions may require either reduction of dosage or alteration of the regimen. There are reports that H₂ antagonists inhibit gastric mucosal ethanol metabolism and thereby elevate blood alcohol levels. Such effects are variable and controversial and, in any event, are not likely to be clinically relevant. The drug interactions of H₂ antagonists have been reviewed by Hansten (1994).

Therapeutic Uses. The clinical use of H₂ receptor antagonists stems from their capacity to inhibit gastric acid secretion, especially in patients with peptic ulceration. In appropriate doses, the various H₂ antagonists appear to produce equivalent therapeutic responses. H₂ receptor antagonists are available for both oral and parenteral administration. Cimetidine (TAGAMET) and ranitidine (ranitidine hydrochloride, ZANTAC) are available as tablets and as a liquid; nizatidine (AXID) is available as capsules; famotidine (PEPCID) is available as tablets, as an oral suspension, and as a solution for intravenous injection. These drugs are well tolerated at doses considerably in excess of those required to produce substantial inhibition of gastric acid secretion. Consequently, despite their short half-lives in plasma, H₂ receptor antagonists can be administered in relatively large quantities once or twice daily to provide effective therapy. Once-daily administration of H₂ receptor antagonists is most effective when the dose is administered before sleep, so that the agents are at their highest concentration when they are acting to block nocturnal gastric acid secretion. In patients with active peptic ulcer disease who are infected with *H. pylori*, therapy to eradicate the bacterium (*see below*) should be given concurrently to help promote healing and prevent recurrence.

Duodenal Ulcer. H₂ antagonists profoundly lower basal and nocturnal secretion of acid and that stimulated by meals and other factors; they reduce both the pain of duodenal ulcer and the consumption of antacids, and they hasten healing. For the treatment of active duodenal and benign gastric ulcers, a large dose before bedtime (cimetidine, 800 mg; ranitidine, 300 mg; nizatidine, 300 mg; famotidine, 40 mg) or half the dose twice daily is an effective regimen. Duodenal ulcers usually heal with 4 to 8 weeks of treatment. Following healing, a maintenance dose (half the daily treatment dose) can reduce the likelihood of recurrent disease. About 10% of patients do not respond in this period, and more prolonged treatment with H₂ antagonists is then of questionable value. After successful treatment, ulcers recur within a year in about 50% of patients; this rate can be reduced to about 20% by the administration of a maintenance dose of an H₂ antagonist once daily at bedtime. Eradication of *H. pylori* reduces the rate of relapse in infected patients.

Gastric Ulcer. H₂ antagonists also accelerate the healing of benign gastric ulcers; treatment for 8 weeks is sufficient for 50 to 75% of patients. A more prolonged treatment, up to 16 weeks, produces a higher rate of healing. The drugs also markedly reduce the rate of relapse when given in maintenance doses at bedtime. Eradication of *H. pylori* should be undertaken in infected patients to reduce the rate of recurrent ulcers.

Zollinger-Ellison Syndrome. In this disease, a non-beta-cell tumor of the pancreatic islets may produce gastrin in a quantity sufficient to stimulate secretion of gastric acid to life-threatening levels. Although H₂ receptor antagonists in high doses may be beneficial, they do not always produce adequate suppression of this gastrin-stimulated acid secretion (*see Figure 37-1*). Inhibitors of the H⁺,K⁺-ATPase are the therapy of choice for this condition (*see below*).

Gastroesophageal Reflux Disease. A major use of H₂ receptor antagonists is for the chronic management of gastroesophageal reflux

disease (GERD), and all four antagonists identified above are now approved for this indication. Treatment of reflux disease requires at least twice-daily dosing (once-nightly dosing is not effective) and may require administration of higher doses than are required for treatment of peptic ulcer diseases.

Other Conditions. H_2 antagonists may be useful whenever it is appropriate to reduce gastric acid secretion. Such conditions include reflux esophagitis, stress ulcers, short-bowel (anastomosis) syndrome, and hypersecretory states associated with systemic mastocytosis or basophilic leukemia with hyperhistaminemia. They also are used as a preanesthetic medication in emergency operations to reduce the danger of aspiration of acidic gastric contents.

Among patients with acute urticaria, a small number develop chronic urticaria that is refractory both to H_1 antagonists and to all efforts to eliminate exposure to potential allergens. Some of these patients respond well to the concurrent administration of an H_1 and an H_2 antagonist, presumably reflecting a contribution to the condition from H_2 receptors in the cutaneous microvasculature (see Chapter 25).

INHIBITORS OF H^+, K^+ -ATPase

The ultimate mediator of acid secretion is the H^+, K^+ -ATPase ("proton pump") of the apical membrane of the parietal cell (see Figure 37-1). Since this pump is unique to parietal cells, a number of specific inhibitors of it have been developed; a family of substituted benzimidazoles were discovered first, and two of these compounds, *lansoprazole* and *omeprazole* (Figure 37-5, A), have been released for clinical use in the United States (see Lindberg *et al.*, 1990; McTavish *et al.*, 1991; and Barradell *et al.*, 1992). These agents offer a means to inhibit acid secretion to any desired level. They are especially useful in patients with hypergastrinemia and may be valuable in those whose peptic ulcer disease is not well controlled by H_2 antagonists.

Proton pump inhibitors contain a sulfinyl group in a bridge between substituted benzimidazole and pyridine rings (see Figure 37-5, A). At neutral pH, omeprazole and lansoprazole are chemically stable, lipid-soluble, weak bases that are devoid of inhibitory activity. These neutral weak bases reach parietal cells from the blood and diffuse into the secretory canaliculi, where the drugs become protonated and thereby trapped. The protonated agent rearranges to form a sulfenic acid and a sulfenamide. The sulfenamide interacts covalently with sulfhydryl groups at critical sites in the extracellular (luminal) domain of the membrane-spanning H^+, K^+ -ATPase (Figure 37-5, B). Full inhibition occurs with two molecules of inhibitor bound per molecule of enzyme. Omeprazole and lansoprazole must thus be considered as prodrugs that need to be activated to be effective. The specificity of the effects of proton pump inhibitors derive from the selective distribution of H^+, K^+ -ATPase, from the requirement for acidic conditions to catalyze generation of the reactive inhibitor, and from trapping of the protonated drug and the cationic

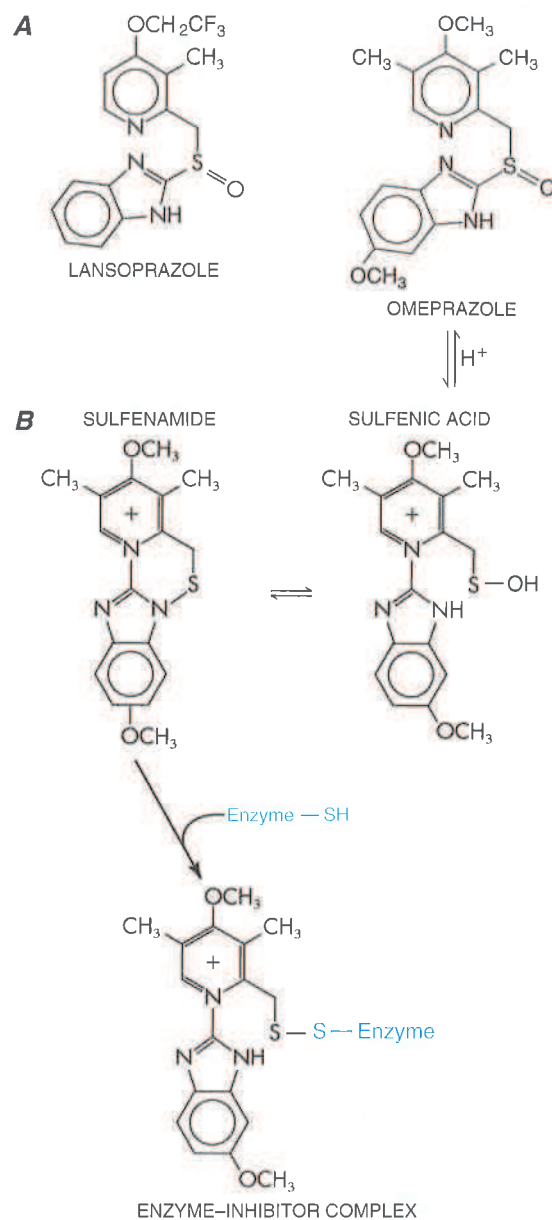


Figure 37-5. Inhibitors of the gastric H^+, K^+ -ATPase.

A. Structures of lansoprazole and omeprazole. **B.** Mechanism of irreversible inhibition of H^+, K^+ -ATPase by pump inhibitors. In the acidic environment of the parietal cell canaliculi, these "pro-drugs" are converted to sulfenamides that interact covalently with sulfhydryl groups in the extracellular (luminal) domain of the proton pump.

sulfenamide within the acidic canaliculi and adjacent to the target enzyme. Administration of omeprazole (Figure 37-5, B) results in permanent inhibition of enzyme activity *in vivo*; secretion of acid resumes only after insertion of new molecules of H^+, K^+ -ATPase into the luminal membrane (see Lindberg *et al.*, 1990; McTavish *et al.*, 1991).

Lansoprazole has a similar mechanism of action. However, some data suggest that the inhibitory effect of lansoprazole may be reversed by a mechanism involving cellular glutathione and that *de novo* synthesis of the proton pump is not essential to restore acid secretion (see Barradell *et al.*, 1992). Newer H^+, K^+ -ATPase agents are being developed that do not covalently bind to the enzyme.

Pharmacological Properties. The pharmacological effects of omeprazole (PRILOSEC) and lansoprazole (PREVACID) result from inhibition of gastric acid secretion. These agents produce only small and inconsistent changes in the volume of gastric juice and in the secretion of pepsin and intrinsic factor and do not affect gastric motility. The following discussion focuses on omeprazole; however, the therapeutic effects of omeprazole and lansoprazole are similar.

Because omeprazole is an irreversible inhibitor of the H^+, K^+ -ATPase, this agent produces a dose-related inhibition of gastric acid secretion that persists after the drug disappears from the plasma (Figure 37-6). The acid inhibitory effect of lansoprazole also lasts longer than would be predicted from its plasma elimination half-life.

Omeprazole and lansoprazole are available for oral administration as delayed-release capsules. It is clinically important to note that, while both are stable at neutral pH, they are destroyed by gastric acid. Therefore, if their microencapsulation is disrupted before swallowing—for example, if the patient breaks open the gelatin-coated capsule and swallows the enteric-coated grains—the neutral

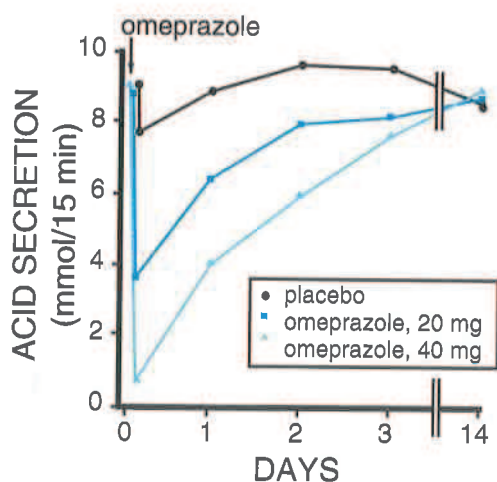


Figure 37-6. Inhibitory effect of omeprazole on secretion of gastric acid.

Maximal secretory responses were elicited in healthy human beings by infusing pentagastrin over a 1-hour period before and at various intervals after a single oral dose of omeprazole. Note the profound and prolonged inhibition. (Adapted from Lind *et al.*, 1983, with permission.)

pH in the mouth and esophagus will break down the microencapsulation, and the drug will be exposed to degradation by gastric acid in the stomach. When the delayed-release capsule is taken appropriately, it releases omeprazole or lansoprazole after the granules leave the stomach; the drug is rapidly absorbed in the intestine. When given in a sufficient dosage (e.g., 20 mg per day for 7 days), omeprazole can reduce the daily production of acid by more than 95%; pretreatment values are not achieved until 4 or 5 days after withdrawal of the drug, presumably reflecting the time required to synthesize and insert new molecules of H^+, K^+ -ATPase into the membrane. One consequence of profound reduction in gastric acidity is increased secretion of gastrin; patients who take the usual therapeutic dose of omeprazole or lansoprazole have a modest hypergastrinemia. Prolonged administration of very high doses of omeprazole to experimental animals causes hyperplasia of oxyntic mucosal cells, presumably because of trophic effects of gastrin on these cells; carcinoid tumors also are produced in rats. Although no evidence of mucosal proliferation has been found in human subjects with long-term administration (up to 6 years), some clinicians are unwilling to administer omeprazole for long-term therapy if a suitable alternative therapy is available. The pharmacological properties of omeprazole have been reviewed (McTavish *et al.*, 1991).

Absorption and Fate. Orally administered omeprazole is absorbed rapidly but to a variable extent; its bioavailability depends on dose and gastric pH and may reach 70% with repeated administration. These properties presumably reflect the lability of the drug in acid and its impact on gastric pH. It is extensively (more than 95%) bound to plasma protein. Omeprazole is cleared from the circulation by hepatic metabolism with a half-time of 30 to 90 minutes; most of the metabolites are excreted in the urine.

Lansoprazole has an oral bioavailability of about 80% and a plasma half-life of about 1.5 hours. Its absorption is reduced if given with food.

Adverse Effects. Omeprazole and lansoprazole are generally well tolerated, and treatment of patients with Zollinger-Ellison syndrome with omeprazole in doses of 60 to 360 mg per day for up to 6 years has not caused serious side effects. About 1.5% to 3% of patients taking omeprazole or lansoprazole experience gastrointestinal effects, including nausea, diarrhea, and abdominal colic; CNS effects (e.g., headache, dizziness, somnolence) have been reported less frequently. Skin rash and transient elevations of the plasma activities of hepatic aminotransferases have been observed occasionally. Although not yet documented with these drugs, bacterial overgrowth in the gastrointestinal tract and development of nosocomial pneu-

monia are potential risks of long-term elevation of gastric pH. In placebo-controlled clinical trials, however, there are no differences between the incidence of adverse effects for H^+ , K^+ pump inhibitors and for placebo treatment.

Drug Interactions. Since omeprazole and lansoprazole interact with cytochrome P450 *in vitro*, inhibition of hepatic metabolism of certain drugs may be of potential importance. Omeprazole reduces the metabolism of phenytoin, diazepam, and the *R* isomer of warfarin. Clinically significant interactions of lansoprazole with these drugs *in vivo* have not been demonstrated.

Therapeutic Uses. Omeprazole and lansoprazole promote healing of ulcers in the stomach, duodenum, and esophagus. They are of particular value in the treatment of patients who do not respond adequately to H_2 receptor antagonists, especially those with Zollinger-Ellison syndrome.

Peptic Ulcers and Reflux Esophagitis. Omeprazole (20 mg/day) produces relief of symptoms and healing in about 90% of patients with duodenal ulcer in 4 weeks. Lansoprazole (15 to 30 mg daily) produces similar effects. In treating gastric ulcer, higher daily doses (40 mg) of omeprazole produce healing in about 90% of patients in 8 weeks. Omeprazole frequently is effective in healing peptic ulcers that are unresponsive to H_2 antagonists. Relapse is a problem when therapy is discontinued, and low-dose maintenance therapy, *e.g.*, using 20 mg of omeprazole for 3 days each week, reduces recurrence of active disease. Overall, the rates of healing and relapse for omeprazole are roughly equivalent to those for the H_2 receptor antagonists. As with the H_2 receptor antagonists, concurrent treatment to eradicate *H. pylori* in infected patients is likely to contribute to reduced recurrence.

Omeprazole is more effective than H_2 receptor antagonists in treating gastroesophageal reflux, which may require long-term treatment. Typically, higher doses of omeprazole (20 to 60 mg daily) are used for this indication than for treatment of peptic ulcers. Lansoprazole has been shown to be effective in patients with reflux esophagitis who were not responsive to an H_2 receptor antagonist. If the tone of the lower esophageal sphincter is reduced or if esophageal peristalsis is impaired, prokinetic agents such as *metoclopramide* or *cisapride* (see Chapter 38) may be useful as a therapeutic strategy.

Zollinger-Ellison Syndrome. The peptic and esophageal ulceration associated with gastrin-producing tumors is often difficult to treat. Omeprazole or lansoprazole is the treatment of choice for this condition. The goal of therapy is to reduce the basal secretion of acid to below 10 mEq per hour. This usually requires administration of at least 60 to 70 mg of omeprazole per day and from 15 mg every other day to 180 mg every day of lansoprazole. 90% of patients are controlled with daily doses of 120 mg.

ERADICATION OF *HELICOBACTER PYLORI*

Helicobacter pylori is a gram-negative rod that colonizes the mucus on the luminal surface of the gastric epithelium. *H. pylori* infection causes an inflammatory gastritis and is

a putative contributor to peptic ulcer disease, gastric lymphoma, and adenocarcinoma (see Blaser and Parsonnet, 1994; Walsh and Peterson, 1994; Symposium, 1994). *H. pylori* infection is widespread, with a prevalence of about 20% in 30-year-old Caucasians and higher in Hispanics and blacks; prevalence increases with age. The great majority of patients (70% to 90%) with duodenal and gastric ulcers have *H. pylori* that can be identified in antral samples. An additional argument for a role of *H. pylori* in peptic ulcer disease comes from studies in which eradication of *H. pylori* correlates with a reduction in the recurrence of ulcers (see reviews of data in Symposium, 1994 and Labenz and Børsh, 1995). The importance of *H. pylori* in duodenal ulcer disease is emphasized by the following observations: (1) Eradication of *H. pylori* alone results in better ulcer healing than placebo treatment; (2) eradication of *H. pylori* concurrently with the use of receptor antagonists enhances the rate of ulcer healing compared to use of H_2 receptor antagonists alone; and (3) antagonists to specific cellular mechanisms of injury induced by *H. pylori* block its ulcerogenic effects. However, since *H. pylori* infection is relatively common in healthy individuals as well, it is unlikely that *H. pylori* infection alone is sufficient to cause ulcers. Nonetheless, eradication of *H. pylori* is recommended in patients with active peptic ulcer disease (new or recurrent, duodenal or gastric) who test positive for *H. pylori* (see Symposium, 1994).

Single-agent therapy of *H. pylori* infections has proven relatively ineffective *in vivo* and has led to the emergence of strains of *H. pylori* that are resistant to drugs, especially to *metronidazole* and *timidazole* (via a mutant nitroreductase activity). Both *amoxicillin* and *clarithromycin* are effective in some patients. Because of resistance developed by *H. pylori*, multiple drugs are needed in some patients. Resistance is less problematic when metronidazole is combined with bismuth and a second antibiotic. Bismuth compounds have no substantial capacity to neutralize gastric acid; their beneficial effects have been ascribed to cytoprotection and may be secondary to the antibacterial effect of bismuth compounds against *H. pylori* in the gastroduodenal mucosa. Double or triple antimicrobial therapies, in combination with antisecretory drugs, are being used successfully to treat peptic ulcers that are due at least in part to *H. pylori* infection. Triple therapy with metronidazole (250 mg, three times daily), a bismuth compound [available in the United States as bismuth subsalicylate (PEPTO-BISMOL), 2 tablets, four times daily; available elsewhere as colloidal bismuth subcitrate (DE-NOL), 120 mg, four times daily], and either tetracycline (500 mg, four times daily) or amoxicillin (500 mg, three times daily) for two weeks is recommended currently and produces eradi-

cation in about 90% of patients. In treating peptic ulcers, the triple therapy is added to an antisecretory medication (H_2 receptor antagonist or proton pump inhibitor), which may be used for up to 6 months or prophylactically. This triple therapy has therapeutic limitations; compliance is a critical issue with such complex regimens; the combined cost of the agents is high; and there are side effects. Nausea, diarrhea, and dizziness are frequent complaints that may restrict the use of triple therapy in the infirm elderly, whose disease often is well-managed by antisecretory drugs. Simpler combinations that have the advantages of few side effects and less complex dosing schedules are being tested. These include combinations of antisecretory agents with an antibiotic (e.g., omeprazole plus clarithromycin, 500 mg, three times daily; or amoxicillin (2 g per day; or ranitidine and bismuth subcitrate plus an antibiotic). Information on metronidazole, tetracycline, amoxicillin, and clarithromycin may be found in Chapters 42, 45, and 47. Bismuth compounds are discussed below. Physicians should expect changes in the recommendations for eradication of *H. pylori* as studies of *H. pylori* and an understanding of its roles in gastric diseases progress.

Bismuth Compounds

As indicated above, bismuth compounds have no substantial capacity to neutralize gastric acid. Their beneficial effects have been ascribed to cytoprotection (enhanced secretion of mucus and HCO_3^- , inhibition of pepsin activity, and accumulation of bismuth subcitrate preferentially in the craters of gastric ulcers). These effects may be secondary to the antibacterial effect of bismuth compounds against *H. pylori* in the gastroduodenal mucosa.

Colloidal bismuth subcitrate is a complex bismuth salt of citric acid that, at acid pH, chelates with proteins in the ulcer base and may form a protective barrier against acid diffusion and peptic digestion. Bismuth has been shown to promote healing of both gastric and duodenal ulcers as effectively as cimetidine and to be effective in preventing ulcer recurrence. The rate of healing of gastric ulcers is somewhat lower. As indicated above, the observed benefits of bismuth likely reflect its antibacterial action against *H. pylori*, and bismuth thus serves as an important component in the "triple therapy" of *H. pylori*.

Bismuth subsalicylate also is used for gastroesophageal reflux and for diarrhea (see Chapter 38).

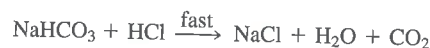
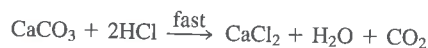
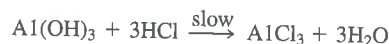
Absorption, Distribution, Clearance. The most readily available compounds are bismuth subsalicylate (PEPTO-BISMOL) in the United States, and bismuth subcitrate (DE-NOL) elsewhere. The poorly water-soluble compounds are largely converted to insoluble bismuth oxide, hydroxide, and oxychloride in the acidic environment of the stomach. Following ingestion, salicylate is absorbed, with greater than 90% recovered in the urine. Plasma levels are similar to levels achieved after a comparable dose of aspirin. About 1% of an oral dose of bismuth is absorbed; the remainder is excreted as insoluble salts in the feces. Absorbed bismuth has a plasma half-life of about 5 days and is excreted in saliva, urine, and bile.

Side Effects Associated with Bismuth Therapy. Plasma concentrations of Bi^{3+} rise with prolonged therapy, but not to dangerous levels. The reaction of bismuth with bacterial H_2S results in the formation of bismuth sulfide, which imparts a black color to the oral cavity and to feces. Salicylate also is absorbed when bismuth subsalicylate is used; however, neither bismuth nor salicylate reaches toxic levels with normal use. Bismuth toxicity, with ataxia, encephalopathy, and osteodystrophy, is possible with excessive overingestion but is generally associated with other bismuth salts. Patients taking large quantities of aspirin or with sensitivity to aspirin also may show sensitivity to the salicylate in bismuth subsalicylate. Bismuth compounds have been shown to reduce the bioavailability of orally administered tetracycline. For a review of recent studies on the gastrointestinal actions of bismuth compounds, see Yoshida and Peura (1993).

ANTACIDS

The function of antacids is to neutralize the HCl secreted by gastric parietal cells. Antacids are compared quantitatively in terms of their acid-neutralizing capacity, defined as the quantity of 1 N HCl (expressed in milliequivalents) that can be brought to pH 3.5 in 15 minutes. The time limit reflects the fact that some formulations may react with acid so slowly that a negligible amount is neutralized during the sojourn of the preparation in the stomach. Commonly used antacids differ in terms of their composition and acid-neutralizing capacities, as summarized in Table 37-1.

Chemical Composition and Properties. Hydroxides of aluminum and magnesium are the most common constituents of antacid preparations. Sodium bicarbonate and calcium carbonate also are used, as are other carbonates, silicates, and phosphates. The antacids react with HCl to form chlorides, water, and carbon dioxide, neutralizing HCl by the following chemical reactions:



The usefulness of antacids is influenced by their rates of dissolution and reactivity, by physiologic effects of the cation, by water solubility, and by the presence or absence of food in the stomach. The very water-soluble $NaHCO_3$ is rapidly cleared from the stomach and presents both an alkali and a sodium load. $CaCO_3$ can neutralize HCl rapidly (depending on particle size and crystal structure) and effectively; however, Ca^{2+} may adversely activate Ca^{2+} -dependent processes, leading to secretion of gastrin and HCl. Both carbonates liberate CO_2 , which can cause abdominal distention and belching with acid reflux.

Table 37-1
Composition and Neutralizing Capacities of Popular Antacid Preparations

PRODUCT	CONTENTS, mg PER TABLET OR PER 5 ml				ACID-NEUTRALIZING CAPACITY, mEq PER TABLET OR PER 5 ml
	Al(OH) ₃	Mg(OH) ₂	CaCO ₃	SIMETHICONE	
<i>Tablets</i>					
Gelusil II	400	400	0	30	21
Maalox TC	600	300	0	0	28
Mylanta II	400	400	0	40	23
Riopan Plus 2		Magaldrate, 1080		20	30
Rolaids		NaAlCO ₃ (OH) ₂ , 325		0	11
Tums Ex	0	0	750	0	15
<i>Liquids</i>					
Gelusil II	400	400	0	30	24
Kudrox	500	450	0	40	28
Maalox TC	600	300	0	0	28
Milk of Magnesia	0	390	0	0	14
Mylanta II	400	400	0	40	25
Riopan Plus II		Magaldrate, 1080		30	30

The hydroxides of aluminum and magnesium are relatively insoluble; therefore, OH⁻ does not accumulate to corrosive levels. Mg(OH)₂ reacts relatively rapidly with H⁺. The related carbonate, MgCO₃, although more soluble, reacts more slowly owing to its crystal structure. Al(OH)₃ acts relatively slowly, can form complex conglomerates, and can provide sustained neutralizing capacity. Thus, combinations of Mg²⁺ and Al³⁺ hydroxides provide a relatively fast and sustained neutralizing capacity. Magaldrate is a hydroxymagnesium aluminate complex that is rapidly converted in gastric acid to Mg²⁺ and Al(OH)₃, which are poorly absorbed and thus provide a sustained antacid effect with balanced effects on intestinal motility.

Some antacid preparations combine Al(OH)₃ and NaHCO₃ to achieve both the rapid effect of the carbonate and the sustained effect of Al(OH)₃. Simethicone, a surfactant that may decrease foaming and hence esophageal reflux, is included in many antacid preparations.

Pharmacological Properties

Gastrointestinal Effects. The acid-neutralizing properties of antacids in the stomach roughly parallel those observed *in vitro*. The pH achieved depends on the form and dosage of the antacid and on whether the stomach is empty or full. The compounds are cleared from the empty stomach in about 30 minutes. The presence of food alone elevates gastric pH to about 5 for approximately 1 hour and prolongs the neutralizing effects of antacids for about 2 hours.

In general, sufficient antacid to maintain gastric pH ≥ 4 probably is required for adequate therapy (see below). Elevation of the pH of

the antrum will increase gastrin secretion, resulting in a compensatory secretion of acid and pepsin. Although small in normal individuals, this effect may be more pronounced in patients with duodenal ulcer. Neutralization also affects the activity of pepsin in the gastric juice. Partial neutralization actually increases peptic activity, the enzyme being nearly four times more active at pH 2 than at pH 1.3. Pepsin activity declines with further neutralization, but active proteolysis occurs until the pH exceeds 5. Above pH 5, pepsin becomes irreversibly inactivated. Elevation of pH also suppresses the acid-catalyzed autoactivation of pepsin from pepsinogen. Thus, in balance, elevation of gastric pH reduces pepsin activity. Al(OH)₃ particles may also reduce pepsin activity by adsorption above pH 3. After the administration of antacids, gastric acid secretion persists after luminal pH has returned to a value at which H⁺ normally inhibits antral gastrin secretion. This "rebound" is small except after large doses of CaCO₃, which can cause an exaggerated and sustained rebound in gastric acid secretion.

Alkalinization of the gastric contents increases gastric motility through the action of gastrin. Al³⁺ can relax the smooth muscle of the stomach and delay gastric emptying, effects that are opposed by those of Mg²⁺. Thus, Al(OH)₃ and Mg(OH)₂ taken concurrently have relatively little effect on gastric emptying. Alkalinization of the gastric contents also increases lower esophageal pressure and esophageal clearance.

Antacids affect bowel motility and secretions. As indicated above, magnesium salts increase intestinal motility, whereas aluminum decreases it; consequently, many commercial antacids contain mixtures of aluminum and magnesium compounds so as not to significantly change bowel function. Because of its capacity to enhance secretion and to form insoluble compounds, CaCO₃ has unpredictable effects on gastrointestinal motility.

Absorption, Distribution, and Excretion. Antacids vary in the extent to which they are absorbed. Antacids that contain aluminum, cal-

cium, or magnesium are less completely absorbed than those that contain NaHCO_3 . Unreacted insoluble antacids pass through the intestines and are eliminated in the feces. When the products from reacted antacids enter the intestine, some of the cations are absorbed.

In persons with normal renal function, the subsequent modest accumulations of Al^{3+} and Mg^{2+} do not pose a problem; with renal insufficiency, absorbed Al^{3+} can contribute to osteoporosis, encephelopathy, and proximal myopathy. Unreacted $\text{Al}(\text{OH})_3$ and $\text{Mg}(\text{OH})_2$ can pass through the intestines as the parent compounds. Al^{3+} also is excreted in the feces as carbonates and hydroxides; Mg^{2+} is eliminated as a variety of soluble salts. Both cations can form insoluble phosphates and other compounds. About 15% of orally administered Ca^{2+} is absorbed, causing a transient hypercalcemia. Although not a problem in normal patients, the hypercalcemia from as little as 3 to 4 g per day can be problematic in patients with uremia. Some Ca^{2+} will be excreted as insoluble Ca^{2+} phosphates and as Ca^{2+} soaps. Absorbed Ca^{2+} is eliminated by urinary excretion, as is Na^+ . In patients with heart failure or hypertension, Na^+ ingestion should be minimized by use of low- Na^+ or Na^+ -free preparations (Table 37-1).

Adverse Effects. Absorption of unneutralized NaHCO_3 will cause alkalosis. Neutralized antacids also may cause alkalosis by permitting the absorption of endogenous NaHCO_3 spared by the addition of exogenous neutralizing equivalents into the gastrointestinal tract. These disturbances of acid-base balance by antacids usually are transient and clinically insignificant in persons with normal renal function.

In the past, when large doses of NaHCO_3 and/or CaCO_3 were commonly administered with milk or cream for the management of peptic ulcer, the *milk-alkali syndrome* occurred frequently. This syndrome results from the ingestion of large quantities of Ca^{2+} and absorbable alkali; effects consist of hypercalcemia, reduced secretion of parathyroid hormone, retention of phosphate, precipitation of Ca^{2+} salts in the kidney, and renal insufficiency. However, therapeutic regimens emphasizing the use of dairy products seldom are employed in current practice.

In general, alkaluria from the long-term use of any antacid predisposes to nephrolithiasis by favoring precipitation of calcium phosphate.

Most antacids can elevate urinary pH by about one pH unit, causing the expected effects on tubular reabsorption and urinary elimination of weak acids and bases (see Chapter 1). The release of CO_2 from bicarbonate and carbonate-containing antacids can cause belching, occasional nausea, abdominal distension, and flatulence. Belching may exacerbate gastroesophageal reflux.

Drug Interactions. By altering gastric and urinary pH, antacids may alter the rates of dissolution and absorption, the bioavailability, and the renal elimination of a number of drugs. As noted above, Al^{3+} and Mg^{2+} compounds alter gastric motility, thereby altering the rate at which drugs reach the absorptive surface of the small intestine. Al^{3+} compounds are notable for their propensity to adsorb drugs and to form insoluble complexes that are not absorbed. Unless bioavailability is also affected, altered rates of absorption have little clinical significance when drugs are given chronically in multiple doses. In general, it is prudent to avoid concurrent administration of antacids and

drugs intended for systemic absorption. Most interactions can be avoided by taking antacids 2 hours before or after ingestion of other drugs.

Thus, through a combination of factors, many antacids decrease the bioavailability of drugs. Instances in which the decrease could be significant clinically include iron, theophylline, quinolone antibiotics, tetracycline, isoniazid, and ketoconazole (dissolution reduced by increased pH). There also is evidence that antacids decrease the bioavailability of ethambutol, some antimuscarinic drugs, benzodiazepines, phenothiazines, ranitidine, indomethacin, phenytoin, nitrofurantoin, vitamin A, fluoride, phosphate, prednisone, and procainamide. Antacids reportedly decrease the bioavailability of atenolol and propranolol and increase that of metoprolol. Antacids increase the dissolution and absorption of the acidic forms of sulfonamides, the rate of absorption of levodopa, and the blood level of valproic acid.

Because alkalization of the urine affects renal clearance of drugs that are weak acids or bases, concurrent antacid therapy increases the rate of elimination of salicylates and phenobarbital and decreases the elimination of amphetamine, ephedrine, mecamylamine, pseudoephedrine, and quinidine. Antacids decrease the hepatic metabolism of ranitidine and reduce the efficacy of nitrofurantoin in the therapy of urinary tract infections. Antacid-drug interactions have been reviewed by D'Arcy and McElnay (1987).

Therapeutic Uses

Peptic Ulcer. In general, other forms of therapy (H_2 receptor antagonists, proton pump inhibitors) are more effective and convenient than antacids. This fact notwithstanding, antacids are efficacious in promoting healing of duodenal ulcers, producing healing roughly equivalent to that of H_2 receptor antagonists after a 4- to 8-week course of therapy, with similar rates of relapse. Antacids are also relatively inexpensive. Although many dosages and schedules have been tried, a total daily dose of 400 mEq of neutralizing capacity, taken in 100-mEq portions an hour after each meal and at bedtime, appears to be effective. The chief drawbacks are lack of patient compliance with the dosing schedule, nocturnal acid secretion, and interactions of antacids with other medications. Antacids are not effective in treating gastric ulcers. In the treatment of Zollinger-Ellison syndrome and giant duodenal ulcers, antacids may be used in conjunction with anti-secretory drugs.

Gastroesophageal Reflux. H_2 receptor antagonists or the H^+ , K^+ -ATPase inhibitor omeprazole are the preferred drugs for treating gastroesophageal reflux. Antacids may still be useful adjuncts for this condition in some patients, since they increase the pressure of the lower esophageal sphincter.

The alginate-containing product GAVISCON reportedly decreases acidic reflux and increases esophageal clearance of acid. This compound has no demonstrable effect on lower esophageal sphincter pres-

sure and is not a potent antacid. The alginate component may protect the mucosa and mechanically impair reflux by forming a viscous layer on the surface of the gastric contents. The efficacy of this product in managing gastroesophageal reflux has not been demonstrated unequivocally.

Miscellaneous Uses. During anesthesia, coma, cesarean section, or endoscopy, aspiration of gastric contents may occur and cause pneumonia or pneumonitis. Prior neutralization of gastric acid provides some protection. The aim should be to keep the pH above 3.5 (possibly as high as 5, to suppress pepsin activity). Antacids may be given just prior to and during the procedure. However, if aspirated, the particulate antacids themselves can cause pulmonary damage, which makes the use of sodium citrate (15 ml) attractive.

Antacids and H_2 antagonists are both effective in the prophylaxis of stress ulceration and consequent acute upper-gastrointestinal hemorrhage (see Gonzalez and Grainger, 1994). The management of upper-gastrointestinal bleeding has been reviewed by Peterson and Laine (1993).

SUCRALFATE

Rationale for Sucralfate Therapy. The mucus layer that covers the gastric and duodenal mucosa, buffered by bicarbonate secreted into this layer by underlying epithelial cells, provides the primary cytoprotective defense against acid-fostered peptic digestion. The mucus layer retards the inward diffusion of both H^+ and large proteins, thus effectively excluding pepsin while protecting against acidic erosion. Mucosal erosion and ulceration characteristic of peptic acid diseases result from pepsin-mediated hydrolysis of mucosal proteins.

The observation that sulfated polysaccharides inhibit pepsin-mediated protein hydrolysis was the rationale for development of cytoprotective agents that would mimic this effect. Other studies demonstrated that the extent of sulfation, rather than the molecular weight of the polysaccharide polymer, was critical. The octasulfate of sucrose was observed to inhibit peptic hydrolysis *in vitro*; reaction of sucrose octasulfate with $Al(OH)_3$ forms a viscous substance, called *sucralfate* (CARAFATE), that is insoluble in water and has a weak buffering action. Sucralfate also binds bile salts, which are implicated in the pathogenesis of gastric ulcers, thus providing another means by which sucralfate may achieve therapeutic utility.

Chemistry. The sucralfate complex formed from sucrose octasulfate and polyaluminum hydroxide has a primary unit that may be represented as $C_{12}H_6O_{11}[SO_3^-Al_2(OH)_5^+]_8 \cdot nH_2O$. When the pH is below 4, there is extensive polymerization and cross-linking of sucralfate to form a sticky, viscid, yellow-white gel. Continued reaction with acid gradually consumes $Al_2(OH)_5^+$ until some sucrose octasulfate moieties are entirely freed of Al^{3+} . Even though the pH in the duodenum is well above 4, the gel retains its viscid, demulcent properties.

Pharmacological Effects. Sucralfate adheres to epithelial cells and adheres very strongly to the base of ulcer craters, so avidly that it is difficult to wash the gel from the crater. In human beings, the gel continues to adhere to ulcerated epithelium for longer than 6 hours; it adheres more to duodenal than to gastric ulcers. This binding to ulcer craters is thought to represent the main therapeutic action of sucralfate. Antacids and food do not appear to affect the integrity of the adherent gel; proteins in foodstuffs adsorb to its surface, and thus add an additional cytoprotective layer.

A variety of mechanisms have been proposed to account for the cytoprotective and healing effects of sucralfate, including stimulation of prostaglandin synthesis, adsorption of pepsin, and stimulation of local production of epidermal growth factor (for a review, see McCarthy, 1991).

Side Effects. The incidence and severity of side effects from sucralfate are very low; only constipation due to Al^{3+} (in 2% of cases) and a sense of dry mouth (less than 1%) appear significant. Occasionally, however, patients complain of significant abdominal discomfort. Effects on plasma Al^{3+} and phosphate metabolism are similar to those described for $Al(OH)_3$ above. Laboratory studies indicate that sucralfate can adsorb and thereby reduce the bioavailability of a number of drugs, including tetracycline, phenytoin, digoxin, cimetidine, ketoconazole, and fluoroquinolone antibiotics. Interactions may be minimized by administration of other medications 2 hours prior to administration of sucralfate.

Clinical Utility. Sucralfate (1 g, one hour before each meal and at bedtime for 4 to 8 weeks) promotes healing of duodenal and gastric ulcers approximately as effectively as H_2 receptor antagonists. As a maintenance therapy, sucralfate seems to be more efficacious in duodenal than in gastric ulcer disease. Sucralfate (1 g, twice daily) is approved in the United States for maintenance therapy of duodenal ulcer. Sucralfate also may be used to prevent stress ulcers. Since the preparation is activated by acid, sucralfate is more effective when administered before meals than after; by the same rationale, sucralfate should not be administered within 30 minutes of the administration of antacids.

Although sucralfate has some beneficial effects against gastroesophageal reflux, the availability and superior efficacy of omeprazole and H_2 receptor antagonists, along with unanswered questions about sucralfate's delivery and dosing schedule, argue against the use of the drug in acid reflux disease. For additional information about sucralfate see McCarthy (1991).

PROSTAGLANDIN ANALOGS

Prostaglandins E_2 and I_2 (PGE_2 and PGI_2), the predominant prostaglandins synthesized by the gastric mucosa, inhibit the secretion of acid and stimulate the secretion of mucus and bicarbonate (see Figure 37-1 and Chapter 26). The ulcerogenic properties of aspirin-like drugs that inhibit the synthesis of prostaglandins suggest a role for these autacoids in normal gastric function. Because the administration of prostaglandins protects the gastric mucosa of animals against various ulcerogenic insults, a number of slowly metabolized prostaglandin analogs have been developed and tested in human beings.

Misoprostol (CYTOTEC), 15-deoxy-16-hydroxy-16-methyl-PGE₁, is available in the United States. Clinical studies indicate that misoprostol is moderately effective in treating duodenal and gastric ulcers. The dosage required to promote ulcer healing (200 μ g, four times daily with food) inhibits gastric acid secretion and is higher than the dose needed to produce cytoprotective effects (enhanced secretion of mucus and HCO₃⁻). Although prostaglandin analogs likely will remain second-line agents in the treatment of patients with peptic ulcer disease, they are particularly valuable as cytoprotective agents in patients who require nonsteroidal antiinflammatory agents. Misoprostol is currently approved for the prevention of gastric ulcer disease induced by nonsteroidal antiinflammatory drugs in patients who must take aspirin-like drugs for the treatment of arthritis or other diseases and who are at high risk for complicated gastric ulcer disease (*see also* Chapter 27).

Side Effects. Effective oral doses of misoprostol cause diarrhea in up to 30% of patients at therapeutic doses, a side effect that may limit its use somewhat. Some abdominal cramping also may occur. These compounds are potential abortifacients and should not be used in women who are pregnant or in whom conception is a possibility. The actions and therapeutic use of misoprostol have been reviewed by Collins (1990). Other congeners of PGE₁ (rioprostil) and PGE₂ (aroprostil, enprostil, trimoprostil) are under study.

MUSCARINIC ANTAGONISTS

Muscarinic cholinergic antagonists can reduce basal secretion of gastric acid by 40% to 50%; stimulated secretion is inhibited to a lesser extent. Selective antagonists of M₁ receptors are as effective as atropine or other nonselective muscarinic antagonists but are less likely to produce the adverse effects that are characteristic of cholinergic blockade (*e.g.*, dry mouth, tachycardia). [These agents are not used for the treatment of acid-peptic disorders in the United States, although pirenzepine and telenzepine are currently in clinical trial in the United States]. These agents have relatively low affinities for M₂ and M₃ receptors (*see* Chapter 7). Since the muscarinic receptors on histamine-containing cells have not been characterized, it is not clear where the M₁ antagonists act. Nor is it known whether or not blockade of M₁ receptors on intramural cholinergic neurons will interrupt transmission of vagal impulses. M₁ antagonists also may inhibit the secretion of gastrin, mucus, and HCO₃⁻ (*see* Figure 37-1).

Although pirenzepine and telenzepine are less effective than H₂ antagonists in reducing acid secretion, M₁ antagonists produced comparable rates of healing of duodenal and gastric ulcers in several clinical trials. Used in maintenance dosage, pirenzepine is equivalent to cimetidine in preventing the recurrence of ulcers. Both pirenzepine and telenzepine are hydrophilic and penetrate the blood-brain barrier poorly. The effective oral dose of pirenzepine is 50 mg two or three times daily. The more potent telenzepine is effective orally at 3 mg/day. Side effects (dry mouth, blurred vision, constipation) may limit the utility of these drugs. Maton and Jensen (1993) have reviewed clinical studies of M₁ antagonists in peptic ulcer disease. The pharmacological properties of muscarinic antagonists are described in Chapter 7.

CARBENOXOLONE

Carbenoxolone is an oleanane derivative of glycyrrhizic acid, a component found naturally in licorice root. It is not approved for use in the United States but has been used in Europe since 1962 for the treatment of peptic ulcers. Carbenoxolone appears to alter the composition and quantity of mucus, thereby enhancing the mucosal barrier to HCl. The mechanism is not clear but may relate to the lipophilic character of carbenoxolone (whereby it binds to membranes) and to its reported capacities to inhibit pepsin activity and to stimulate gastric glycoprotein synthesis.

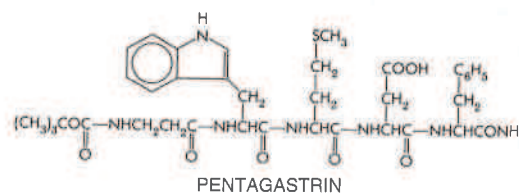
In the treatment of peptic ulcer disease, carbenoxolone is more effective than placebos but no more effective than H₂ receptor antagonists. For gastroesophageal reflux, carbenoxolone produces variable results.

Carbenoxolone is a steroid congener and exhibits significant mineralocorticoid activity. Thus, Na⁺ and fluid retention, hypertension, hypokalemia, and impaired glucose tolerance are frequently observed. These clinically significant side effects constitute major deterrents to the use of carbenoxolone. Although other mineralocorticoids do not have anti-ulcer properties, concurrent administration of spironolactone interferes with the therapeutic effects of carbenoxolone.

PROMOTERS OF GASTRIC SECRETION: GASTRIN AND ITS ANALOGS

To evaluate gastric secretory problems, it may be useful to determine whether or not parietal cell function is normal. Use of histamine (with an H₁ histamine receptor antagonist), H₂ agonists, or muscarinic agonists is limited by adverse effects. Gastrin and its analogs cause fewer and less severe side effects and are more useful for this purpose.

Pentagastrin. Gastrin, a heptadecapeptide, is a potent physiological secretagogue that is released from the pyloric antrum by vagal stimuli and in response to feeding. Smaller fragments of the peptide also are fully active, and a synthetic pentapeptide, pentagastrin, is available to test gastric function; its structure is as follows:



The most prominent action of pentagastrin is to stimulate the secretion of gastric acid, pepsin, and intrinsic factor. Pentagastrin also stimulates pancreatic secretion, inhibits absorption of water and electrolytes from the ileum, relaxes the sphincter of Oddi, and increases blood flow in the gastric mucosa. Although it contracts the smooth muscle of the lower esophageal sphincter and the stomach, pentagastrin delays gastric emptying. The half-life of pentagastrin in the circulation is about 10 minutes.

After subcutaneous injection of 6 μ g/kg of pentagastrin (PENTAVLON), the diagnostic dose, pentagastrin elicits reproducible gastric secretory responses comparable to those induced by histamine or betazole. Side effects are usually minor and transient; these may in-

clude nausea, hiccups, the urge to defecate, flushing, tachycardia, faintness, and dizziness. Allergic reactions are rare. Gastric secretion begins within 10 minutes, peaks within 20 to 30 minutes, and lasts about an hour.

PROSPECTUS

The treatment of peptic ulcer disease has relied on neutralization or reduction of gastric acidity. Knowledge of the details of the acid secretory pathway has led to improved means of reducing acidity, most recently to the widespread use of H_2 receptor antagonists and proton pump inhibitors. Future generations of these agents may offer some advantages over currently available drugs.

However, acidity is only one facet of peptic ulcer disease, and we may expect therapeutic advances to focus on other aspects of the formation and prevention of ulcers. Safe and specific means of altering bicarbonate and mucus secretion to enhance gastric and pyloric cytoprotection may become available. Furthermore, we can anticipate an increase in our understanding of the contribution of bacterial pathogens to the etiology of peptic ulcer disease. Such knowledge is likely to lead to new and more effective regimens for the eradication of *Helicobacter pylori*. This may lead to acceleration in the healing process and a reduction in the rate of recurrence.

For further discussion of peptic ulcer disease, Zollinger-Ellison syndrome, and gastroesophageal reflux disease, see Chapters 251 and 252 in *Harrison's Principles of Internal Medicine*, 13th ed., McGraw-Hill, New York, 1994.

BIBLIOGRAPHY

MONOGRAPHS AND REVIEWS

- Barradell, L.B., Faulds, D., and McTavish, D. Lansoprazole. A review of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficacy in acid-related disorders. *Drugs*, **1992**, 44:225–250.
- Binder, H.J., and Donaldson, R.M., Jr. Effect of cimetidine on intrinsic factor and pepsin secretion in man. *Gastroenterology*, **1978**, 74:371–375.
- Black, J. Reflections on the analytical pharmacology of histamine H_2 -receptor antagonists. *Gastroenterology*, **1993**, 105:963–968.
- Blaser, M.J., and Parsonnet, J. Parasitism by the “slow” bacterium *Helicobacter pylori* leads to altered gastric homeostasis and neoplasia. *J. Clin. Invest.*, **1994**, 94:4–8.
- Collins, P.W. Misoprostol: discovery, development, and clinical applications. *Med. Res. Rev.*, **1990**, 10:149–172.
- D'Arcy, P.F., and McElnay, J.C. Drug-antacid interactions: assessment of clinical importance. *Drug Intell. Clin. Pharm.*, **1987**, 21:607–617.
- Deakin, M., and Williams, J.G. Histamine H_2 -receptor antagonists in peptic ulcer disease. *Drugs*, **1992**, 44:709–719.
- Labenz, J., and Börsch, G. Toward an optimal treatment of *Helicobacter pylori*-positive peptic ulcers. *Am. J. Gastroenterology*, **1995**, 90: 692–694.
- Lind, T., Cederberg, C., Ekenved, G., Hagland, U., and Olbe, L. Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin stimulated acid secretion in man. *Gut*, **1983**, 24:270–276.
- Lindberg, P., Brandstrom, A., Wallmark, B., Mattsson, H., Rikner, L., and Hoffmann, K.J. Omeprazole: the first proton pump inhibitor. *Med. Res. Rev.*, **1990**, 10:1–54.
- McCarthy, D.M. Sucralfate. *N. Engl. J. Med.* **1991**, 325:1017–1025.
- McTavish, D., Buckley, M.M., and Heel, R.C. Omeprazole. An updated review of its pharmacology and therapeutic use in acid-related disorders. *Drugs*, **1991**, 42:138–170.
- Symposium. NIH Consensus Development Panel on *Helicobacter pylori* in peptic ulcer disease. *J.A.M.A.*, **1994**, 272:65–69.
- Wormsley, K.G. Safety profile of ranitidine. A review. *Drugs*, **1993**, 46:976–985.
- Atkinson, A.J. Jr., and Craig, R.M. Therapy of peptic ulcer disease. In, *Peptic Ulcer Disease. Mechanisms and Management*. (Molinoff, P.B., ed.) Healthpress Publishing Group, Inc., Rutherford, N.J. **1990**, pp. 83–112.
- Goldschmiedt, M., and Feldman, M. Gastric Secretion in Health and Disease. In, *Gastrointestinal Disease: Pathophysiology, Diagnosis, Management*, 5th ed. (Sleisenger, M.H., and Fordtran, J.S., eds.) Saunders, Philadelphia, **1993**, pp. 524–544.
- Gonzalez, E.R., and Grainger, J. Management of stress-related mucosal damage and its consequences in the critically ill patient. In, *A Pharmacologic Approach to Gastrointestinal Disorders*. (Lewis, J.H., ed.) Williams & Wilkins, Baltimore, **1994**, pp. 47–74.
- Hansten, P.D. Drug interactions of gastrointestinal drugs. In, *A Pharmacologic Approach to Gastrointestinal Disorders*. (Lewis, J.H., ed.) Williams & Wilkins, Baltimore, **1994**, pp. 535–563.
- Maton, P.N., and Jensen, R.T. H^+/K^+ ATPase inhibitors, anticholinergic agents, antidepressants, and gastrin receptor antagonists as gastric acid antisecretory agents. In, *Gastrointestinal Pharmacotherapy*. (Wolfe, M.W., ed.) Saunders, Philadelphia, **1993**, pp. 85–112.
- Meredith, G.A. *The Ordeal of Richard Feverel*. (1859, revised in 1878.) New American Library of World Literature, New York, **1961**, p. 13.
- Peterson, W.L., and Laine, L. Gastrointestinal bleeding. In, *Gastrointestinal Disease*, 5th ed. (Sleisenger, M.H., and Fordtran, J.S., eds.) Saunders, Philadelphia, **1993**, pp. 162–192.
- Soll, A.H. Gastric, duodenal, and stress ulcer. In, *Gastrointestinal Disease: Pathophysiology, Diagnosis, Management*, 5th ed. (Sleisenger, M.H., and Fordtran, J.S., eds.) Saunders, Philadelphia, **1993**, pp. 580–679.
- Yoshida, C.M., and Peura, D.A. Gastroduodenal mucosal protection. In, *Gastrointestinal Pharmacotherapy*. (Wolfe, M.W., ed.) Saunders, Philadelphia, **1993**, pp. 113–137.