FLEISER D. KESSLER F Endoscopic YAG laser therapy for carcinoma of the esophagus: A new form of palliative treatment. Gastroenterology 85:600, 1983
GELFORD M et al: Isosorbide dinitrate and nifedipine treatment of achalasia: A chemical. manometric and radionuclide evaluation. Gastroenterology 83:963, 1982
GOYAL RK: Disorders of the circopharyngeus muscle. Otolaryngol Clin North Am 17:115, 1984
KELSEN D Chemotherapy of esophageal cancer. Semin Oncol 11:159, 1984
KIKENDALL JW et al: Pill-induced esophageal injury—case reports and review of the medical literature. Dig Dis Sci 28174. 1983
LEICHMAN L et al: Properative chemotherapy and radiation therapy for patients with cancer of the esophagus: A potentially curative approach. J Clin Oncol 2:75, 1984
MCDONALD GB et al: Esophageal infections in immunosuppressed patients after marrow transplantation. Gastroenterology 88:1111, 1985
SPECHLER SJ. GOYAL RK: *Barrett's Esophagus: Pathophysiology, Diagnosis and Treatment*. New York, Elsevier, 1985
TRIER JS. BJORKMAN DJ: Esophageal. gasmc and intestinal candidiasis. Am J Med 77:39, 1984
VANTRAPPEN G, HELLEMANS J: Treatment of achalasia and related motor disorders. Gastroenterology 79144, 1980

235 PEPTIC ULCER

JAMES E. McGUIGAN

The termpeptic ulcer is used to refer to a group of ulcerative disorders of the upper gastrointestinal tract which appear to have in common the participation of acid-pepsin in their pathogenesis. The major forms of peptic ulcer are chronic duodenal and gastric ulcer. The Zollinger-Ellison syndrome, which is caused by gastrin-releasing tumors (gastrinomas), may also be considered a form of peptic ulcer.

Although our present knowledge of the etiology of peptic ulcer is incomplete, information from studies in humans and in experimental animals indicates that acid-pepsin is crucial for development of peptic ulcer. The presence or absence of peptic ulcer is determined by the delicate interplay between aggressive factors (secreted gastric acid and pepsin) and defensive factors (mucosal resistance). Peptic ulcer is produced when the aggressive effects of acid-pepsin dominate the protective effects of gastric or duodenal mucosal resistance. Why do not all humans develop peptic ulcer? The normal capacity of gastric and proximal duodenal mucosa to resist the corrosive effects of acid-pepsin is extraordinary and unique. This resistance to acid-pepsin is not shared by other tissues—hence the susceptibility of the esophageal mucosa to injury when exposed to refluxed gastric juice and the frequent ulceration of the small intestine at the site of surgical attachment to actively secreting gastric mucosa.

Much has been learned concerning the mechanisms regulating gastric secretion and about a variety of factors which appear important in the development of peptic ulcer. Consideration of gastric physiology provides an understanding of some elements responsible for producing peptic ulcer as well as a rational basis for its treatment.

GASTRIC PHYSIOLOGY RELATED TO PEPTIC ULCER

The gastric mucosa possesses an extraordinary capacity to secrete acid. Parietal (oxyntic) cells secrete hydrochloric acid by a process involving oxidative phosphorylation. Parietal cells, located in mucosal glands in the body and fundus of the stomach. can secrete hydrogen ions at a concentration 3 million times that found in blood. Hydrogen ions are secreted into the gastric lumen by a proton pump mechanism involving a specific hydrogen–potassium adenosine triphosphatase (H^+,K^+-ATPase) located on the microvilli of the secretory canaliculi of the parietal cells. The estimated concentration of HCl secreted directly by parietal cells is approximately 160 m*M*. Each secreted hydrogen ion (H^+) is accompanied by a chloride ion (Cl^-). With increased gastric hydrogen ion secretion, there is a reciprocal decrease in sodium ion secretion. For each hydrogen ion secreted into the gastric lumen, one bicarbonate ion (HCO_3^-) is returned via the gastric venous circulation. accounting for the ***alkaline*** tide. which reflects directly the magnitude of gastric H^+ secretion. Bicarbonate is released from carbonic acid; the latter is generated from carbon dioxide by parietal cell carbonic anhydrase. The two-component hypothesis for secretion of gastric juice proposes that parietal cells secrete pure **HCl.** which is mixed (in various proportions) with nonparietal cell alkaline secretions, similar in ionic composition to extracellular fluid.

Multiple ***chemical, neural,*** and ***hormonal*** factors participate in regulation of gastric acid secretion. Acid secretion is stimulated by gastrin and by cholinergic postganglionic vagal fibers via muscarinic receptors on parietal cells. Gastrin, the most potent known stimulant of gastric acid secretion, is present in cytoplasmic secretory granules in gastrin cells (or G cells) which are interspersed singly or in small clusters among other epithelial cells principally in the mid and deeper portions of the antral pyloric glands. Gastrin, as most, if not all, the gastrointestinal regulatory peptides, is present in multiple molecular forms (Fig. 235-1). The major form of tissue gasmn is heptadecapeptide gastrin (G-17) which contains 17 amino acid residues. Gastrin II is the form of gastrin in which the tyrosyl residue at position 12 is sulfated, and gastrin I is the nonsulfated form. Approximately two-thirds of circulating serum gastrin consists of a larger molecular species of gastrin, namely, "big gastrin." or G-34. This species of gastrin contains 34 amino acids, the carboxyl-terminal 17 of which are identical with heptadecapeptide gastrin and may also be present in sulfated (G-34 II) or nonsulfated (G-34I) forms. Although G-17 has a shorter half-life than G-34, on a molar basis circulating G-17 is approximately as potent as G-34 in stimulating gastric acid secretion.

More than 90 percent of antral mucosal gastrin is in the form of G-17. Gastrin is also present in duodenal mucosa, the highest concentration being in the most proximal duodenum (approximately 10 percent of the antral concentration). The mucosal concentration of gastrin and the proportion as G-17 decrease with progression down the duodenum. The effects of gastrin and the vagus on gastric acid secretion are intimately related. Vagal stimulation increases gastric acid secretion by (1) directly stimulating parietal cells, (2) stimulating release of gastrin into the circulation. and (3) lowering the parietal cell threshold for response to circulating gastrin concentrations. There is also evidence that certain vagal branches or fibers inhibit gastrin release.

Histamine is present in large concentrations in mast cells in the lamina propria of the parietal cell–containing regions of the gastric mucosa. Histamine-containingmast cells are located in close proximity to parietal cells, with a ratio of one mast cell to every two or three parietal cells. For many years views have differed on the importance of histamine in stimulating gastric acid secretion; some suggested that histamine is the "final common pathway" for cholinergic and

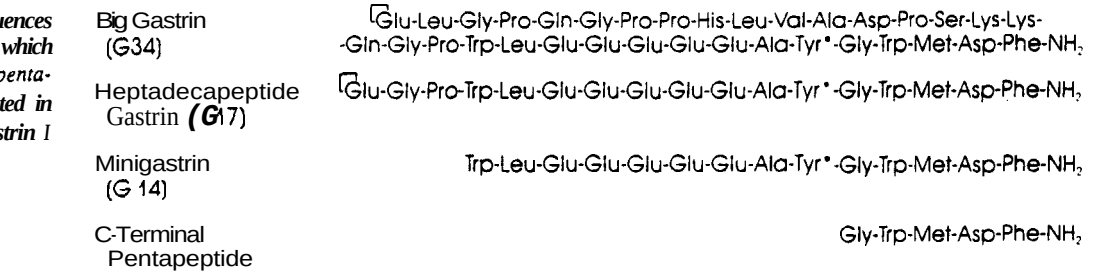

FIGURE 235-1 *Amino acid sequences of selected gastrin peptides. all of which contain the common C-terminal pentapeptide amide. (*Tyrosyl is sulfated in gastrin II and nonsulfated in gastrin I molecules.)*

gastrin stimulation of parietal cell acid secretion. while others were skeptical about any role for histamine in the acid secretory process.

Interest in the role of histamine in acid secretion was renewed by the discovery of H-2-receptor antagonists which competitively inhibit the action of histamine on H-2 receptors (located on gastric parietal, cardiac atrial. and uterine smooth-muscle cells). These drugs exert negligible effect on H-1 receptors, which are readily inhibited by conventional antihistamines. H-2-receptor antagonists (e.g., cimetidine and ranitidine) inhibit both basal acid secretion and secretory responses to feeding, gastrin, histamine, hypoglycemia. and vagal stimulation. Most data support the conclusions that (1) histamine plays an important role in stimulating gastric acid secretion, and that (2) histamine acts in concert with gastrin and cholinergic activity on parietal cells, which bear receptors for histamine, gastrin. and acetylcholine. but that (3) there is still uncertainty as to whether histamine is the final common effector molecule in the stimulation of parietal cell secretion.

Food ingestion is the major physiologic stimulus of gastric acid secretion. Traditionally, gastric acid secretion has been classified into three phases-cephalic, gastric, and intestinal. This classification is of some value in examining the multiple factors which regulate gastric acid secretion. The ***cephalicphuse*** represents the gastric acid secretory response to the sight, smell, taste, and anticipation of food. The ***gastric phuse*** is induced by the presence of food in the stomach. The ***intestinal*** phuse is due to the entry or presence of food within the lumen of the small intestine. Although these three phases are convenient for considering the diverse contributions to gastric acid secretion, each phase is complex and not necessarily due to a single stimulatory control mechanism.

The cephalic phase appears to be mediated primarily by the vagus, which increases gastric acid secretion by stimulation of parietal cells directly and to a lesser extent by stimulating the release of gastrin into the circulation. The gastric phase results from stimulation of chemical and mechanical receptors in the gastric wall by luminal contents. Mechanical distention of the stomach stimulates gastric acid secretion but results in little, if any, gastrin release; this mechanical effect is inhibited by atropine and appears to be mediated by vagal reflexes. Food in the stomach promotes gastric acid secretion by increasing gastrin release, principally due to the ***protein*** content and the ***products*** of ***protein digestion*** contained in the meal; oral glucose and fat cause slight increases in serum gastrin but do not stimulate gastric acid secretion. Food in the proximal small intestine stimulates the intestinal phase of gastric acid secretion. A peptone meal (which contains partially hydrolyzed meat protein) introduced into the small intestine stimulates gastric acid secretion but not gastrin release. It has been proposed that food in the small intestine induces release of an intestinal hormone, presumably a polypeptide, which stimulates gastric acid secretion. This substance is believed to be distinct from gastrin and, unlike gastrin. appears to be degraded substantially during its portal transit through the liver.

Ingestion of both caffeine-containing and caffeine-free *coffee* stimulates gastric acid secretion: both forms of coffee stimulate gastrin release. Ingestion of ethanol and ethanol-containing beverages stimulates gastric acid secretion. Specifically, ingestion of 5 and 10% ethanol solutions and 10% bourbon whiskey results in prompt stimulation of gastric acid secretion without increasing gastrin release; however. white wine stimulates both gastric acid secretion and gastrin release. Furthermore. intravenous ethanol stimulates gastric acid secretion, suggesting that both systemic and local mechanisms are involved. Intravenous ***calcium*** stimulates acid secretion and produces minimal increases in serum gastrin levels. Oral calcium has been reported to stimulate gastric acid secretion directly, i.e., without an increase in serum calcium or gastrin concentrations. Except in patients with gastrinoma, hypercalcemia is usually not associated with acid hypersecretion or increases in serum gastrin.

Inhibition of gastric acid secretion can be produced by several mechanisms. Acid secretion may be inhibited by acid in the stomach or duodenum, by hyperglycemia, or by hypertonic fluids or fat in the duodenum. Reduction of the intragastric pH to 3.0 produces partial inhibition of gastrin release; further reduction to pH 1.5 or below blocks the release of gastrin to almost all stimuli. There is evidence that ***somatostatin*** is involved in the inhibition of gastrin release produced by acid in the gastric lumen. Somatostatin is present in high concentrations in antral mucosal endocrine cells (D cells) which possess cytoplasmic processes that extend to neighboring gastrin cells. The action of somatostatin in inhibiting gastrin release appears to be mediated by its local (paracrine) effects on gastrin cells. The cytoplasmic processes of somatostatin cells also extend to intimate contact with parietal and other cells in the acid-secreting portions of the stomach. Somatostatin is believed to reduce gastric acid secretion by inhibiting gastrin release and by directly inhibiting parietal cell secretion. Acid in the duodenum also inhibits gastric acid secretion; this may be secondary to stimulating the release of secretin and/or other peptides capable of inhibiting gastric acid secretion. ***Secretin*** is a linear polypeptide containing 27 amino acids bearing structural similarities to glucagon. Secretin is released from endocrine cells (S cells) in the mucosa of the small intestine in response to mucosal acidification. Fat in the duodenum also inhibits gastric acid secretion; gastric inhibitory peptide (GIP) has been proposed as a candidate for this enterogastrone action; however, this effect for GIP remains to be proved. The mechanisms by which hyperglycemia or intraduodenal hyperosmolality inhibit gastric acid secretion are not known. Additional peptides identified in the mucosa of the gastrointestinal tract which have the capacity to inhibit gastric acid secretion include glucagon-like peptides (e.g., glicentin), vasoactive intestinal peptide (VIP), and urogastrone; the latter appears to be structurally and functionally identical with epidermal growth factor. Vasoactive intestinal peptide, which is located in neurons, is unlikely to inhibit gastric acid secretion as a circulating hormone, since it is inactivated during its portal passage through the liver. The extent to which these peptides contribute to the regulation of gastric acid secretion is not clear.

The proteolytic effects of ***pepsins*** and the corrosive effects of acid appear to be integral components in the tissue injury which leads to peptic ulceration. Acid catalyzes the cleavage of inactive pepsinogen molecules to active pepsins and also provides the appropriate pH required for pepsin activity. Pepsin activity is substantially reduced above pH 4.0, and these enzymes are irreversibly inactivated at neutral or alkaline pH. There are a variety of pepsinogens and pepsins in gastric juice. Pepsinogens (and their corresponding active pepsins) have been classified by immunochemical techniques as either PG I (pepsinogens 1 through 5) or PG II (pepsinogens 6 and 7). Pepsinogen I is present in chief and mucous cells in the body and fundus of the stomach. Pepsinogen II is located in cells of the pyloric glands, Brunner's glands of the duodenum, mucous cells of the gastric cardiac glands, and the same cells in which PG I is found. Both PG I and PG II are present in plasma, while only PG I can be detected in urine. A high degree of correlation exists between serum concentrations of PG I and maximal gastric acid secretion. In general, agents which stimulate gastric acid secretion also stimulate pepsinogen secretion. Cholinergic action is particularly potent in promoting pepsinogen secretion. Secretin, although it inhibits gastric acid secretion, stimulates pepsinogen secretion.

Parietal cells also secrete ***intrinsicfactor.*** Agents which stimulate gastric acid secretion also lead to secretion of intrinsic factor.

The precise mechanisms whereby the normal stomach and duodenum resist the corrosive effects of acid-pepsin (i.e., ***mucosal resistance)*** have not been defined. A variety of factors have been proposed as potential contributors to mucosal resistance. Gastric mucus, secreted by gastric mucous cells, is present in solution in gastric juice and as an insoluble mucus gel layer which coats the mucosal surface of the stomach. It has been suggested that ***gastric mucus*** may play a role in mucosal defense against injury, and thus in preventing peptic ulceration. Mucus secretion is enhanced by mechanical or chemical irritation and by cholinergic stimulation. Gastric mucus is a large polymeric glycoprotein (2×10^6 mol wt)

containing four subunits connected by disulfide bridges. Depolymerization of the glycoprotein subunits of mucus, which may be produced by peptic digestion or disruption of disulfide bonds. renders the glycoprotein incapable of forming a viscous gel. When intact, this mucus gel serves as an unstirred layer which permits ionic diffusion but is impermeable to penetration by macromolecules such as pepsin (34,000 mol wt). Bicarbonate ions are secreted by gastric surface epithelial cells (nonparietal cells) and enter the unstirred layer of mucus gel; this mechanism facilitates the development of a microenvironment with a substantial hydrogen ion gradient between the gel opposing the gastrin luminal contents (more acid) and the gel surface facing and in intimate contact with the apical surfaces of gastric mucosal cells (more alkaline). Pepsin secreted into the gastrin lumen is denied reentry by the impermeable mucus gel, thereby potentially protecting the mucosal cells from proteolytic injury. Gastric mucus also contains glycoprotein blood group substances. Approximately three-fourths of the population secrete gastric juice containing these ABO(H) substances and those individuals are referred to as secretors.

Normally the gastric luminal epithelial cell surfaces and intercellular tight junctions provide an almost completely impermeable barrier to back-diffusion of hydrogen ions from the lumen. This ***gastric mucosal barrier*** may participate in mucosal resistance to acid-peptic ulceration. This barrier may be interrupted by various agents including bile acids, salicylates. alcohol, and weak organic acids, thus permitting *back-diffusion* of ***hydrogen ions*** from the lumen to intra- and intercellular sites. Such back-diffusion may result in cellular injury, release of histamine from mast cells. further stimulation of acid secretion, damage to small blood vessels, mucosal hemorrhage, and superficial ulceration. Interruption of the gastric mucosal barrier may be responsible (at least in part) for the hemorrhagic erosive gastritis associated with salicylate and ethanol ingestion and may also contribute to other forms of gastric mucosal injury.

However, the relationship between the gastric mucosal barrier and mucosal resistance to chronic peptic ulcer has not been completely elucidated. ***Decreased mucosal blood flow,*** accompanied by back-diffusion of available hydrogen ions, also appears *to* contribute to gastric mucosal damage. Maintenance of normal mucosal blood flow is an essential component of mucosal resistance to injury. *Prostaglandins are* present in abundant quantities in the gastric mucosa. Various prostaglandins, particularly those of the E series, have been shown to inhibit gastric mucosal injury due to a wide variety of agents. It is possible that endogenous prostaglandins contribute to mucosal resistance and may thereby have a ''cytoprotective'' function. Mild mucosal injury or irritation may induce prostaglandin synthesis, thereby potentially enhancing mucosal resistance to injury, a concept referred to as ***adoptive cyroprotection.***

Other mucosal factors, some of which are genetic, but which have not been clearly defined, apparently contribute to the ability of the gastric mucosa to resist or permit the development of peptic Ulceration.

MEASUREMENT OF GASTRIC ACID SECRETION

Since HCI secretion by the stomach appears to be an important factor in the production of peptic ulcer disease, measurement of basal and stimulated gastric acid secretion may be of value in the assessment of peptic ulcer patients. In general, basal and stimulated acid outputs in females are approximately two-thirds to three-fourths those found in males. The range of values for normal subjects is extremely broad and overlaps substantially with those found in patients with duodenal ulcer, gastric ulcer, and even the Zollinger-Ellison syndrome. Mean basal acid output (BAO) in normal males without known ulcer disease is about *1.5* to 2.0 meq/h. In duodenal ulcer patients mean basal acid output averages from 4 to 6 meq/h, again with a wide degree of variation. Patients with gastric ulcer tend to have gastric acid secretory rates which are normal or even slightly less than those of normal subjects.

Measurement of gastric acid output is not helpful in either diagnosing peptic ulcer or excluding it. Thus measuring gastric acid secretion is clearly not necessary in all patients with duodenal ulcer. However, detection of gastric acid hypersecretion is of value when the Zollinger-Ellison syndrome is suspected. Measurement of gastric acid output is useful to detect achlorhydria, as found in patients with pernicious anemia. Since patients with benign gastric ulcer virtually always secrete some acid, pentagastrin-fast achlorhydria in a patient with a gastric ulcer almost always indicates malignancy. Measurement of gastric acid secretion is indicated in the search for the cause of ulcer recurrence after surgery for peptic ulcer.

In order to measure gastric acid output, a radiopaque gastric tube is passed so that its tip is located in the most dependent portion of the stomach. With the patient in a reclining or semirecumbent position on the left side, the position of the tube is verified by fluoroscopy. Gastric contents *are* aspirated and discarded. Basal gastric acid secretions *are* then collected in four consecutive 15-min intervals to determine the I-h basal acid output. Secretion volume and acid concentration (titrated with 0.1 ***N*** sodium hydroxide to pH 7.0 or calculated by formula from the pH of the aspirated gastric juice) are measured, and acid output is expressed as milliequivalents per hour.

A variety of substances have been used to stimulate maximal acid output (MAO) by the stomach. These have included ***histamine,*** ***betazole*** (Histalog)—a structural analogue of histamine—and ***pentagastrin*** (Peptavlon). Histamine, the first standard stimulant to be used for gastric acid secretory testing, requires the simultaneous administration of an antihistaminic agent (H-I-receptor antagonist) to inhibit untoward systemic side effects. Betazole possesses fewer undesired side effects of histamine and does not require the concomitant administration of an antihistamine. Pentagastrin (*N-tert*-butyloxycarbonyl-β-Ala-Try-Met-Asp-Phe-NHJ contains the biologically active carboxyl-terminal tetrapeptide amide portion of the gastrin molecule and is currently the preferred and most commonly used agent to induce **maximal** acid secretion. Following collection of basal acid secretion gastric juice is collected for four additional consecutive 15-min periods after the subcutaneous injection of pentagastrin (6 μg/kg). The MAO is the expression of the milliequivalents of acid aspirated during the 1 h after pentagastrin administration. Peak acid output (PAO) is calculated by combining the **two** highest consecutive 15-min acid outputs following pentagastrin injection and multiplying by 2.

DUODENAL ULCER

GENERAL CONSIDERATIONS Duodenal ulcer is a chronic and recurrent disease. The ulcer is usually deep and sharply demarcated. It tends to penetrate through the submucosa and often into the muscularis propria. The ulcer floor contains no intact epithelium and usually consists of a zone of eosinophilic necrosis resting on a base of granulation tissue surrounded by variable amounts of fibrosis. The ulcer bed may be clear or contain either blood or a proteinaceous exudate with entrapped erythrocytes and acute and chronic inflammatory cells. More than *95* percent of duodenal ulcers occur in the first portion of the duodenum. and approximately 90 percent of these are located within 3 cm of the junction of the pyloric and duodenal mucosa. Duodenal ulcers are usually round or oval, but they may be irregular or elliptic. They are usually less than 1 cm in diameter. Rarely, duodenal ulcers may be extremely large (3 to 6 cm in diameter) and may be mistaken radiographically for the entire duodenal bulb. These giant ulcers often escape radiologic detection and are usually identified directly by endoscopy or *at* surgery or postmortem examination.

The absolute prevalence of duodenal ulcer in the population is not known. Estimates have ranged from 6 to 15 percent. This variation may be related to the populations examined, differences in study design and diagnostic methods (e.g., endoscopy vs. radiological examination), and perhaps to actual changes or differences in frequency of duodenal ulcer disease. The best current estimates suggest

most common single hematologic defect after peptic ulcer surgery and may result from either blood loss (e.g., with persistent or recurrent ulcer) or from iron malabsorption. Patients with gastric resection malabsorb dietary iron but have normal absorption of iron salts; therefore they will respond favorably to treatment with therapeutic oral iron preparations. Folate deficiency may result from either reduced dietary intake or impaired folate absorption. Except for the anemia produced by blood loss in association with early recurrent ulcer disease, the development of anemia after peptic ulcer surgery is gradual, usually occurring several years postoperatively.

The nature of the anemia after ulcer surgery should be clarified by determination of the red blood cell morphology and by measurements of serum iron, folate, and vitamin B_{12}. Iron or folate deficiency may be treated by oral replacement. Vitamin B_{12} deficiency should be treated with monthly intramuscular injections of the vitamin.

OSTEOMALACIA AND OSTEOPOROSIS Osteoporosis and osteomalacia may develop after partial or complete gastrectomy but occur rarely after vagotomy and pyloroplasty. Osteomalacia is extremely frequent following gastrojejunostomy or Billroth II anastomosis. These bone changes are believed to result from malabsorption of calcium and vitamin D. Patients may develop bone pain and have pathologic fractures. The incidence of bone fractures in men following gastric resection has been estimated to be almost twice that of control subjects of similar age. Reduced bone density requires years to develop and can be identified by x-ray. Patients with osteomalacia usually have increased levels of serum alkaline phosphatase and may have reduced serum calcium concentrations. These patients should be treated by supplemental oral vitamin D and calcium. In fact, the frequency of osteoporosis and osteomalacia after partial or complete gastrectomy is sufficiently great that treatment with vitamin D and calcium should probably be instituted and continued indefinitely in these patients, especially females, following gastric resection.

GENERAL MALABSORPTION (See Chap. 237) Mild, chemically demonstrable steatorrhea is common in patients after ulcer surgery. Weight loss is more common after partial gastric resection than with vagotomy without resection and occurs in approximately 60 percent of patients in whom a portion of the stomach has been removed. The major cause of weight loss after peptic ulcer surgery is reduced food intake. On a 100-g fat diet, loss of stool fat seldom exceeds 15 g per day (normal individuals, less than 7 g per day). The causes of maldigestion and malabsorption after peptic ulcer surgery include rapid gastric emptying, reduced dispersion of food in the stomach, reduced bile concentrations in the gut lumen, increased rate of transit of the meal through the small intestine, and reduced or delayed pancreatic secretory responses to feeding. Steatorrhea and weight loss, sometimes accompanied by vitamin B_{12} malabsorption, may develop as a result of bacterial overgrowth, especially in patients with afferent loop bacterial stasis. Overt symptoms and other manifestations of malabsorption appearing after surgery for peptic ulcer may also be due to other preexisting conditions, including latent celiac sprue and chronic pancreatitis.

CARCINOMA AFTER PARTIAL GASTRECTOMY Several studies have documented an increased incidence of adenocarcinoma of the stomach in duodenal ulcer patients following partial gastric resection and after vagotomy and drainage without resection. This usually develops 10 or more years after ulcer surgery. The possibility of carcinoma of the stomach should be considered when abdominal symptoms, which may be similar to or distinct from those due to the original ulcer, appear many years after apparently successful surgery.

ZOLLINGER-ELLISON SYNDROME (GASTRINOMA)

In 1955 Zollinger and Ellison described the syndrome which bears their names, i.e., ulcer disease of the upper gastrointestinal tract, marked increases in gastric acid secretion, and nonbeta islet-cell tumors of the pancreas.

ETIOLOGY AND PATHOGENESIS Zollinger and Ellison. in their original description of the syndrome. suggested that the ulcer disease in these patients resulted from liberation of a secretagogue from the islet-cell tumors which accounted for the often enormously increased rates of gastric acid secretion. Their proposal was proved correct when in 1960 extracts of Zollinger-Ellison (2-E) tumors were shown to stimulate gastric acid secretion. Subsequently. it was found that the pancreatic tumors contained gastrin and that large amounts of this hormone were released into the circulation, producing the pathophysiologic characteristics of the syndrome. These gastrin-containing tumors are, therefore, now referred to as *gastrinomas*. Gastrin has been demonstrated in these tumors by chemical isolation of polypeptides with amino acid compositions and peptide mapping patterns identical with those of human gastrin molecules. In addition, large amounts of gastrin have been demonstrated by radioimmunoassay in gastrinomas and in serums of patients with the Z-E syndrome.

Most gastrinomas are found within the pancreas. Multiple, apparently primary, tumors are common. Pancreatic gastrinomas may be single or multiple and may vary in size from 2 mm to more than 20 cm in diameter. In from one-half to two-thirds of patients multiple gastrinomas are present within the pancreas; however, more than half of these are not identified at surgery. Pancreatic gastrinomas are most common in the body or tail of the pancreas. Approximately 13 percent of patients with this syndrome have tumors in the wall of the proximal duodenum. Gastrinomas have also been located less commonly in other sites, including the hilum of the spleen and very rarely in the stomach. Primary gastrinomas, surrounded by lymphoid tissue, have been found in proximity to the pancreas, proximal duodenum, and spleen. These may be confused with, but are distinct from, metastasis to regional lymph nodes. In rare instances, the Z-E syndrome has resulted from ectopic gastrin-containing tumors, e.g., parathyroid and ovarian adenomas. Many, and when sought for, most, gastrin-secreting islet-cell tumors have been found to contain multiple hormones, which may or may not be released, but are usually clinically silent. These have included adrenocorticotropic hormone, glucagon, insulin, pancreatic polypeptide. and vasoactive intestinal peptide. The absolute frequency of multiple hormones contained in or released by these tumors is not known. Approximately one-third of patients with gastrinomas have increases in serum concentrations of *pancreatic polypeptide.* About two-thirds are histologically or biologically malignant, and about half have spread to the liver when the tumor is identified. Malignant gastrinomas usually grow slowly. From one-half to two-thirds of patients with gastrinomas have metastases, most commonly to regional lymph nodes and liver; spread may also be to peritoneal surfaces, spleen. bone, skin, or mediastinum. Gastrinomas have light-microscopic similarities to carcinoid tumors and may be mistaken for carcinoid tumors, especially when arising from the mucosa of the small intestine or stomach. Pancreatic islet-cell hyperplasia occurs in approximately 10 percent of patients with the Z-E syndrome. Hyperplasia of the islets, accompanying recognizable or unidentified gastrinoma. appears to be an association or a consequence rather than a cause of excess gastrin release, since gastrin is not present in the hyperplastic tissue.

In most gastrinomas approximately 90 to 95 percent of gastrin is in the form of heptadecapeptide gasmn (G-17 or little gasmn), with most of the remainder being big gastrin (G-34). In contrast, approximately two-thirds of circulating gastrin in gastrinoma patients is G-34; most of the remainder of circulating gastrin is G-17. However, smaller amounts of even larger forms of gastrin and smaller gastrin fragments can be detected in the serum. The parietal cell mass is substantially expanded to from three to six times normal, secondary to the trophic effects of gastrin on parietal cells.

In from 20 to 25 percent of patients with the Z-E syndrome. the gastrinoma is a component of the multiple endocrine neoplasia type I (MEN-I) syndrome, an autosomal dominant disorder with a high degree of penetrance and great variability in expressivity. Patients with MEN-I may have hyperplasia, adenomas, or carcinoma involving the parathyroid glands, pancreatic islets, and pituitary: the organs

involved are in that order of frequency. Hyperparathyroidism is present in 87 percent of patients with the MEN-I syndrome. and gastrinoma is present in approximately half of these patients (see chap. 334).

While the true incidence of the Z-E syndrome is not known, estimates are that it accounts for 0.1 to 1 percent of peptic ulcers. The Z-E syndrome may occur at any age. but initial manifestations are most common between ages 30 and 60.

CLINICAL FEATURES From 90 to 95 percent of patients with gastrinomas develop ulceration of the gastrointestinal tract at some point during the course of their disease. Profound gastric hypersecretion is found in most, but not all, patients. Symptoms are often similar to those seen in patients with typical peptic ulcer disease. However, the ulcer symptoms may be more fulminant, progressive, and persistent, and usually respond poorly to usual medical and surgical peptic ulcer treatment programs. The anatomic site of the ulcers in patients with gastrinoma is similar, but not identical, to that of patients with common types of peptic ulcer. About 75 percent of gastrinoma patients have ulcers in the first portion of the duodenum or in the stomach; these are usually single, but may be multiple. When multiple ulcers occur, they are frequently located not only in the first portion of the duodenum, but also in the remainder of the duodenum or even the jejunum. In one large series, 14 percent of the ulcers were found in the duodenum beyond its first portion, and 11 percent in the jejunum. Prompt recurrence of ulcer, often with hemorrhage or perforation, after peptic ulcer surgery without total gastrectomy (in which the Z-E syndrome had not been recognized) is characteristic of gastrinoma.

Diarrhea occurs in about 40 percent of patients, and about 7 percent of patients with gastrinoma may have diarrhea in the absence of ulcer disease. The diarrhea is due to the outpouring of large amounts of hydrochloric acid into the proximal duodenum and can be reduced or eliminated by aspiration of gastric juice. The excessive acid has been shown to reduce the pH within the lumen of the proximal and distal jejunum to as low as 1 and 3.6, respectively. Inflammatory changes may develop in the mucosa of the small intestine, presumably secondary to the injurious effect of the increased amounts of acid and pepsin. Steatorrhea, which is less common than diarrhea, appears to result from inactivation of pancreatic lipase by the large concentration of acid in the proximal small intestine and from decreases in luminal bile acids. The decrease in bile acid concentration of the intraluminal contents is caused by precipitation of the major bile acids at low pH. This leads to impaired micelle formation which, in turn, reduces the intestinal absorption of fatty acids and monoglycerides (see Chap. 237). Vitamin B_{12} malabsorption, not correctable by addition of intrinsic factor, has been detected in some patients with the Z-E syndrome. Although the secretion of intrinsic factor appears normal, the reduced pH within the gut interferes with intrinsic factor mediation of vitamin B_{12} absorption. This can be corrected by neutralization of the intestinal contents. The mechanism by which low pH in the gut interferes with intrinsic factor action is not known.

Diarrhea in patients with gastrinoma is invariably accompanied by gastric acid ***hypersecretion.*** (This does not occur in patients with common duodenal ulcer with similar rates of hypersecretion of gastric acid; the reason for this difference is not known.) Severe diarrhea is also seen with other nonbeta islet-cell tumors of the pancreas, which are usually associated with ***hyposecretion*** of gastric acid or even achlorhydria [pancreatic cholera or WDHA (watery diarrhea, hypokalemia. and achlorhydria) syndrome]. In most cases, the pancreatic cholera syndrome appears *to* be due *to* tumor release of VIP (see Chaps. 334 and 255).

DIAGNOSIS The presence of a gastrinoma should be suspected in patients with a compatible clinical history, especially in those with evidence of marked acid hypersecretion. Two-thirds of gastrinoma patients have basal gastric acid outputs (BAO) which exceed 15 meq/h. In some instances the basal output may be greater than 100 meq/h. However, as stated earlier, there is substantial overlap in the rates of gastric acid secretion among patients with gastrinoma, duodenal ulcer, and normal subjects. Gasmnoma patients often have basal acid output rates which are greater than 60 percent of those induced by maximal stimulation (MAO). In most normal subjects and duodenal ulcer patients basal acid secretory rates are less than 60 percent of maximal secretion. However, because of frequent patient variations, with exceptions to these guidelines by patients with gastrinomas and common duodenal ulcers, the use of the BAO/MAO ratio is of no value in the certain identification of gastrinoma patients.

Some radiographic features may suggest and support the diagnosis of the Z-E syndrome. Large mucosal folds may be demonstrated in the stomach, duodenum, and, in some instances. the jejunum. The lumen of the stomach and small intestine often contains large amounts of fluid. Radiographic features of most ulcers in these patients, except when they are multiple or distal in location, are similar to the common peptic ulcer. Arteriography is of limited value in identifying patients with gastrinoma; primary tumors or hepatic metastases demonstrated at surgery have been identified in only from 20 to 30 percent of gastrinoma patients. Some reports suggest that computerized axial tomography may be of slightly greater value in identifying primary or metastatic gastrinoma. Endoscopic retrograde pancreaticoduodenography (ERCP) has not proved to be of assistance in the diagnosis or exclusion of pancreatic gastrinomas. A small number of duodenal wall gastrinomas have been identified and confirmed histologically by duodenoscopy.

The diagnosis in a patient with clinical features consistent with the Z-E syndrome depends upon the demonstration of ***increased serum gastrin levels*** by radioimmunoassay. Fasting serum gastrin levels in normal subjects and patients with typical duodenal ulcer average approximately 40 to 50 pg/mL and usually do not exceed 150 pg/mL. Patients with gastrinoma almost always have fasting serum gastrin levels which are greater than 200 pg/mL and have been reported as high as 450,000 pg/mL. Approximately half of these patients have fasting serum gastrin levels which are less than 1000 pg/mL.

Several provocative tests have been used to evaluate patients with possible gastrinoma, especially in those who do not exhibit pronounced hypergastrinemia (i.e., serum gastrin greater than 1000 pg/mL). These tests utilize the measurement of serum gastrin levels in response to intravenous calcium infusion, secretin injection, or ingestion of a standard test meal (see Table 235-1).

In the ***secretin injection test,*** secretin (Kabi secretin, 2 units per kilogram) is given intravenously over 30 to 60 s. (Boots secretin is approximately one-sixth as potent as Kabi secretin prepared by the Karolinska Institute. Stockholm. Boots secretin should not be used, since it contains large amounts of gastrin-like material which is immunoreactive with antibodies to gastrin and, therefore, can spuriously increase serum gastrin concentrations.) Gastrin is measured in serum samples obtained before injection of secretin and at 5-min intervals thereafter for 30 min. In normal individuals and patients with common duodenal ulcer, secretin produces either no change or small reductions or small increases in serum gastrin levels. In contrast, in gastrinoma patients intravenous secretin induces substantial increases in serum gastrin. The gastrin levels increase promptly, usually at 5 min, (and virtually always by 10 min), by at least 200 pg/mL. The *calcium infusion test* involves constant 3-h intravenous infusion of calcium gluconate (5 mg calcium per kilogram per hour). Serum samples for gastrin measurements are obtained before and at 30-min intervals for 4 h after initiation of infusion. In gastrinoma patients serum gastrin concentrations usually increase above the basal serum gastrin by at least 50 percent or by more than 400 pg/mL. The third provocative test involves the ***feeding of a standard meal;*** gastrin is measured in serum samples obtained before the meal and at 15-min intervals for 90 min. In gastrinoma patients peak serum gastrin levels do not increase (or increase minimally) and do not reach values 50 percent greater than fasting levels (see Table 235-1).

The secretin injection test is the provocative test of greatest value

the posterior and lateral columns undergo demyelination, and the cerebrum itself. Signs and symptoms include numbness and paresthesias in the extremities (the earliest neurologic manifestations), weakness, ataxia, and poor finger coordination. There may be sphincter disturbances. Reflexes may be diminished or increased. The Romberg and Babinski signs may be positive, and position sense and vibration sense are usually diminished. Disturbances of mentation will vary from mild irritability and forgetfulness to severe dementia or frank psychosis. It should be emphasized that occasionally ***neurologic disease may occur in a patient with a normal hematocrit.***

In the usual patient, in whom hematologic problems predominate, the blood and bone marrow show characteristic megaloblastic changes which are described under "Diagnosis" below. The anemia may be very severe—hematocrits of 15 to 20 are not infrequent—but is surprisingly well tolerated by the patient because it develops so slowly.

Pernicious anemia The most common cause of vitamin B_{12} deficiency in temperate climates is pernicious anemia, in which intrinsic factor secretion ceases owing to atrophy of the gastric mucosa. It is most frequently seen in individuals of northern European descent and is much less common in southern Europeans, blacks, and Orientals. Men and women are equally affected. It is a disease of the elderly, the average patient presenting near age 60; it is rare under 30, although typical pernicious anemia can be seen in children under 10 (juvenile pernicious anemia). Inherited conditions in which a histologically normal stomach secretes either an abnormal intrinsic factor or none at all will cause vitamin B_{12} deficiency which appears in infancy or early childhood.

On the basis of incomplete evidence, pernicious anemia is currently thought to be caused by an autoimmune reaction against gastric parietal cells. There is considerable evidence for immunologic abnormalities in pernicious anemia. The incidence of pernicious anemia is substantially increased in patients with other diseases thought to be of immunologic origin, including Graves' disease, myxedema. thyroiditis, idiopathic adrenocortical insufficiency, vitiligo, and hypoparathyroidism. Patients with pernicious anemia also have abnormal circulating antibodies related to their disease: 90 percent have antiparietal cell antibody while 60 percent have anti-intrinsic factor antibody. Antiparietal cell antibody is also found in 50 percent of patients with gastric atrophy without pernicious anemia as well as in 10 to 15 percent of an unselected patient population, but anti-intrinsic factor antibody is usually absent from these patients. Relatives of patients with pernicious anemia show an increased incidence of the disease, and even clinically unaffected relatives may have anti-intrinsic factor antibody in their serum. A final point supporting an immunologic basis for pernicious anemia is the fact that corticosteroids have been reported to reverse the disease both pathologically and clinically.

The destruction of parietal cells in pernicious anemia is thought to be mediated by the cellular immune system. Humoral factors such as anti-intrinsic factor antibody probably have little role in the pathogenesis of the disease, a view supported by the observation that pernicious anemia is unusually common in patients with agammaglobulinemia.

Pathologically, the most characteristic finding in pernicious anemia is gastric atrophy which involves only the acid- and pepsin-secreting portion of the stomach; the antrum is spared. Other pathologic changes, which are secondary to the deficiency of vitamin B_{12}, include megaloblastoid alterations in the gastric and intestinal epithelium and the neurologic changes described above. The abnormalities in the gastric epithelium are evident as cellular atypia in gastric cytology specimens. a finding which must be carefully distinguished from the cytologic abnormalities seen in gastric malignancy.

The ***clinical manifestations*** are primarily those of vitamin B_{12} deficiency, as described above. The disease is of insidious onset and progresses slowly. An additional physical finding is the tendency of patients with pernicious anemia to be fair-haired or prematurely gray. Laboratory examination will reveal hypergastrinemia and pentagastrin-fast achlorhydria as well as the hematologic and other laboratory abnormalities discussed below in "Diagnosis."

Through appropriate replacement therapy, patients with pernicious anemia should experience complete and lifelong correction of all abnormalities which are due to vitamin B_{12} deficiency, except to the extent that irreversible changes in the nervous system may have occurred prior to treatment. These patients, however, are unusually subject to gastric polyps and have about twice the normal incidence of cancer of the stomach. In view of the latter complication, patients should be followed with frequent stool guaiac examinations together with further diagnostic studies when indicated.

Postgastrectomy Following total gastrectomy or extensive damage to gastric mucosa as, for example, by ingestion of corrosive agents, megaloblastic anemia may develop because the source of intrinsic factor has been removed. In such patients the absorption of orally administered vitamin B_{12} is impaired. Megaloblastic anemia may also follow partial gastrectomy, but the incidence is lower than after total gastrectomy, in which vitamin B_{12} malabsorption occurs in 100 percent of patients. The cause of vitamin B_{12} deficiency after partial gastrectomy may be intestinal overgrowth of bacteria, but it does not always respond to antibiotics.

intestinal organisms The macrocytic anemia seen in association with intestinal strictures, diverticula, anastomoses, and "blind loops" may be attributed to colonization of the small intestine by large masses of bacteria which divert vitamin B_{12} from the host. Steatorrhea may also be seen under these circumstances, because bile salt metabolism is disturbed when the intestine is heavily colonized with bacteria. Hematologic responses have been observed after administration of oral antibiotics such as tetracycline and ampicillin.

Megaloblastic anemia is seen, in Scandinavia especially, in persons harboring the tapeworm D. *latum*. The anemia has been attributed to competition by the worm for vitamin B_{12}. Destruction of the worm eliminates the problem.

ileal abnormalities Vitamin B_{12} deficiency is commonly found in tropical sprue, while it is an unusual complication of nontropical sprue (gluten-sensitive enteropathy; see Chap. ***237).*** Virtually any disorder which compromises the absorptive capacity of the distal ileum can result in vitamin B_{12} deficiency. Specific entities include regional enteritis, Whipple's disease, and tuberculosis. Segmental involvement of the distal ileum by disease can cause megaloblastic anemia without any other manifestations of intestinal malabsorption such as steatorrhea. Vitamin B_{12} malabsorption is also seen after ileal resection. The Zollinger-Ellison syndrome (intense gastric hyperacidity due to a gastrin-secreting tumor) may cause vitamin B_{12} malabsorption by acidifying the small intestine. This will retard the transfer of the vitamin from R binder to intrinsic factor and will impair the binding of the vitamin B_{12}–IF complex to the ileal receptors. Chronic pancreatitis may also cause vitamin B_{12} malabsorption by impairing the transfer of the vitamin from R binder to intrinsic factor. This abnormality can be detected by tests of vitamin B_{12} absorption (see below, Schilling test), but it is invariably mild and never causes clinical vitamin B_{12} deficiency. Finally, there is a rare congenital disorder, described by Imerslund, in which a selective defect in vitamin B_{12} absorption is accompanied by proteinuria.

FOLIC ACID DEFICIENCY Patients with folic acid deficiency are more apt to be malnourished than those with vitamin B_{12} deficiency. Accordingly. they are likely to appear wasted. The gastrointestinal manifestations are similar to, but may be more widespread and more severe than those of, pernicious anemia. Diarrhea is often present, and cheilosis and glossitis are also encountered. However, in contrast to vitamin B_{12} deficiency, neurologic abnormalities do not occur.

The hematologic manifestations of folic acid deficiency are the same as those of vitamin B_{12} deficiency. Folic acid deficiency can generally be attributed to one or more of the following factors: increased demand for folate, inadequate intake. and malabsorption.

Inadequate intake Folic acid malnutrition is commonly encountered among a number of groups. Alcoholics frequently become folate-deficient because their main source of caloric intake is in the form of alcoholic beverages. Distilled spirits are virtually devoid of folic acid, while beer and wine do not contain enough of the vitamin to satisfy the daily requirement. In addition, alcohol may interfere with folate metabolism. Narcotic addicts are also prone to become folate-deficient because of malnutrition. Many indigent and elderly individuals who subsist primarily on canned foods or "tea and toast" and occasional teenagers whose diet consists of soft drinks and potato chips develop folate deficiency.

Increased demand Tissues with a relatively high rate of cell division such as the bone marrow or gut mucosa have a large requirement for folate. Therefore, patients with chronic hemolytic anemias or other causes of very active erythropoiesis may become deficient if their high folate requirement is not met by dietary intake. Likewise, a pregnant woman may become deficient in folic acid because of the high demand of the developing fetus. Folate deficiency may also occur during the growth spurts of infancy and adolescence.

Malabsorption Folic acid deficiency is a common accompaniment of tropical sprue. Both the gastrointestinal symptoms and malabsorption are improved by the administration of either folic acid or antibiotics by mouth. Patients with nontropical sprue (gluten-sensitive enteropathy) may also develop significant folic acid deficiency which parallels other parameters of malabsorption. Similarly, alcohol-related folate deficiency may be due in part to malabsorption. In addition, other primary small-bowel disorders are sometimes associated with vitamin deficiency. These entities are all discussed in Chap. 237.

DRUGS Next to deficiency of folate or vitamin B_{12}, the most common cause of megaloblastic anemia is drug ingestion. Drugs which cause megaloblastic anemia do so by interfering with DNA synthesis, either directly or by antagonizing the action of folate. They can be classified as follows:

1 ***Direct inhibitors of DNA synthesis.*** The drugs in this category are used in the treatment of malignancy. Their efficacy depends on their ability to disrupt DNA synthesis. They include purine analogues (6-thioguanine, azathioprine, 6-mercaptopurine), pyrimidine analogues (5-fluorouracil, cytosine arabinoside), and certain other drugs which interfere with DNA synthesis by a variety of mechanisms (hydroxyurea. procarbazine).

2 ***Folate antagonists***. The most toxic of these is methotrexate, an exceedingly powerful inhibitor of dihydrofolate reductase which is used in the treatment of certain malignancies. Much less toxic, but still capable of inducing a megaloblastic anemia, are several weak dihydrofolate reductase inhibitors which are used to treat a variety of nonmalignant conditions. These include pentamidine, trimethoprine, triamterene, and pyrimethamine.

The megaloblastic changes in methotrexate poisoning appear to result from the following sequence of events. In methotrexate-poisoned cells, the methylation of dUMP to dTMP is grossly impaired. As a consequence, the phosphorylation of dUMP to dUTP, normally a very minor reaction, becomes a major route of dUMP metabolism. The capacity of a highly specific dUTP pyrophosphatase to degrade dUTP back to dUMP is exceeded under these conditions, and dUTP accumulates in the cell. This dUTP is incorporated into newly synthesized DNA, because DNA polymerase cannot distinguish between dUTP and the closely related normal substrate, dTTP. As a result, defective strands of DNA are produced in which T is partly replaced by U. The U-containing regions of these defective strands are recognized by a specific repair system. which excises them and attempts to replace them with normal DNA. In methotrexate-poisoned cells, however, there is so much dUTP and so little dTTP that the new DNA is also likely to be defective. It is this futile cycle of faulty replication. error excision. faulty repair. etc., which explains the megaloblastic pattern of DNA synthesis in methotrexate-poisoned cells. The megaloblastic changes in folate and vitamin B_{12} deficiency might have a similar biochemical origin.

3 ***Nitrous oxide.*** Nitrous oxide inhalation causes the destruction of endogenous vitamin B_{12}. As ordinarily used, this anesthetic does not destroy enough of the vitamin to cause clinical manifestations. Repeated or protracted exposure, however, may lead to a megaloblastic anemia. Fatal megaloblastic anemia has been reported in patients with tetanus who were given nitrous oxide continuously for weeks.

4 ***Others.*** A number of drugs antagonize folate by mechanisms which are poorly understood but are thought to involve an effect on absorption of the vitamin by the intestine. In this category are certain anticonvulsants [phenytoin (Dilantin), primidone (Mysoline)] and phenobarbital (Luminal). Megaloblastic anemia induced by these agents is mild.

OTHER Hereditary Megaloblastic anemia may be seen in several hereditary disorders. It is a regular feature of orotic aciduria, a defect in pyrimidine metabolism which is also characterized by retarded growth and development as well as the excretion of large amounts of orotic acid, and which is due to a deficiency of orotidylic decarboxylase and phosphorylase. Megaloblastic anemia has been reported in a single case of the Lesch-Nyhan syndrome, a condition resulting from a deficiency of hypoxanthine-guanine phosphoribosyltransferase whose clinical manifestations include gout, mental retardation, and self-mutilation. It has also been described in methylmalonic aciduria due to a defect in the biosynthesis of the *two* metabolically active alkyl cobalamins, though it is not seen in methylmalonic aciduria due to methylmalonyl CoA mutase deficiency. Congenital folate malabsorption causes megaloblastic anemia, accompanied by ataxia and mental retardation. Megaloblastic anemia has been reported to accompany the congenital deficiency of other folate-metabolizing enzymes including formiminotransferase, dihydrofolate reductase, and N^5-methyltetrahydrofolate reductase. These deficiencies are less well documented than is congenital folate malabsorption. Megaloblastic changes as well as multinuclearity of red blood cell precursors are seen in the marrow of certain patients with congenital dyserythropoietic anemia, a group of inherited disorders characterized by mild to moderate anemia presenting at any age and pursuing a benign course.

Transcobalamin II deficiency, as well as the congenital abnormalities in vitamin B_{12} absorption described previously, causes pronounced deficiencies in vitamin B_{12} in infancy or early childhood, with all the accompanying manifestations. Megaloblastic anemia is not seen in hereditary transcobalamin I deficiency.

Acquired idiopathic anemia Some patients with acquired sideroblastic anemia and other forms of refractory anemia show megaloblastic erythropoiesis. Megaloblastic changes are restricted to the red blood cell series; large granulocyte precursors and giant metamyelocytes are not seen (*see* below). Both are associated with an increased incidence of acute leukemia.

Megaloblastic changes are seen in erythremic myelosis and acute erythroleukemia (di Guglielmo) where red blood cell precursors are prominently involved. Here, the marrow is characterized by bizarre erythroid maturation, with multinuclearity and multipolar mitotic figures in the red blood cell precursors. Erythremic myelosis is discussed further in Chap. 292.

DIAGNOSIS The finding of significant macrocytosis [mean corpuscular volume (MCV) > 96 fl] suggests the presence of a megaloblastic anemia. Other causes of macrocytosis include hemolysis, liver disease, alcoholism, hypothyroidism, and aplastic anemia. If the macrocytosis is marked (MCV > 110 fl), the patient is much more likely to have a megaloblastic anemia. The reticulocyte count is low, and the leukocyte and platelet count may also be decreased, particularly in severely anemic patients. The blood smear (Fig. A5-2) demonstrates marked anisocytosis and poikilocytosis, together with macroovalocytes which are large. oval. fully hemoglobinized erythrocytes typical

stein syndrome to only occasional patients with the infertile male syndrome. The patients with a negative family history are believed to be the result of new mutations.

Hormone dynamics are similar in all disorders of the androgen receptor. Plasma testosterone levels and rates of testosterone production by the testes are normal or higher than normal. The elevated rate of testosterone production is caused by the high mean plasma level of LH, which in turn is due to defective feedback regulation caused by resistance to the action of androgen at the hypothalamic-pituitary level. Elevated LH concentration is probably responsible also for the increased estrogen production by the testes (see Chap. 330). (In normal men most estrogen is derived from peripheral formation from circulating androgens, but when plasma LH is elevated the testes secrete significant amounts of estrogen into the circulation.) Thus, resistance to the feedback regulation of LH secretion by circulating androgen results in elevated plasma LH levels, and this in turn results in the enhanced secretion of both testosterone and estradiol by the testes. Gonadotropin levels rise even higher (and menopausal symptoms may develop) when the testes are removed. indicating that gonadotropin secretion is under partial regulatory control. Presumably, in the steady state and in the absence of an androgen effect, estrogen alone regulates LH secretion. a control that is purchased at the expense of an elevated plasma estrogen concentration for a male. The hormonal changes in the infertile male syndrome are similar to those in the other receptor disorders but less marked. Some men with this syndrome do not have an elevation of plasma LH or plasma testosterone.

Feminization in these disorders is the result of two interlocking phenomena. First, androgens and estrogens have antagonistic effects at the peripheral level, and virilization occurs in normal men when the ratio of androgen to estrogen is 100 to 1 or greater; in the absence of androgen action the cellular effect of estrogen is unopposed. Second, the production of estradiol is greater than that of the normal male (although less than that of the normal female). Variable degrees of androgen resistance coupled with variably enhanced estradiol production result in different degrees of defective virilization and enhanced feminization in the four clinical syndromes.

Each of these four syndromes is the result of an abnormality of the androgen receptor. Initially fibroblasts cultured from the skin of some subjects with complete testicular feminization were shown to have a near absence of high-affinity dihydrotestosterone binding. Subsequently, other individuals with complete testicular feminization as well as subjects with incomplete testicular feminization, Reifenstein syndrome, and the infertile male syndrome have been found to have either a decreased amount of an apparently normal receptor or a qualitatively abnormal androgen receptor.

Receptor-positive resistance. A category of androgen resistance that does not appear to involve either the Sa-reductase or the androgen receptor was first identified in a family with the syndrome of testicular feminization. Subsequent patients have been described with a variety of phenotypes ranging from incomplete testicular feminization to findings similar to those in the Reifenstein syndrome. The hormonal profile is similar to that seen in the receptor disorders. The site of the molecular abnormality in these patients is unclear. It could be due to defects of the androgen receptor too subtle to be detected by the usual assay. If the defect is truly distal to the receptor. there could be failure of generation of specific messenger RNA or an abnormality of RNA processing. Indeed. the disorder may represent a heterogeneous group of molecular abnormalities. Management depends on the phenotype.

Persistent müllerian duct syndrome Men with this disorder have normal penile development but have in addition bilateral fallopian tubes, a uterus, and an upper vagina, and variable development of the vas deferens. The subjects commonly present with inguinal hernias which contain the uterus, and cryptorchidism is common. Most have uninformative family histones, but several pairs of siblings have been described in whom the condition must be inherited either as an autosomal recessive or an X-linked recessive mutation. Because the external genitalia are well developed and the patients masculinize normally at puberty, it is assumed that during the critical stage of embryonic sexual differentiation the fetal testes produced a normal amount of androgen. However. müllerian regression does not occur for one of three possible reasons: failure of the fetal testis to produce miillenan-inhibiting substance. poor timing of the release of müllerian-inhibiting substance, or failure of the tissues to respond to this hormone. To minimize the chance of tumor development and to maintain virilization, a primacy or staged orchiopexy should be performed. Malignancy in the uterus or vagina has not been described, and because the vasa deferentia are closely associated with the broad ligaments, the uterus and vagina should be left in place to avoid disruption of the vasa deferentia during removal and consequently to preserve possible fertility.

Developmental defects of the male genitalia **HYPOSPADIAS** Hypospadias is a congenital anomaly in which the urethra terminates in an abnormal position along the midline of the ventral surface of the penis at some site between the normal urethral meatus and the perineum. This malformation is often associated with some degree of ventral contraction and bowing of the penis (chordee). The disorder occurs in 0.5 to 0.8 percent of male births in the United States. It is common to categorize hypospadias as glandular (involving the glans penis), penile. or perineoscrotal. Since penile development is mediated by androgens, it is assumed that hypospadias results from some defect in earlier androgen formation or androgen action during embryogenesis. Indeed hypospadias occurs in most disorders of male sexual differentiation. A rare cause of hypospadias is maternal ingestion of progestational agents early in pregnancy. However, the known causes (single gene defects, chromosomal abnormalities, and maternal drug ingestion) at best can account for only about one-fourth of cases, and the etiology of most remains unknown. The management is surgical.

CRYPTORCHIDISM The normal descent of the testis is perhaps the most poorly understood portion of male sexual differentiation, both in regard to the nature of the forces that result in the movement and to the hormonal factors that regulate the process. In anatomic terms testicular descent can be divided into three phases: (1) transabdominal movement of the testis from its site of origin above the kidney to the inguinal ring, (2) formation of the opening in the inguinal canal (processus vaginalis) through which the testis exits the abdominal cavity, and (3) actual movement of the testis through the inguinal canal to its permanent site in the scrotum. This entire process occurs over a 6- to 7-month period during gestation. beginning at about the sixth week and not completed in some normal individuals until after birth. Whatever its involvement, androgen is probably not the sole hormone responsible for normal descent. Failure of any of the above anatomic events can be responsible for the failure of descent of one or both testes that occurs in 3 percent of full-term males and 30 percent of premature male infants. Cryptorchidism can be classified as intraabdominai, retractile (intermittently in the groin), obstructed (permanently in the groin), and high scrotal. Most are retractile and descend permanently by 6 weeks to 3 months of age so that the incidence of failure of descent in late teenagers is only 0.6 to 0.7 percent. It is this latter category that requires intervention.

The cryptorchid testis functions poorly after puberty, but the extent to which maldescent is the result of an abnormality of the testis or the cause of abnormal function is unknown. Two general theories have been advanced as to the etiology — inadequate intraabdominal pressure and deficient endocrine function of the testis either because of deficient testosterone synthesis or inadequate formation of miillenan-inhibiting substance. Indeed, hereditary defects that result in inadequate development of intraabdominal pressure or inadequate development of the testes themselves can cause cryptorchidism. As is true for hypospadias, however, the known causes of cryptorchidism constitute only a small fraction of the cases, and the etiology in most remains to be identified. Two complications of cryptorchidism are important: spermatogenesis cannot occur at the temperature of the abdominal cavity, and it is therefore necessary to

correct the process as early as possible to allow possible fertility. However. the fact that infertility is common in men who have been treated for unilateral as well as bilateral cryptorchidism suggests that maldescent is usually the consequence rather than the cause of the testicular malfunction. There is also a greater frequency of malignancy in undescended testis, and all should be surgically corrected for this reason (see Chap. 297).

REFERENCES

DE LA CHAPELLE A: The etiology of maleness in XX men. Hum Genet 58:105, 1981

DONAHOE PK et al: Mixed gonadal dysgenesis. pathogenesis and management. J Pediatr Surg 14:287, 1979

EDMAN CD et al: Embryonic testicular regression: A clinical spectrum of XY agonadal individuals. Obstet Gynecol 49:208, 1977

GEORGE FW, WILSON JD: Sexual differentiation, in *Campbell's Textbook of Urology*. 5th ed, PC Walsh et al (eds). Philadelphia. Saunders, 1986. pp 1804–1818

GORDON DL et al: Pathologic testicular findings in Klinefelter's syndrome. 47,XXY vs 46,XY/47,XXY. Arch Intern Med 130:726, 1972

GRIFFIN JE et al: Congenital absence of the vagina. The Mayer-Rokitansky-Kuster-Hauser syndrome. Ann Intern Med 85:224, 1976

——, WILSON JD: Disorder of sexual differentiation, in *Campbell's Textbook of Urology*. 5th ed, PC Walsh et al (eds). Philadelphia, Saunders, 1986. pp 1819–1855

GRUMBACH MM, CONTE FA: Disorders of sexual differentiation. in *Williams' Textbook of Endocrinology*, 7th ed, JD Wilson, DW Foster (eds). Philadelphia, Saunders, 1985, pp 312–401

LEONARD JM et al: The classification of Klinefelter's syndrome, in Generic *Mechanism of Sexual Development*. HL Vallet, IH Porter (eds). New York. Academic, 1979

MCDONOUGH PG et al: Phenotypic and cytogenetic findings in eighty-two patients with ovarian failure-changing trends. Fertil Steril 28:638, 1977

NEW M et al: Congenital adrenal hyperplasia and related conditions. in *Metabolic Basis of Inherited Disease*. 5th ed, JB Stanbury et al (eds). New York, McGraw-Hill, 1983. pp 973–1000

SIMPSON JL: *Disorders of Sexual Differentiation*. New York, Academic, 1976, p 466

—— Gonadal dysgenesis and sex chromosome abnormalities: Phenotypic-karyotypic correlations, in *Generic Mechanisms of Sexual Development*, HL Vallet. IH Porter (eds). New York, Academic, 1979

—— et al: XY gonadal dysgenesis: Genetic heterogeneity based upon clinical observations, H-Y antigen status and segregation analysis. Hum Genet 58:91, 1981

VAN NIEKERK WA: True hermaphroditism. Pediatr Adolesc Endocrinol 8:80, 1981

WIWN JD et al: The androgen resistance syndromes: 5α-Reductase deficiency. testicular feminization and related disorders, in *The Metabolic Basis of Inherited* Disease. 5th *ed*. JB Stanbury et al (eds). New York, McGraw-Hill, 1983, pp 1001–1026

ZAH W et al: Mixed gonadal dysgenesis. A case report and review of the world literature. Acta Endocrinol Suppl 197:3, 1975

334 DISORDERS AFFECTING MULTIPLE ENDOCRINE SYSTEMS

R. NEIL SCHIMKE

Multiple endocrine gland hyper- or hypofunction can result from mechanisms other than a primary abnormality in the hypothalamic-pituitary axis. While not common, certain of the conditions that affect multiple endocrine systems are inherited and thus have significance out of proportion to their frequency.

SYNDROMES WITH MULTISYSTEM HYPERFUNCTION

MULTIPLE ENDOCRINE NEOPLASIA, TYPE I (MEN I) This disorder, also termed the *Wermer syndrome,* comprises tumors or hyperplasia of the parathyroids, pancreatic islet cells, pituitary, adrenal cortex, and thyroid. The clinical presentation is variable, depending on which of the potentially affected glands is hyperfunctioning at the time of diagnosis, About two-thirds of patients have adenomas of two or more endocrine systems, and one-fifth develop tumors of three or more systems.

The majority of affected subjects present with one of the following problems: (1) peptic ulcer and its complications. (2) hypoglycemia, (3) hypercalcemia and/or nephrocalcinosis, (4) complaints referable to pituitary dysfunction such as headaches, visual field defects, and secondary amenorrhea. and (5) multiple lipomas of the skin. A minority (probably <10 percent) come to medical attention with acromegaly, Cushing's syndrome. nonfunctional thyroid adenomas. hyperthyroidism. hepatomegaly (due *to* metastatic liver disease). or Rushing (associated with the carcinoid syndrome).

Parathyroid involvement in MEN I may be asymptomatic for prolonged periods. although most patients eventually show some signs of hyperparathyroidism. Tumors of the islet cells may elaborate excessive insulin or gasmn. Insulinomas cause hypoglycemia (Chap. 329), whereas excess gastrin secretion causes the Zollinger-Ellison syndrome with its multifocal or atypically located ulcers and massive hypersecretion of gastric acid. Symptoms may be identical with those of ordinary peptic ulcer. but there is a higher incidence of complications, including perforation, bleeding, and obstruction. Diarrhea is frequent, often with steatorrhea. Radiographic findings include giant gastric rugae, duodenal nodularity, ectopic ulcers in the esophagus, lower duodenum, and jejunum. and intestinal hyperperistalsis. Associated endocrine abnormalities consistent with the MEN syndrome are present in over one-quarter of patients with the Zollinger-Ellison syndrome and in half of the first-degree relatives of such patients. MEN I should be considered in a patient with the Zollinger-Ellison syndrome even when *no* other endocrine abnormalities are apparent.

Islet-cell tumors may also produce glucagon. vasoactive intestinal polypeptide (VIP), prostaglandins, adrenocorticotropic hormone (ACTH), parathyroid hormone. antidiuretic hormone (ADH), serotonin, somatostatin, calcitonin. and pancreatic polypeptide (also see Chap. 329). Glucagonomas cause hyperglycemia. weight loss, stomatitis, and a peculiar skin rash called *necrotizing migratory erythema.* VIP and prostaglandins have been implicated in the watery diarrhea (pancreatic cholera) syndrome sometimes seen in MEN I. Cushing's syndrome may be due to an adrenal adenoma or may occur as a consequence of ectopic ACTH production by an islet tumor or a thymic carcinoid. Some adrenal adenomas produce aldosterone or adrenal androgens. Involvement of the thyroid gland is uncommon in MEN I, but goiter. simple adenoma, and thyroiditis have all been reported. Other features of MEN I include small-intestinal and bronchial carcinoid tumors, schwannomas. thymomas, multiple lipomas, inclusion cysts, and cutaneous leiomyomas.

Patients with MEN I may develop symptoms at any age. but the condition presents rarely in childhood or after the age of 60. Affected individuals may demonstrate multiple endocrine system involvement simultaneously, or months to years may elapse between the discovery of one adenoma and the appearance of the next. Once the diagnosis is established, the patient must be surveyed periodically for appearance of new facets of the syndrome. By the same token, all first-degree relatives should be studied. A reasonable approach for screening relatives at risk is as follows: (1) review history for symptoms of peptic ulcer disease. hypoglycemia, renal calculi, lipomas, or hypopituitarism; (2) examine for multiple lipomas: (3) assay serum calcium, phosphorus, prolactin. and gastrin. Upper gastrointestinal series and sella turcica x-rays have proved of no value as screening tests. Serum pancreatic polypeptide determinations may be useful in centers where the assay is available.

The fundamental lesion in MEN I is unknown. Some have considered the basic abnormality to be in the islet cells with their extensive capability for hormone synthesis, attributing changes in the other glands to secondary effects of islet hormone hypersecretion. Others have classified MEN I as a neurocrestopathy implicating faulty differentiation or regulation of the embryonic neural crest, which is the anlage of at least part of the endocrine system. The endocrine components of the neural crest have been classified into a subsystem of APUD cells, so named because of their capacity for amine precursor uptake and decarboxylation. The evidence supporting the contention that all APUD cells are derived from neural crest is not strong; instead. cells of diverse origin probably develop similar characteristics; i.e., they represent a structural-functional convergence.

The pituitary and parathyroid tumors in MEN I are usually benign, but pancreatic tumors are frequently malignant. Surgical removal of the affected gland is the usual therapy, although standard radiation techniques may be employed for the pituitary tumors, and homergocryptine is useful in prolactinomes. Hyperparathyroidism may be due to a single adenoma, but diffuse hyperplasia of more than one gland is more common. In some centers selective venous catheterization with measurement of serum parathyroid hormone levels can be used to differentiate between those possibilities. Since new adenomas may arise in normal glands left after removal of an adenoma (and since second operations are difficult because of scar formation), some have advocated removal of all the parathyroid glands with transplantation of extirpated fragments into the thigh or forearm, where they can be easily removed should hyperparathyroidism recur. Successful transplantation obviates the need for long-term therapy of hypoparathyroidism. In hypergasmnemia due to islet-cell lesions, total gastrectomy has been used to prevent recurrent peptic ulcers, and in rare cases distant metastases have regressed after this procedure. Histamine-2-receptor antagonists are efficacious in controlling the hyperacidity and diarrhea seen with hypergastrinemia.

MULTIPLE ENDOCRINE NEOPLASIA, TYPE II (MEN II OR IIA) MEN II, also known as the *Sipple* syndrome, consists of pheochromocytoma (frequently bilateral and occasionally extraadrenal). medullary thyroid carcinoma (MTC), and, in about half of the reported cases, parathyroid hyperplasia. MEN II can be related more directly to abnormal neural crest development than can MEN I, since both the adrenal medulla and the parafollicular or C cells of the thyroid originate in neural crest. However, there is no evidence that the parenchymal component of the parathyroid glands are so derived. The parafollicular cell elaborates calcitonin, the primary marker of medullary carcinoma of the thyroid. MTC is not common, comprising less than 10 percent of thyroid malignancies. At least 10 percent of MTC cases are familial, usually appearing as a component of MEN II or MEN III (see below). Medullary carcinoma may also occur in families without other associated endocrine dysfunction; this form is also transmitted as an autosomal dominant trait. MTC may present as a thyroidal mass or be clinically silent and undetectable by palpation or radioiodine scanning. The diagnosis is usually established by immunoassay of serum calcitonin, provided ectopic sites of calcitonin production can be excluded, e.g., breast, lung, and pancreatic islet-cell tumors. Occasionally, basal serum calcitonin levels are borderline in at-risk individuals, and measurement of plasma levels after calcium-pentagastrin infusion can be used to establish the diagnosis. MTC may on occasion secrete substances other than calcitonin, including ACTH, prolactin, serotonin, VIP, histamine, and various prostaglandins, resulting in a confusing array of symptoms.

The pheochromocytoma of MEN II may produce the classic signs of catecholamine excess as described in Chap. 326 or be asymptomatic. Approximately 7 percent of patients who present with pheochromocytomas also have MTC. Symptoms of hyperparathyroidism rarely bring the patient with MEN II to initial clinical attention.

Examination of cells from both the MTC and the pheochromocytoma components of MEN II using X-linked gene markers has led to the conclusion that the inherited defect produces multiple clones of abnormal cells; tumors then develop from a second mutation in the abnormal clone, accounting for the appearance of varying clinical patterns. Other tumors in MEN II include gliomas, glioblastomas, and meningiomas, all of which may be derived from the neural crest.

The age of the patient at the time of diagnosis varies from 2 to 67 years. C-Cell hyperplasia of the thyroid may precede development of malignancy by many years, making early screening studies for calcitonin elevation mandatory in all family members at risk. The only effective therapy for MTC is surgical removal of the entire thyroid, as the tumor is probably always multifocal in origin. Limited node dissection is often indicated since the cancer may progress slowly despite an aggressive histologic appearance, and prolonged survival is seen in patients with known metastatic disease. Serum calcitonin levels can be used to assess completeness of surgical removal of the tumor and in concert with selective venous catheterization may be utilized to locate distant metastases that are surgically accessible. Neither standard radioiodine nor x-ray therapy is helpful in disseminated medullary thyroid cancer, and chemotherapy has been of limited value (see Chap. 324). The pheochromocytomas are usually benign and are also treated surgically. Unresectable malignant pheochromocytoma requires long-term sympathetic blockade. A new radiopharmaceutical, *meta*-iodobenzyl guanidine, shows promise as both a diagnostic and a therapeutic agent.

MULTIPLE ENDOCRINE NEOPLASIA, TYPE III (MEN III OR IIB) MEN III also consists of medullary thyroid carcinoma and pheochromocytoma, but affected individuals have striking dysmorphic features such as neuromas of the conjunctival, labial, and buccal mucosa, the tongue, the larynx, and the gastrointestinal tract; hence the alternate designation of the condition as the *mucosal neuroma* syndrome. Other physical findings include enlarged corneal nerves, "blubbery" lips, soft-tissue prognathism, and a habitus resembling that seen in the Marfan syndrome with hypotonia, lax joints, kyphoscoliosis, genu valgus, and pes cavus. The patients may have cafk au lait spots or a diffuse lentiginous type of skin pigmentation along with cutaneous neuromas or neurofibromas. Megacolon may occur.

MEN III and MEN II appear to be distinct syndromes. For example, both parathyroid hyperplasia and production of hormones other than calcitonin by MTC are rare in MEN JII. The mean survival of patients with MEN III is around 30 years compared with 60 years for those with MEN II, suggesting a more malignant course in the former disorder, although histologically the thyroid tumors appear to be identical. As with MEN II treatment of the medullary carcinoma is surgical. The unusual physical features of MEN III should immediately suggest the diagnosis of underlying thyroid malignancy. MTC has been documented in asymptomatic children with MEN III, and C-cell hyperplasia has been found at operation as early as 15 months of age. Clinically, the associated pheochromocytomas behave as expected (Chap. 326).

McCUNE-ALBRIGHT SYNDROME This condition is characterized by the triad of polyostotic fibrous dysplasia, cafk au lait spots. and isosexual precocity, the latter occurring predominantly but not exclusively in females. The isosexual precocity may be hypothalamic in origin, but gonadotropin-independent ovarian function has been implicated in some cases (see Chap. 331). Cushing's syndrome, gigantism or acromegaly, and hyperprolactinemia may also occur in affected patients. The Cushing's syndrome may result from abnormal ACTH production or adrenal adenomas. Nodular toxic goiter and pheochromocytoma have also been reported. The bone lesion resembles that seen in hyperparathyroidism, and parathyroid hyperplasia has been described histologically but not clinically. The condition is usually sporadic, but pedigrees compatible with autosomal dominant inheritance have been seen. The cause of the condition is unknown (see Chap. 339).

SYNDROMES WITH MULTISYSTEM HYPOFUNCTION

POLYGLANDULAR DEFICIENCY SYNDROME (SCHMIDT SYNDROME) (See also Chaps. 324 and 325) The prototype of a polyglandular deficiency state is the Schmidt syndrome, originally described as the presence of both Addison's disease and lymphocytic thyroiditis in a single patient. This syndrome has subsequently been expanded to include any combination of adrenal insufficiency, lymphocytic thyroiditis, hypoparathyroidism, and gonadal failure. Diabetes mellitus is a frequent accompaniment. The manifestations may be so extensive as to simulate panhypopituitarism; rarely, true pituitary deficiency has been described. The first evidence of endocrinopathy generally appears in adult life. The most significant laboratory feature, in addition to the low levels of circulating hormones, is the presence of antibodies to one or more endocrine glands. The antibodies may be directed against a clinically normal gland, but with time hypofunction usually supervenes. Additional evidence for an immune