Endocrine Factors In Peptic Ulcer

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The concept that the endocrine glands influence the pathogenesis of peptic ulcer is recent in origin. Only 10 years have passed since the delineation of the Zollinger-Ellison syndrome, which undoubtedly served as a major stimulus to the study of endocrine influence in peptic ulcer. The incidence of peptic ulcer in the general population is not known for certain and, therefore, it is difficult to say whether the incidence of peptic ulcer is increased or decreased in various endocrine disorders. For purposes of discussion, a 5 to 10% incidence of peptic ulcer in the general population is assumed, a figure derived from postmortem studies of this problem.

Physicians should not make peptic ulcer a final diagnosis, but should instead try to ascertain initiating and aggravating factors. Table I lists areas of study that have received attention as possible factors in the pathogenesis of peptic ulcer.

Table I

Areas of Study in Pathogenesis of Peptic Ulcer

1) Acid-peptic influence
2) Mucosal-protective barrier (tissue resistance)
3) Genetic factors
4) Effects of drugs
5) Effect of chronic lung disease
6) Relation to cirrhosis of the liver and chronic pancreatitis
7) Endocrine influence

In the past, factors stimulating gastric acidity have been investigated to the neglect of those inhibiting acid formation. This is understandable since it has been more difficult to arrange experiments for study of the latter. Another problem has been the inability to completely isolate excitatory stimuli of gastric secretion from inhibitory stimuli. In addition, the experimental models and animal species used for study have not always been easy to relate to human peptic ulcer disease.

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**Fifth Medical Division.
The investigation of factors that protect the gastric mucosa from acid peptic digestion has heretofore received little attention. This again is understandable since it has been easier to study the chemistry and physiology of gastric acidity than of gastric mucus. More recently attempts have been made to evaluate the role of gastric mucus and tissue resistance in the causation of peptic ulcer. While it is true that the acid-peptic factor is of prime importance in the development of peptic ulcer, factors that normally protect the gastric mucosa from peptic ulceration as well as the intrinsic tissue resistance in the gastric mucosa may be equally important.

Peptic ulcer occurs frequently in siblings, but this in itself does not prove a genetic factor since family environment has an effect. However, the high incidence of blood group O among peptic ulcer patients supports the role of a genetic influence. Each person appears to be individually and genetically endowed with a prescribed number of gastric parietal cells. This number is increased in the presence of an ulcer diathesis and is the final common pathway under the influence of various stimuli that increase and inhibit gastric secretion. In the Zollinger-Ellison syndrome and multiple endocrine adenoma-peptic ulcer complex, the parietal cell mass is increased, but it is not clear whether this is genetically determined or results from prolonged stimulation by gastrin arising in the ulcerogenic tumors of the pancreas.

A number of drugs have been incriminated as causing an increased incidence of peptic ulcer. Among the more important are corticosteroids, aspirin, butazolidine, and reserpine. While several of these have been reported to stimulate gastric secretion, there are observations suggesting that a reduction in the protective gastric mucus also occurs after drug administration and may be equally important.

The incidence of peptic ulcer in several disease states is higher than that observed in the general population. For instance, peptic ulcer occurs frequently (20% in some series) in patients with chronic obstructive lung disease. Gastric acidity is not increased in these patients so other considerations such as decreased tissue resistance and the chronic use of drugs such as salicylates and corticosteroids may be important. It has been suggested that the increased incidence of peptic ulcer observed in chronic obstructive lung disease occurs only in those patients who have increased sweat chloride levels, but there is uncertainty about the specificity of the sweat chloride test.

An increased incidence of peptic ulcer occurs in patients with cirrhosis of the liver, and this incidence may be even greater following portacaval shunting. It has been suggested that histamine formed in the intestinal mucosa is shunted past the liver in such instances and, therefore, is not inactivated by histaminase in the hepatic cells. Peptic ulcer has been reported to occur more frequently in patients with chronic pancreatitis, although a recent study in a relatively small series does not support this contention. In this same study, the level of gastric secretion in 19 male patients with pancreatitis was found to be decreased from normal; this is contrary to previous observations in animals with experimentally induced pancreatic inflammatory disease.
PEPTIC ULCER

In Table II several endocrine conditions whose relationship to peptic ulcer disease has been studied are listed in an order of increasing importance.

Table II

Possible Endocrine Factors in Peptic Ulcer

1) Pituitary
2) Gonads
3) Beta cell tumors of the pancreas (insulin)
4) Adrenals
5) Parathyroids
6) Carcinoid tumors
7) Non-beta cell tumors of the pancreas (gastrin)
8) Multiple endocrine adenomatosis (MEA)

Pituitary insufficiency in animals and man results in decreased gastric secretion and acidity, which can partially be restored to normal after the administration of thyroid, cortisone and growth hormone. Hyperfunctioning pituitary tumors are not associated with an increased incidence of peptic ulcer, except when such tumors are associated with other endocrine tumors, especially alpha cell tumors of the pancreas. However, in the latter instance, the occurrence of peptic ulcer is very high even when pituitary tumors are not a part of the multi-endocrine syndrome, which suggests that pituitary influence is not critical in ulcer diathesis.

Further study should perhaps be given to the relationship of the gonadal activity to peptic ulcer since there is a decreased incidence in females during the reproductive age. However, before puberty and after the menopause the incidence of peptic ulcer in the two sexes is about equal. Pregnancy appears to protect against the occurrence of peptic ulcer, at least in the first two trimesters, and estrogens have actually been used in the treatment of peptic ulcer disease.

Hypoglycemia is a potent stimulus of gastric secretion through activating centers in the hypothalamus and brain stem, with subsequent stimulation of the vagal nerves. However, despite this the incidence of peptic ulcer is not increased in patients with beta cell tumors of the pancreas unless accompanied by non-beta cell hyperplasia or adenoma formation.

There has been considerable study attempting to relate adrenocortical function to peptic ulcer. At necropsy, the incidence of adrenal hyperplasia and adenomas is increased threelfold in patients with peptic ulcer when compared to those without peptic ulcer. Physicians in the past have tended to minimize the importance of small adrenal adenomas found at necropsy in a variety of medical conditions. This will have to be reevaluated in view of the recent evidence that small adrenocortical adenomas are the cause of primary aldosteronism. Studies of plasma and urinary levels of cortisone have failed to support the view that adrenal hyperfunction exists
in patients with peptic ulcer disease, except at the time of acute ulcer exacerbation. There is reduced gastric acidity in patients with Addison's disease and, for some reason, replacement therapy with only small (physiologic) doses of cortisone is associated with an increased incidence of peptic ulcer.

It was commonly accepted in the past that peptic ulcer is a major complication of corticosteroid therapy. Acceptance of this is less widespread at present. It is true that administration of large doses of corticosteroids results in increased gastric acidity, but not to levels found in the Zollinger-Ellison syndrome. The type and dose of corticosteroid administration has relevance to the peptic ulcer tendency as does the duration of therapy. It is hard to find controlled series when all these factors are taken into consideration.

The incidence of peptic ulcer occurring in the natural course of various diseases has not always been considered when studying the potential untoward effects of corticosteroid therapy. Rheumatoid arthritis is a disease where the incidence of peptic ulcer with or without the administration of corticosteroids appears to be the same. Recent experiments have demonstrated a reduction in protective gastric mucus following the administration of corticosteroids which could result in a greater exposure of the gastric and duodenal mucosa to aggressive acid-peptic influences. However, if administration of corticosteroids does increase the incidence of peptic ulcer, the fact that peptic ulcer is not increased in Cushing's disease has never been satisfactorily answered.

During the past decade there has been considerable debate as to whether peptic ulcer disease is increased in hyperparathyroidism. When peptic ulcer patients are screened for underlying hyperparathyroidism, it is found in less than 1%. In one study 4 patients with hyperparathyroidism were found when 300 consecutive peptic ulcer patients were screened, but 1 of these patients was subsequently demonstrated to have multiple endocrine adenomatosis and an ulcerogenic tumor of the pancreas. When peptic ulcer occurs in patients with hyperparathyroidism, the possibility of underlying multiple endocrine adenomatosis should always be considered. This is especially true if the patient has primary chief cell hyperplasia rather than a single parathyroid adenoma. Other endocrine adenomas and hyperplasia may be difficult to exclude, even at operation and postmortem examination.

The incidence of peptic ulcer in several series of patients with hyperparathyroidism has varied from 10 to 25%. Such patients may have peptic ulcer symptoms and dyspepsia without actual X-ray evidence of peptic ulcer. It is not uncommon for such symptoms to subside after removal of a parathyroid adenoma. A study frequently quoted is that of Ostrow in which a 10% incidence of peptic ulcer was demonstrated in a large series of patients with hyperparathyroidism — an incidence stated to be only slightly above that found in the general population. It should be emphasized that many of the patients in this composite series were studied before 1950 when less emphasis was placed on the gastrointestinal manifestations of hyperparathyroidism.
In a postmortem study of 812 patients with peptic ulcer, five examples of parathyroid pathology were encountered: four of parathyroid hyperplasia and one of parathyroid carcinoma. This finding does not reflect the true incidence of parathyroid pathology in peptic ulcer, for the parathyroid glands are frequently overlooked in routine necropsy. Few adequate evaluations have been made of parathyroid pathology occurring normally or in any disease state. In the future, more careful attention should be given to this in the postmortem examination.

A reduction in gastric secretion and acidity occurs in hypoparathyroidism and can be corrected by intravenous calcium or by parathyroid extract. In acute experiments, intravenous calcium given to normal subjects will increase gastric secretion, but not to the levels seen in ulcerogenic tumors of the pancreas. While reports vary, no evidence proves that gastric secretion is altered during chronic hyperparathyroidism; removal of a parathyroid adenoma does not result in any significant reduction of gastric secretion. Menge reports that parathyroid extract given to rats will increase the production of gastric mucus which theoretically might protect against the formation of peptic ulcer. Additional observations in the same laboratory demonstrated that parathyroid extract offered protection against corticosteroid-induced ulcers. Therefore, if the incidence of peptic ulcer is increased in hyperparathyroidism, the absence of gastric hypersecretion and the presence of increased gastric mucus suggest other operative mechanisms. As mentioned previously, at least some of these patients have underlying polyendocrine involvement and ulcerogenic tumors of the pancreas.

In a report of patients with intestinal carcinoids, 8 of 21 had peptic ulcer. This is somewhat surprising in view of the fact that the administration of serotonin reduces gastric secretion. It is possible, however, that intestinal carcinoids may be the source of gastrin which might have an ulcerogenic influence. The difficulty in differentiating alpha cell tumors of the pancreas from carcinoid tumors of the intestinal tract is well known. Analysis of intestinal carcinoids for gastrin-like substances would be of interest to help clarify this reported high incidence of peptic ulcer.

The Zollinger-Ellison syndrome is now well established and here there is a reasonable explanation for the high incidence of multiple and intractable peptic ulcers. In both the Zollinger-Ellison and multiple endocrine adenomatosis syndromes, a gastrin-like substance has been isolated from the pancreatic tumors which causes gastric hypersecretion when injected into animals. Patients with the Zollinger-Ellison syndrome have a high incidence of other endocrine adenomas and hyperplasia which may become apparent only after many years of observation.

In conclusion, proof is lacking that increased function of the pituitary, adrenals, parathyroids or the beta cells of the pancreas enhances the incidence of peptic ulcer found in the general population. It is possible that normal function of these glands is necessary in a permissive role for the influence of other ulcerogenic factors. On
the other hand, the high concentration of gastrin in certain non-beta cell tumors of the pancreas offers an excellent explanation for the increased incidence of peptic ulcer disease in the Zollinger-Ellison syndrome and the multiple endocrine adenoma-peptic ulcer complex.

REFERENCES


