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## PEPTIC ULCERATION AND HORMONAL STATES

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THE TERM "peptic ulcer" does not bear an etiologic connotation, but merely localizes the ulceration to those parts of the gastrointestinal tract which are or may be exposed to gastric secretions.<sup>1</sup> The fundamental fault which leads to the development of these lesions is unknown. However, it has been postulated that an imbalance in those factors that protect the gastric mucosa from self-digestion and those that increase this possibility is at fault.<sup>1,2</sup> Although peptic ulcers seldom form in the absence of peptic activity, i.e. the secretion of hydrochloric acid and pepsin, the presence of an increased amount of such substances only predisposes the patient to ulceration, and does not cause ulceration.<sup>2</sup>

Defensive factors include a postulated intrinsic mucosal resistance to peptic digestion; mucin, which buffers pH and forms a protective adhesive shield over the mucosa; local mucosal blood flow, whose permanent or temporary interruption can lead to acute ulceration; and intrinsic mechanisms which reduce gastric secretion and motility, that is antral mechanisms which are activated by local acid pH, and the duodenal mechanism, which is activated by local acid conditions, fat, or hypertonic secretions,<sup>2</sup> and is mediated by enterogastrone.

Aggressive factors include vagal hyperactivity, the influence of gastrin, of parietal cell mass, cephalic stimulation of peptic secretion through the hypothalamic-pituitary-adrenal system, and local mucosal trauma.<sup>2</sup> It has been noted that gastric ulcers are usually associated with a low volume of gastric secretion suggesting reduction of defensive factors, whereas duodenal ulceration is found with gastric hypersecretion.<sup>1,2</sup> Peptic ulcers are estimated to occur at some time in 5 to 10 per cent of persons in this country,<sup>3,4</sup> with an annual incidence of 0.15 to 0.38 per cent.<sup>5</sup>

### *Multiple Endocrine Adenoma Syndrome*

Several endocrine abnormalities have been associated with a change in the incidence of peptic ulcer.<sup>4</sup> Many of these endocrine changes have been found to be frequently occurring in the same patient although not necessarily at the same time.<sup>6</sup> These changes have been grouped together in the syndrome of multiple endocrine adenomata, and about 35 per cent of patients having this syndrome have peptic ulcerations.<sup>1</sup>

Among the organs involved in this syndrome are the pancreas (non-beta cell adenomas, diffuse islet of Langerhans hyperplasia, and insulinomas), the adrenal

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cortex, the thyroid infrequently,<sup>1,10</sup> pituitary, parathyroid,<sup>1,2,4,5,7-10</sup> and very occasionally also may include functioning carcinoids of the small bowel.<sup>11</sup>

One explanation of the occurrence of multiple endocrinopathies in one patient is that this is an inherited syndrome, as many such cases were found to have a familial occurrence, environmental factors were felt to be unlikely, and the frequency of this association of rare lesions made such a chance occurrence improbable. The syndrome may be carried by an autosomal dominant gene, and the peptic ulceration may be primary to the syndrome and not secondary to malfunction of any of the individual glands.<sup>6,12,13</sup> It is interesting to note that these endocrine glands and the upper gastrointestinal tract all develop at the fourth through fifth embryological week of life.<sup>6</sup>

### *Hypothalasmus*

Investigations have shown two distinct means by which the hypothalamus can increase gastric secretion. It is to be noted that an increase in peptic activity does not necessarily mean that an ulcer will develop, but this does shift the balance of forces such that ulceration is more likely to occur. The first hypothalamic mechanism is purely neural in nature; it originates in the anterior hypothalamus, is mediated by the vagus nerve, and causes gastric hypersecretion 30 to 60 minutes after anterior hypothalamic stimulation, with a duration of three hours.<sup>14</sup> The second mechanism occurs on stimulation of the posterior hypothalamus and is mediated humorally through the pituitary-adrenocortical system. Its effects are equal in magnitude to those of the other mechanism but do not reach a maximum for 150 to 180 minutes and return to the resting state after five hours. This latter response can be similarly induced by exogenous ACTH, corticoids or epinephrine, and is blocked by adrenalectomy.<sup>2,14</sup>

The increase in gastric hydrochloric acid secretion induced by insulin exhibits features of both hypothalamic mechanisms, and administration of insulin to vagotomized or (not both) adrenalectomized animals produces the delayed or prompt responses, respectively.<sup>14</sup>

### *Pituitary*

Peptic ulcer is only coincidentally associated with pituitary adenoma when the adenoma is a solitary endocrine tumor, but frequently when the pituitary tumor is part of the syndrome of polyglandular endocrine adenomatosis.<sup>6,13</sup> The pituitary adenoma in this syndrome are usually eosinophilic or chromophobe,<sup>9</sup> and most of the carefully studied patients have shown evidence of hypopituitarism.<sup>10</sup> Thus only 1 per cent of acromegalics also have peptic ulcers, and hypophysectomy in experimental animals markedly reduces both parietal cell mass and gastric secretion.<sup>2,15</sup> It has also been noted that Pitressin given parenterally will experimentally induce acute peptic ulcers which usually heal rapidly, possibly by causing gastric mucosal ischemia which is followed by local hemorrhages.<sup>2,3</sup>

### *Adrenal Cortex*

The adrenal gland is important in the genesis of peptic ulcer because it supplies the final link in the pathway by which emotional stress influences gastric secretion.<sup>2</sup>

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The adrenal cortical hormones are essential for normal gastric secretion.<sup>2,16</sup> Addison's disease is frequently associated with achlorhydria and rarely with chronic peptic ulcers. However, replacement corticosteroid therapy, in low dosage, is frequently associated with peptic ulceration of the stomach or duodenum.<sup>2,3,5,16,17</sup>

In Cushing's syndrome there is increased gastric secretion of pepsin and acid, which is returned to normal levels by subtotal adrenalectomy,<sup>2,16</sup> and by a delay in the formation of granulation tissue.<sup>16</sup> Although adrenal tumor or hyperplasia is rarely found at autopsy in peptic ulcer patients,<sup>5</sup> and the levels of urinary corticosteroids are not high in the polyglandular syndrome with ulcers,<sup>15</sup> the incidence of adrenal adenoma or hyperplasia is still three times as high in an autopsied peptic ulcer group as in a control group.<sup>5</sup> Yet peptic ulcers are found in only 1 per cent of Cushing's syndrome patients who have hyperfunctioning adrenocortical tumors.<sup>15,18</sup>

It is of interest that contrary to endogenous hyperadrenocorticism, exogenous hyperadrenocorticism is often associated with the production or activation of peptic ulceration.<sup>2,19,20</sup> However, not all patients with current or previous peptic ulceration are made worse by this therapy and ulcers may heal while exogenous corticoids are being taken.<sup>20</sup> In a discussion of this difference between the frequency of peptic ulceration due to endogenous or exogenous corticosteroids, a concept was advanced that a lesser frequency was found in Cushing's syndrome due to its having multiple endocrine imbalances; glucocorticoid, mineralocorticoid, and androgen.<sup>11</sup> It is also interesting to note the absence of fever, abdominal rigidity and severe pain in those cases of peptic ulceration associated with endogenous or exogenous hypercorticism when the ulceration develops a free perforation.<sup>20</sup>

The mechanism by which the hypothalamic-pituitary-adrenal system is associated with peptic hyperactivity has been discussed. However, its role in the pathogenesis of peptic ulceration is more controversial. Most authors appear to feel that this system does not induce ulceration but rather "permits" its development if the balance of factors shifts in favor of the aggressive components.<sup>3,5,17</sup>

### *Adrenal Medulla*

Local acute peptic ulcers have been induced experimentally with adrenalin, as they have been with Pitressin.<sup>2,3</sup> However, peptic ulcers are found even more rarely with adrenal medullary tumors than with Cushing's syndrome, the incidence being less than 1 per cent.<sup>15</sup>

### *Parathyroid*

Parathyroid malfunction has also been associated with a changed incidence of peptic ulceration. Parathormone, through its regulation of serum calcium levels, has been found to influence gastric secretions. Hypoparathyroidism has been associated with decreased gastric secretion of acid and pepsin,<sup>2,12</sup> and it is said that peptic ulceration only rarely occurs with hypoparathyroidism<sup>4</sup> although there is little evidence that such an association has ever been sought.<sup>12</sup>

The parathyroid gland is composed of three cell types, the water-clear cell, the chief cell, and the oxyphil cell. Cases of secondary hyperparathyroidism due to renal disease are associated with chief cell hyperplasia whereas primary hyperplasia usually involves the water-clear cells.<sup>12,13</sup>

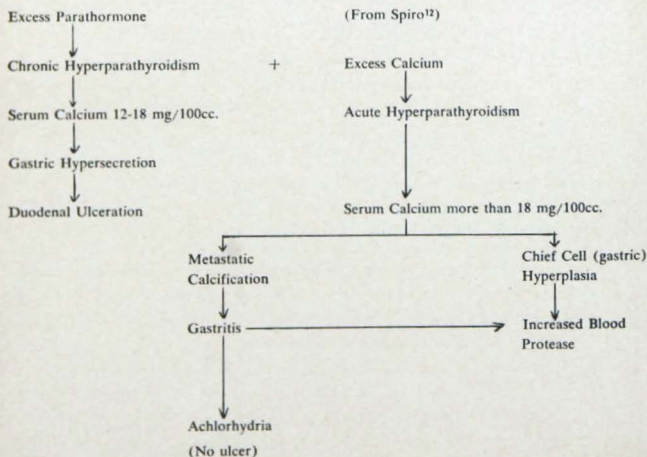
An increased incidence of duodenal ulceration has been reported with parathyroid

hyperfunction, with figures varying from 13 to 25 per cent.<sup>9,12,21</sup> These ulcers may also be more refractory to medical management than the usual duodenal ulcer, where the serum calcium level is normal,<sup>12</sup> and are sometimes cured by parathyroidectomy.<sup>2,14,15</sup>

It is important to recognize the difference in peptic ulceration that occurs in acute and in chronic states of hypercalcemia, only the chronic form having been discussed. A gradual development of hypercalcemia characterizes chronic hyperparathyroidism and the serum calcium level is usually less than 16 mg. per cent, whereas in acute hypercalcemia the serum calcium levels are usually 18-19 mg. per cent<sup>12</sup>

Acute exogenous hyperparathyroidism in animals leads to metastatic calcification in areas of relative alkalinity, that is sites of secretion of acid. These sites most commonly are the lungs, kidney and stomach. In the stomach such calcifications are interstitial, and occur around the chief and parietal cells. This may cause necrosis of the lower part of the gastric glands and may be associated with hemorrhagic gastritis, which leads to achlorhydria.<sup>12</sup>

One of the dangers of chronic hypercalcemia is acute hypercalcemia, since such patients commonly have peptic ulceration that is treated with a large milk intake. The gastritis that develops may be manifested by epigastric pain and intractable vomiting, and studies may show duodenal deformity although the patient may have achlorhydria which does not respond to histamine stimulation. Microscopic calcification has been found in the stomachs of patients with acute hypercalcemia and low gastric secretion, but has never been reported in the stomach of those with chronic hypercalcemia and gastric acid and pepsin hypersecretion.<sup>12</sup>



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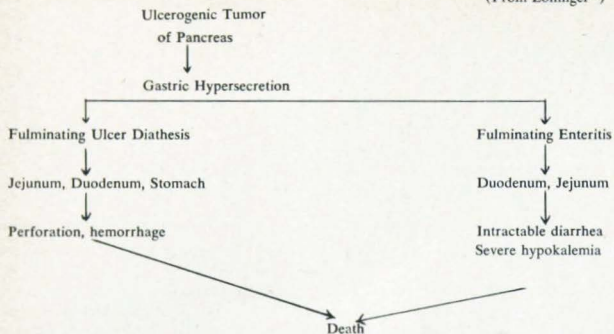
### *Pancreas*

The pancreas has long been suspected to play a role in the pathogenesis of peptic ulcerations but it was not until 1948 that it was suggested that an endocrine pancreatic secretion was strongly implicated. Such a factor was suspected due to the observation that spontaneous duodenal ulceration occurred in experimental animals when the exocrine pancreatic secretions were prevented from entering the small intestine (external fistula or ligation of the pancreatic ducts), unless a pancreatectomy was also performed. This was felt to be due to a pancreatic hormone stimulating gastric secretion, and ulceration normally being prevented by the presence of neutralizing pancreatic and biliary secretions in the small intestine; ulceration would occur if the protective factors were removed unless the stimulus to hypersecretion was also removed.<sup>22</sup>

In 1955 Zollinger and Ellison reported the occurrence of peptic ulcers in association with pancreatic tumors that did not produce insulin. Other symptoms of this disease were atypical location of the ulceration (distal duodenum or jejunum) or ulceration of the more common sites (esophagus, stomach or duodenal bulb);<sup>1,8,12</sup> intractability of the ulcer to usual medical therapy, surgical therapy short of total gastrectomy, or external irradiations;<sup>2,7,15</sup> and gastric hypersecretion, even with a twelve hour nocturnal secretion of two or more liters containing 100 or more units of free acid — normal twelve hour gastric secretion being less than 400 cc. containing 18 or less units of free acid.<sup>1,23</sup> The marked hypersecretion may cause a syndrome of diarrhea with hypokalemia with or instead of peptic ulceration.<sup>1,7,13,15</sup> Giant gastric rugae, sometimes with hypoproteinemia, may also be seen.<sup>1,7</sup>

The pancreatic lesion may be tumor (90 per cent) or diffuse islet hyperplasia (10 per cent), the latter being more commonly associated with the polyglandular syndrome.<sup>1,7</sup> The "pancreatic" tumors need not be in the pancreas, but may be in the duodenal wall, splenic hilus, or other aberrant location, and may be found in multiple sites. About two-thirds of such tumors have microscopic features of malignancy, and one-third have spread beyond the pancreas when detected; half such metastases function without regard to size and growth and metastatic spread appears to be very slow. Death from such tumors usually occurs due to ulcer complications rather than to tumor mass.<sup>1,7,13,15</sup>

The pancreatic islet is made up of several different cells, which have been named alpha, beta, delta, and gamma. Few such tumors have shown insulin hyperactivity (hypoglycemia relieved by glucose) but several insulinomas have been reported with peptic ulceration and the polyglandular syndrome.<sup>1,2,7,12</sup> Some of the islet cell tumors have been considered to be largely made up of alpha cells<sup>4</sup> but no ulcerogenic effect has been found with glucagon, the alpha cell hormone. No hormone or function has been ascribed to the delta or gamma cells. Thus, the ulcerogenic mechanism remains unknown, although production of gastrin has also been suggested.<sup>2,7,13,15</sup>

(From Zollinger<sup>13</sup>)

### Thyroid

Failure of the thyroid or other "target" gland has been suspected as being the stimulus to the development of the polyglandular syndrome. However, neither hypothyroidism<sup>6</sup> nor thyroid adenoma<sup>2</sup> have been frequently found in association with the syndrome. Although hyperacidity is found with hyperthyroidism, the incidence of peptic ulceration is smaller than in the population at large.<sup>6</sup>

### Gonad

It has been noted that peptic ulcers tend to heal or become less symptomatic during pregnancy,<sup>24,25</sup> although no beneficial effect was seen with the ulceration associated with the Zollinger-Ellison syndrome.<sup>13,15</sup> Conversely menstruation and menopause are said to have an adverse effect on peptic ulceration.<sup>2</sup>

It has also been noted that estrogen will tend to prevent experimental ulcers due to Cinchopen.<sup>2</sup> However, cirrhotics have both an increase in circulating estrogens and an increased incidence of peptic ulceration.<sup>25</sup> In a study of dogs given prolonged exposure to histamine stimulation and androgens or estrogens no change in gastric secretion, or incidence or location of peptic ulceration was seen.<sup>25</sup> Similarly, no explanation is apparent for the increased frequency of duodenal ulceration in men with equal sex incidence of gastric ulceration.<sup>2</sup>

### Carcinoid Syndrome

Functioning carcinoids may cause an increased incidence of peptic ulceration when associated with the polyglandular syndrome<sup>11</sup> as well as when they occur independently.<sup>2,26,27</sup> Both gastric and duodenal ulcerations<sup>26-29</sup> have been reported. The symptoms of this syndrome are due to the production of increased amounts of Serotonin by the tumor. Serotonin is produced from dietary tryptophan by converting it to 5-hydroxytryptophan and then to 5-hydroxytryptamine (Serotonin). It is excreted as 5-hydroxyindole acetic acid (5HIAA).<sup>28</sup> Normally only 1 per cent

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of ingested tryptophan follows this pathway, but in the carcinoid syndrome up to 60 per cent is converted to Serotonin. The normal serum Serotonin level is 0.03-0.40 mcg/cc and the 5HIAA urinary excretion normally is 2-10 mg/24hr. Serotonin is normally found in gastrointestinal chromaffin cells, blood platelets, mast cells, brain and lung.<sup>28,30</sup> Serotonin is also found in large amounts in bananas and cheese.<sup>27</sup>

Carcinoids may be found anywhere in the gastrointestinal tract below the gastric cardia, and are also found in the gall bladder, gonads and lungs. About 85 per cent are found in the appendix or terminal ileum.<sup>26,27</sup> Symptoms are rarely produced until metastases have been seeded, especially to the liver.<sup>26</sup> Other symptoms associated with that malignant carcinoid syndrome include cyanotic flushing beginning about the head, asthma, pulmonary stenosis and tricuspid insufficiency, arthritis of the small joints, telangiectasia and the hyperpigmentation of pellagra, diarrhea, dependent edema, Raynaud's phenomena, and less often tachycardia and systolic or diastolic hypertension.<sup>28-30</sup>

The symptoms may be induced by palpation of the tumor, ethanol ingestion, excitement, eating, defecation, or an enema.<sup>27,30</sup> Antihistamines and serotonin antagonists have been used with little success in the management of these symptoms and radiation is of no benefit. Surgical removal of as much tumor as possible is the only known beneficial therapy.<sup>27</sup> Death is usually due to congestive heart failure or severe diarrhea and malnutrition, seldom from metastases.<sup>29</sup>

In summary, the etiology of peptic ulceration is seldom known. It does occur with increased frequency in association with certain endocrinopathies, which have been briefly discussed.

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