MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

September 17, 1970

John S. Fordtran, M.D.

PATHOPHYSIOLOGY OF PEPTIC ULCER AND GASTRIC HYPERSECRETION

Clinical Observations

1. Since duodenal ulcer of a chronic nature never occurs in patients who are achlorhydric (pernicious anemia, etc.), the presence of gastric acid and pepsin is a prerequisite for ulcer development. [Recently, two patients with benign gastric ulcer were reported who were achlorhydric after maximum histamine stimulation (1), but the location of the aspirating tube was not proven to be in the stomach by fluoroscopy.] Acid and pepsin are often grouped as the aggressive factor.

2. Duodenal ulcer may develop in patients who secrete less acid than the mean value for normal subjects; conversely, some patients have extremely high rates of acid and pepsin secretion, yet fail to develop an ulcer crater. These observations prove that decreased mucosal resistance plays a role in at least some cases of ulcer.

3. Although a large area of sensitive mucosa is exposed to acid-pepsin, generally only a circumscribed area becomes affected by an ulcer. This is true for massive hypersecretory states associated with gastrin-producing tumors (Zollinger-Ellison syndrome) as well as in the usual type of ulcer disease. It also holds true in experimental studies when large amounts of acid and pepsin are perfused through a loop of duodenum (2). Thus, <u>locally</u> impaired resistance must also be postulated.

4. While it is logical to assume that a chronic peptic ulcer begins as an acute erosion, it should be noted that superficial erosions, in the stomach at least, are common in normal and ulcer patients, but that these heal promptly. Similarly, gastric and duodenal biopsies heal promptly, even in patients with active ulcer craters. These facts again strongly suggest a local tissue defect at the site of a chronic peptic ulcer.

5. Often stated, but not proven:

a. That peptic ulcer may heal in the absence of a change in gastric acidity. It is true that ulcers may heal without medical treatment, and that acid secretion is the same before and after duodenal ulcer is healed by medical therapy (4), but this does not prove that gastric acidity remained unchanged during the healing process. With medical therapy, of course, acidity is deliberately reduced. Acidity during spontaneous healing has not been studied.

b. That the high secretory rates seen in patients with duodenal ulcer are present for years before the ulcer develops. This may be true, but it has not been proven. Most of the evidence is based on follow-up studies of doctors who had acid secretory studies performed while they were in medical school. The most recent analysis concluded that "there is an almost even probability that the differences shown could have been due to chance" (3).

References:

1. Cocking, J. B., and MacCaig, J. N.: Effect of low dosage carbenoxolone sodium on gastric ulcer healing and acid secretion. Gut 10:219-225, 1969.

2. Ivy, A. C., Grossman, M. I., and Bachrach, W. H.: Peptic ulcer. The Blakiston Company, Philadelphia-Toronto, 1950.

3. Baron, J. H.: Gastric secretion in relation to subsequent duodenal ulcer and family history. Gut 3:158, 1962.

4. Levin, E., Kirsner, J. B., and Palmer, W. L.: Twelve-hour nocturnal gastric secretion in uncomplicated duodenal ulcer patients; Before and after healing. Proc. Soc. Exp. Biol. & Med. 69:153-156, 1948.

5. Grossman, M. I.: The pathologic physiology of peptic ulcer. Am. J. Med. 29:748, 1960.

Hypoxia as a Cause of Decreased Local Resistance

The mucous membrane of the stomach has a rich blood supply, consisting of arborizing capillaries which appear to fill almost completely the glandular area, "like a vascular sponge" (1). The arrangement of mucosal vessels is the same in all parts of the stomach.

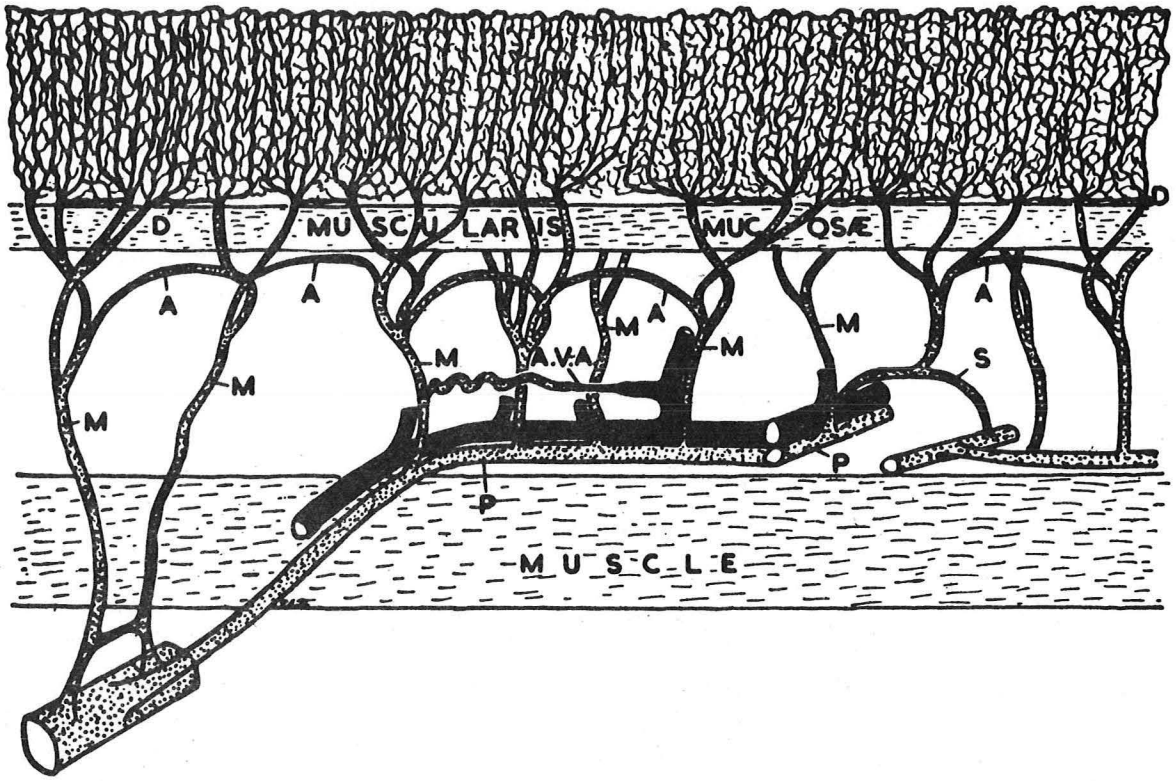


Diagram of the vascular arrangement in the stomach well, drawn after microscopic dissections of injected stomachs. On the left is shown the lesser curve, with mucosal arteries M arising from the left gastric artery outside the stomach wall. On the right the pattern as seen in anterior and posterior wall, where the mucosal arteries arise from a plexus of vessels beneath the muscularis mucosae. In the center, an arteriovenous anastomosis is shown.

The vessels of the stomach wall anastomose freely. The mucosal arteries of the anterior and posterior wall arise from a plexus of vessels beneath the muscularis mucosae, whereas on the lesser curvature the mucosal arteries arise from the left gastric artery, outside the stomach wall.

A/V shunts are prominent beneath the muscularis mucosae, and these operate to circumvent the large mucosal capillary bed. The effectiveness of the mucosal shunt system is striking--they are responsible for the marked blanching engorgement of the mucosa in response to various emotional stimuli, known since the work of Beaumont on Alex St. Martin.

Observations of the capillary network <u>in vivo</u> show that alternate opening and closing of capillaries is a normal phenomenon. Thus, alternating ischemia

and plethora is a normal condition. Although the majority of gastroduodenal shunts act in concert, paradoxical activity among neighboring shunts exists.

Thus, whatever the physiological mechanisms of control may be, channels exist that are capable of bringing large quantities of blood to the mucosa, or transferring blood from one point to another in the stomach or duodenal wall. The A/V shunts provide a means of rapidly directing blood into or away from the mucous membrane, by purely local action involving relatively few vessels. Presumably, the shunts are under the control of nervous and hormonal influences.

By using the distal two-thirds of the human stomach excised at operation for duodenal ulcer, it is possible to determine the size of the A/V anastomoses in the living state, and to make preliminary inquiries into the passage of circulating fluid through these channels. This is done by perfusing the vessels of the excised stomach with plasma; the stomach remains apparently healthy and active for at least 8 hours, as judged by acid secretion. A/V shunt function is measured by the number of small glass spheres which, when injected into the arterial circulation, are recovered from the veins--the more beads recovered, the more the shunts are open, and the less the mucosa is perfused. Acetylcholine, for instance, markedly increases mucosal blood flow (i.e., reduces recovery of beads and by inference closes the shunts).

The system of A/V anastomoses can produce local hypoxia in two ways: (a) if the shunt is open ischemia results, (b) if the shunt is closed for prolonged periods plethora may be produced, and this is also believed to cause hypoxia.

There are several reasons to select plethoric hypoxia as the explanation for mucosal damage rather than ischemic hypoxia. First, erosion (as studied by gastroscopy or gastrotomy) develops as a sequel to mucosal engorgement. Second, pharmacologic preparations commonly used to produce acute experimental ulcers (other than vasopressin) cause shunt closure and plethora. The same is true for vagus activity.

If a focal lesion is to develop as a result of abnormal shunt activity, a prolonged abnormal function of one or two shunts must be postulated. Methods to study such a phenomenon are not available, but many believe the local breakdown of tissue resistance may have a vascular basis.

References:

1. Barclay, A. E., Bentley, F. H.: The vascularization of the human stomach. A preliminary note on the shunting effect of trauma. Brit. J. Radiol. 22: 62-67, 1949.

2. Barlow, T. E., Bentley, F. W., and Walder, D. N.: Arteries, veins and arteriovenous anastomoses in the human stomach. SGO 93:657-671, 1951.

3. Sherman, J. L., and Palmer, E. D.: Hypoxia of vascular origin in the development of gastroduodenal ulcer disease. In Skoryna, S. C.: Pathophysiology of Peptic Ulcer, J. B. Lippincott Company, 1963.

The Mucosal Barrier

The theory of the protective action of mucin is illustrated in the following figure, taken from Heatley (1). Although antral mucus, studied in vitro, does not significantly impede the diffusion rate of HCl or pepsin, it is thought to be an effective barrier by virtue of its ability to retard mixing of luminal HCl-pepsin with the neutral solution that is believed to be secreted by the antral and duodenal mucosa. Thus, provided that some neutral fluid is secreted by the antral cells, the surface of the mucosa would be in contact with neutral fluid, regardless of the amount of acid within the stomach. Pepsin would diffuse through the mucous barrier, but on entering regions of successively higher pH, would become inactive and finally destroyed. The organization would maintain itself by continued renewal, depending on the quality and quantity of the secreted mucus.

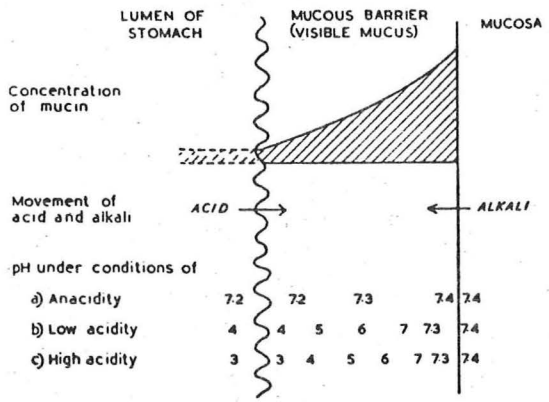


Diagram of imaginary concentration and pH gradients within the "visible" mucus layer on the gastric mucosa when contents of stomach are: a, anacid; b, weakly acid; and c, strongly acid. The directions of movement of acid and alkali are also shown.

The fact that non-secretors of ABH blood group substance have a slight but significantly higher incidence of ulcer than those who secrete the Lewis blood group substances (all people secrete one or the other of these blood group substances, and the total amount secreted is approximately the same) (2) suggests that ABH mucoproteins might be more protective than the Lewis factor.

Studies on aspirated gastric mucus (which may not accurately reflect the "mucous barrier") have failed to reveal differences that would logically suggest that ulcer patients secrete a mucus which is less protective than that secreted by control subjects. High rates of gastric acid and pepsin secretion might be deleterious to mucus by causing it to flocculate rather than to form a gel (5).

Menguy (6) has reviewed the evidence that aspirin is injurious to the gastric mucosa (even that administered parenterally as per rectum), and that this effect is not mediated via enhanced acid and pepsin secretion. Rather, he has found that aspirin profoundly reduces the rate of mucous secretion and also alters the composition of mucus.

Recent evidence suggests that the rising incidence of gastric ulcer in Australian women is due to aspirin ingestion (7).

The "defective mucous barrier" theory is much alive, although still not proven. It would be of great interest to compare gastric mucus in individuals with high acidity but no ulcer (i.e., good resistance) to the mucus from patients with ulcer and low acid secretion (low resistance group) rather than from random groups of normal and ulcer patients, as has been done in the past.

References:

1. Heatley, N. G.: Mucosubstance as a barrier to diffusion. Gastroenterology 37:313-317, 1959.

2. Grossman, M. I.: The pathologic physiology of peptic ulcer. Am. J. Med. 29:748, 1960.

3. Curt, J.R.N., and Pringle, R.: Viscosity of gastric mucus in duodenal ulceration. Gut 10:931-934, 1969.

4. Hoskins, L. C., and Zamcheck, N.: Studies on gastric mucus in health and disease. II. Evidence for a correlation between ABO blood group specificity, ABH (O) secretor status, and the fucose content of the glycoproteins elaborated by the gastric mucosa. Gastroenterology 48:758-767, 1965.

5. Schrager, J.: The chemical composition and function of gastrointestinal mucus. Gut 11:450-456, 1970.

6. Menguy, R.: Gastric mucosal injury by aspirin. Gastroenterology 51:430-432, 1966.

7. Chapman, B. L., and Duggan, J. M.: Aspirin and uncomplicated peptic ulcer. Gut 10:443-450, 1969.

Psychosomatic Studies

Psychoanalytic studies, pioneered by Alexander, have led to the generalization that patients with duodenal ulcer have in common a conflict related to the persistence of strong infantile wishes to be loved and cared for, on the one hand, and their repudiation by the adult ego (shame, pride, etc.) or by external circumstances, on the other.

Thus, as a group, patients with duodenal ulcer show intense needs that are principally "oral" in nature, and which are exhibited in terms of wishing to be fed, to lean on others, to seek close bodily contact with others, and in general to have a marked dependency on others. Satisfaction of their needs for external support and satisfaction is attempted by many maneuvers; when these fail, the frustration arouses anger that cannot be expressed for fear that their source of support will be lost. Consequently, these subjects do not make complaints or express anger--instead they deny or internalize hostile impulses with a resulting tendency to depression. The need to please and placate authority figures as potential sources of affection is striking.

It should be emphasized that similar psychosomatic patterns can be demonstrated in subjects without any gastrointestinal disturbances; consequently, psychic conflict, specific or otherwise, cannot be the sole determinant in precipitating a duodenal ulcer.

The actual development of an ulcer, on the background of the conflict as described above, is usually associated with a significant social event, characterized by quite obvious fear of a loss of love and security, intensification of persistent infantile passive and oral dependent wishes, the frustration of such wishes and the activation of passive-aggressive conflicts. The association of ulcer with air raids, with the stress of the second line rather than the front troops, in "executive monkeys", etc., would seem to confirm this view.

The psychosomatic theory has been summarized by Weiner, et al:

> It would appear that there are three parameters which may contribute to the precipitation of duodenal ulcer: a physiologic parameter, which determines the susceptibility of the duodenum to ulceration; a psychological parameter, which determines the relatively specific psychic conflict that induces psychic tension; and a social parameter, which determines the environmental event that will prove noxious to the particular individual. Accordingly, a duodenal ulcer should develop when an individual with a sustained rate of gastric hypersecretion and the aforementioned psychic conflict is exposed to an environmental situation that mobilizes conflict and induces psychic tension.

Weiner, et al. reported a study designed to evaluate the role of these three parameters in the precipitation of duodenal ulcer. The degree of gastric secretion comprised the physiologic parameter. The style of interpersonal interaction that could be inferred from projective and other psychological techniques comprised the psychological parameter. The exposure to 16 weeks of basic training comprised the environmental situation that might prove noxious to some and not to other subjects.

2,073 draftees were studied at random. High and low secretors were chosen for study on the basis of serum pepsinogen level. Those investigators working with the draftees did not know the specific results of the serum pepsinogen, only that some were high and some were low. A total of 120 men were selected for a battery of psychological tests and GI x-rays. The men were then sent to basic training camp. Subsequently, all but 13 men were again given the psychological tests and roentgenological examinations between the 8th and 16th weeks of the basic training period.

The figure on the following page illustrates the normal distribution of values for pepsinogen. Sixty-three of 300 hypersecretors and 57 of 179 hyposecretors were selected for study.

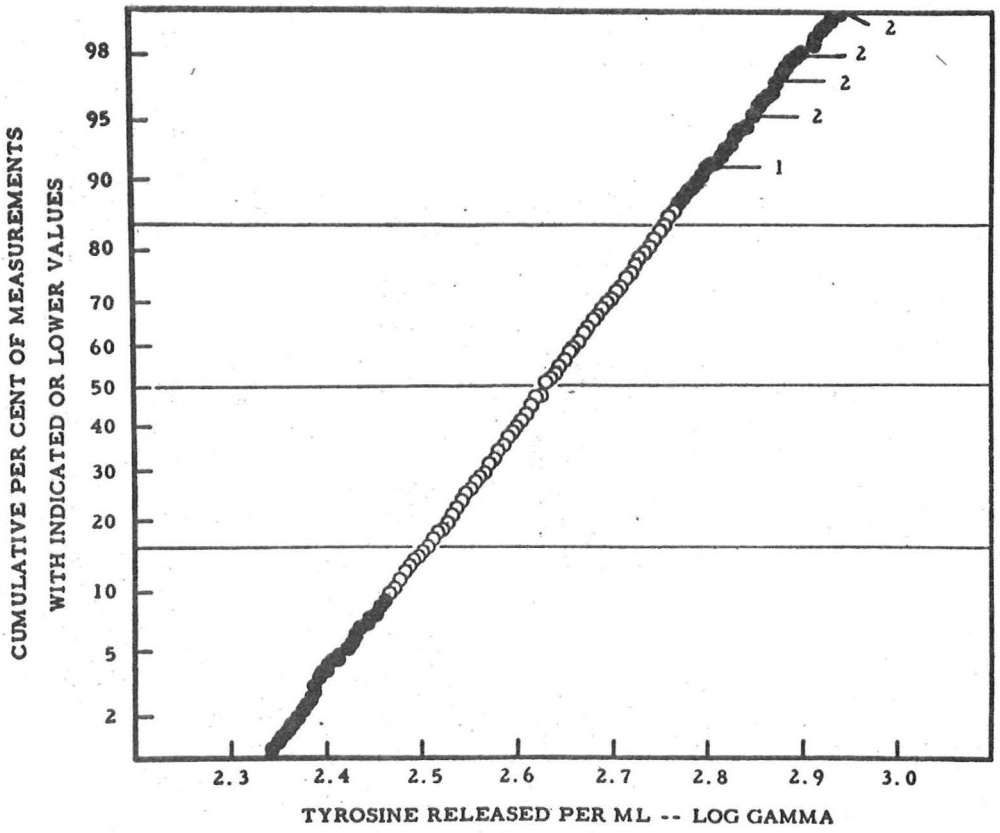
The first GI x-ray showed a duodenal ulcer (old or active) in 4 men, all in the hypersecretor group. The second x-ray, after several weeks of basic training, showed 5 additional men with duodenal ulcer, and all were in the hypersecretor group.

By means of a cluster of 20 psychologic criteria, it was possible to distinguish the two groups to the extent that 85% of the 120 men could be assigned correctly to their secretor groups. Only 6 of 63 hypersecretors could not be accurately classified.

Other than for the intensity of their attempt to maintain relationships, the hypersecretors who developed duodenal ulcer could not be separated from the rest of the hypersecretor group.

The data strongly suggest that hypersecretors as a group have a characteristic psychic make-up, regardless of whether or not they develop or have a duodenal ulcer. As a group, they are predisposed to ulcer development. Which comes first (the psychologic conflict or the hypersecretion), or whether both are inherited together (perhaps along with tendency to be blood group O and non-secretors of the ABO blood group substance) is not known.

The psychological pattern of duodenal ulcer patients who are not hypersecretors has apparently not been determined. This would seem a critical issue in the pathogenesis of ulcer.



Distribution of blood serum pepsinogen concentrations: the frequency distribution of the logarithm of the concentration of the pepsinogen in the serum plotted on a probit scale. The subjects selected for special study were among those designated with closed circles. The numerals refer to individuals with duodenal ulcer.

Since twin and sibling studies suggest that serum pepsinogen (and therefore secretory capacity of the stomach) is genetically determined, Weiner, et al. favor the concept that the inherited high secretory capacity may play a role in determining the psychological make-up.

References:

1. Mirsky, I. A.: Physiologic, psychologic, and social determinants in the etiology of duodenal ulcer. Am. J. Dig. Dis. 3:285-314, 1958.

2. Weiner, H., Thaler, M., Reiser, M. F., and Mirsky, I. A.: Etiology of duodenal ulcer. I. Relation of specific psychological characteristics to rate to gastric secretion (serum pepsinogen). Psychosomatic Medicine 19:1-10, 1957.

3. Kehoe, M. J., and Brink, E. J.: Gastric secretion in a set of healthy identical twin brothers: a psychophysiological study using hypnosis. Psychosomatic Medicine 28:768, 1966. (Consistent differences appear to be environmental in view of identical genetic heritage.)

4. Coddington, R. D., Kohler, W.: The relation between maternal affect and gastric secretion in twin infants: a preliminary report. Idem., p. 769.

5. Pilot, M. L., Rubin, J., Schafer, R., and Spiro, H. M.: Duodenal ulcer in one of identical twins. A follow-up study. Psychosomatic Medicine 25:285-291, 1963.

6. Reichsman, F., Samuelson, D., and Engel, G. L.: Behavior and gastric secretion. II. A study of a four-year-old girl with a gastric fistula. Psychosomatic Medicine 27:483, 1965.

7. Welsh, J. D., and Wolf, S.: Geographical and environmental aspects of peptic ulcer. Am. J. Med. 29:754-760, 1960.

Pepsinogen and Pepsin

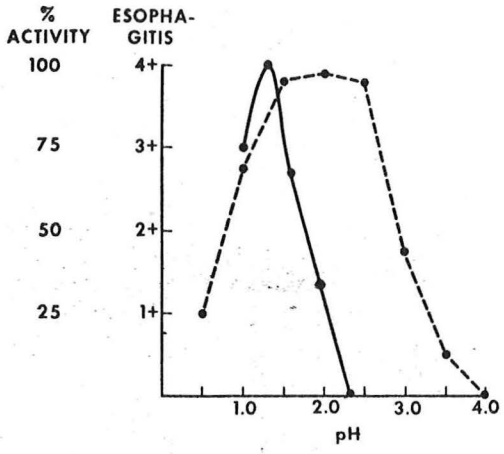
Under basal conditions, and after various stimulants, the rate of pepsinogen secretion in normal subjects and in patients with ulcer is correlated with the rate of acid secretion (1). Pepsinogen concentration in serum and urinary pepsinogen secretion are increased in patients with duodenal ulcer. Serum and urinary pepsinogen do not fluctuate with changes in the rate of gastric pepsin secretion produced by meals, and it is likely that variations in pepsinogen levels in blood and urine reflect mainly variations in gastric secretory capacity for pepsin secretion rather than changes in the rate of pepsinogen secretion over a short time period (2).

Recently, Samloff and Townes (3) have shown that human pepsinogens are clearly separable into two distinct groups on the basis of electrophoretic mobility. Further studies are needed to determine whether qualitative or quantitative differences are factors in the pathogenesis of peptic ulcer.

The separation of the role of acid and pepsin in the production of peptic ulcer, peptic esophagitis, etc., has been difficult. Some workers have stressed the role of acid as the ulcerogen, others have emphasized the importance of pepsin. Pepsin activity cannot, of course, be dissociated from that of acid because pepsin is active only in the presence of acid.

Goldberg, et al. (4) have carefully studied this problem using a cat esophagitis model. Acid solutions of pH 1.0 (about 127 mEq/L) caused a severe esophagitis, even in the complete absence of pepsin. As a matter of fact, addition of pepsin to such solutions did not increase the severity of the esophagitis, which was probably due to protein denaturation. At pH 1.6 (31 mEq/L) and at pH 2.0 (12 mEq/L), esophagitis was produced only when pepsin was added to the acid solution. At these pH levels it is likely that pepsin produced esophagitis by protein digestion.

Therefore, it appears that with this model pepsin is an important factor in causing esophagitis within the pH range of 1.6 to 2.0. At very high levels of acidity, acid alone can produce injury.



In vivo pH-pepsin activity curve, with esophageal proteins as substrate (———), is compared with that of an in vitro pH-pepsin activity curve utilizing hemoglobin as substrate (-----).

The figure shows a comparison of in vivo and in vitro (hemoglobin substrate) pH activity curves. It is clear that pepsin-pH activity curves vary, depending on the substrate. Of considerable interest is the fact that a pH change from 1.5 to 2.5 would virtually eliminate esophagitis. It is easily possible to effect such a pH change in the stomach of patients with duodenal ulcer by the administration of antacids. On the other hand, it is often not possible to achieve pH 4 (the level required to prevent hemoglobin digestion) for prolonged periods by giving antacids to ulcer patients. Hopefully, the pepsin-pH activity curve for duodenal mucosa resembles that for the cat esophagitis and not that for hemoglobin.

References:

1. Hunt, J. N.: Some notes on the pathogenesis of duodenal ulcer. Am. J. Dig. Dis. 2:445, 1957.

2. Hirschowitz, B. I.: Pepsinogen: its origins, secretion and excretion. Physiol. Rev. 37:475, 1957.

3. Samloff, I. M., and Townes, P. L.: Electrophoretic heterogeneity and relationships of pepsinogens in human urine, serum and gastric mucosa. Gastroenterology 58:462, 1970.

4. Goldberg, H. I., Dodds, W. J., Gee, S., Montgomery, C., and Zboralske, F. F.: Role of acid and pepsin in acute experimental esophagitis. Gastroenterology 56:223, 1969.

Acid

It has been known for years that the mean rate of acid secretion in patients with duodenal ulcer is higher than in control subjects, no matter what the conditions of the study (basal, histamine, etc.). By contrast, mean secretion rate in gastric ulcer patients tends to be lower than normal, although the scatter is wide. To a degree, the low secretion rate in some gastric ulcer patients may be an artifact, since gastritis often surrounds an ulcer crater, and this may diminish the functional parietal cell mass (1). Furthermore, it has been suggested that the low secretion rates in gastric ulcer may be due to enhanced gastric permeability to hydrogen ions, so that secreted acid may diffuse across the gastric mucosa and not be collected in the sample of gastric juice (2). There is some experimental evidence to support this hypothesis (3), although an abnormality in HCO_3^- secretion rather than H^+ absorption has not been ruled out.

According to Baron, who studied 70 duodenal ulcer patients, there is a threshold rate of peak acid secretion (maximum histamine test), below which patients do not get duodenal ulcer (4). This value is 15 mEq/hr in males and 18 mEq/hr in females. Only 2 of 157 patients in two other large series had peak acid secretion rates below these levels (5,6). The lowest value for all three series of patients was 10.4 mEq/hr.

The mechanism of gastric hypersecretion in duodenal ulcer patients is a matter of intense interest. Impaired inhibition of acid secretion as a possible cause of hypersecretion has been examined, with negative results (7). There is no support for an increased reactivity of parietal cells in ulcer patients. That hypersecretion is not caused by the ulcer crater has been proven by the finding that secretion rates are the same before and after the crater has healed under medical therapy (8).

There is now general agreement that one major factor involved in the hypersecretory state of duodenal ulcer patients is an increased number of parietal cells. This has been verified by direct counting, and indirectly from the peak acid response to histamine, which is known to correlate closely with the parietal cell mass (9,10).

The cause of the increased parietal cell mass is not known with certainty, although most workers favor a genetic etiology. The supposedly higher incidence of duodenal ulcer among relatives of patients with duodenal ulcer (11-13), the significantly higher incidence of blood group O and ABO non-secretor status (genetically determined traits) in ulcer patients (14), and data in twins and siblings support this contention (15).

Thus, at the present time it seems best to assume that the parietal cell mass is genetically determined. The next question is, can it be modified by environmental factors? There is good evidence that the parietal cell mass can be increased by chronic hypergastrinemia, as seen in patients with the Zollinger-Ellison syndrome (16). Apparently the chronic stimulation of gastric secretion characteristic of these patients results in a hypertrophy of the parietal cell mass. Experimentally, histamine, hypercalcemia and portacaval shunts have a similar effect (17-20).

The Parietal Cell Mass

With these exceptions, there was, until recently, no evidence that the parietal cell mass fluctuated significantly in the usual group of patients with duodenal ulcer, and it was generally assumed that the parietal cell mass was fairly constant in a given individual. According to Sircus (21), when tests were repeated on one or more occasions in 15 subjects over a 2-year period, the coefficient of variation was 9.7%.

In 1967, Weir reported a normal man who was studied three times in 1964, with less than 1.5 mEq/hr peak acid secretion on each occasion. When studied again one year later, he secreted greater than 20 mEq/hr on two occasions (22). A transient gastritis was postulated.

Waterfall reported one normal and one duodenal ulcer patient who had a marked fall in their peak acid response to gastrin. In the normal patient, parietal cell antibody and gastritis was demonstrated, possibly related to the pentagastrin injections (23,24).

We studied the peak acid response to histamine at 3-month intervals over a 1-2 year period in 33 "run of the mill" duodenal ulcer patients. Five (15%) showed a convincing and significant sequential change in their parietal cell mass during the 1 to 1-1/2 year period of observation. Most showed a decrease and one showed an increase. Some case reports will be described subsequently.

Basal Secretory Drive

Do patients with run of the mill duodenal ulcer have some sort of enhanced stimulation of acid secretion in the basal state?

A popular concept since the time of Cushing (1932) is that hypersecretion in ulcer patients is caused by parasympathetic overactivity, due in turn to overactivity of the hypothalamus. Parasympathetic overactivity, mediated by the vagus nerve, might thus lead to basal hypersecretion, and this in turn to enhanced parietal cell mass. The fact that vagotomy reduces basal hypersecretion has been used as evidence in support of this concept (25), but this view has not met with general acceptance because vagotomy also reduces acid secretion to all stimuli, including histamine and gastrin (14,26,27). Thus, an equally plausible interpretation of the vagotomy effect is that vagal tone modulates the responsiveness of the parietal cells to all stimuli.

Hunt (27) has argued that if the basal hypersecretion of patients with duodenal ulcer were due to overactivity of the vagus, one would expect that vagotomy would reduce basal secretion by a larger percentage than it reduces acid secretion in response to histamine--a fall in basal secretion first because of the general reduction of peripheral reactivity, and a second and further fall due to withdrawal of stimuli to secretion. This second fall is not observed after vagotomy.

Hunt, Kay, Card and Sircus (28) have analyzed two large series of duodenal ulcer patients and a group of controls with regard to the percentage of the maximum secretory capacity activated by the stimuli of basal secretion. They concluded that there is no need to postulate any abnormal secretory drive to the parietal cells during basal conditions. After a similar analysis, Baron concluded that some duodenal ulcer patients, especially men with a parietal cell mass that is not elevated, may

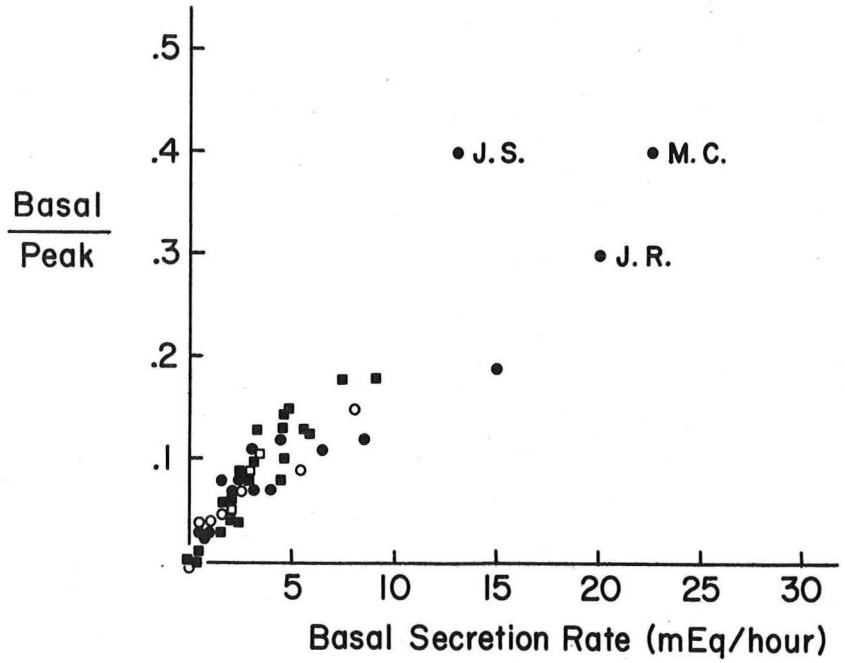
have an abnormal basal secretory drive (29). The validity of his conclusion has been challenged on statistical grounds (30).

Singh, et al. (30) have recently shown that vagal block with hexamethionium bromide and atropine reduced basal and peak histamine secretion to an equal extent in normals and in patients with duodenal ulcer. They conclude that "these findings negate the thesis of vagal hypertonicity to explain hypersecretion in duodenal ulcer patients."

The apparent conclusion from these studies is that the basal secretory rate of ulcer patients is simply a fraction of the peak acid response, and that the basal secretory drive is approximately equal in almost all duodenal ulcer patients, and the same for ulcer patients as for normal subjects. Most recent studies have, therefore, focused on the peak histamine response as a measure of the parietal cell mass, and the significance attached to this measurement increased when it was shown that after a normal meat meal the secretory response is the same as the peak histamine response, and therefore maximal (31).

Analysis of Data Collected With Drs. Norgaard, Polter and Wheeler

The data in the next figure represent the average of from 4 to 6 studies on each individual subject. It is presumably more reliable than data collected in most other series, where in general only one study was done on each patient. Ten control subjects (house staff, medical students and technicians) were studied in a



similar fashion (open symbols). Squares represent those treated with anticholinergics, which were taken continuously except for 2 days before each test. Circles indicate patients or normal subjects on placebo.

Conclusions:

1) Normals and duodenal ulcer patients have the same ratio of basal/peak when expressed as a function of basal secretion rate.

2) The ratio of basal/peak rises as the rate of basal secretion rises.

3) Therefore, basal secretion rate is not simply a constant fraction of parietal cell mass, and

4) Subjects with high basal secretion have either a higher basal secretory drive or an increased reactivity to normal stimuli, compared to subjects with low basal secretion rates.

5) Prolonged treatment with anticholinergic agents does not affect this relationship, nor does this therapy reduce the parietal cell mass (data not shown, but have been reported in reference 32).

Our tentative interpretation is: 1) that basal secretory drive is higher in ulcer and normal subjects with high basal secretion than in those with low basal secretion, 2) that basal secretory drive can stimulate parietal cell hyperplasia, and 3) that the extent to which the parietal cell mass can hypertrophy is limited, no matter how potent the basal drive.

Case Reports

M.C., 35-year-old man

1964-1969 Ulcer-like symptoms

7/8/69 Melena, x-ray showed severe duodenal ulcer deformity and prominent duodenal folds.

7/10/70 Readmitted for study by Dr. Stuart Frank. Mild ulcer symptoms. PE normal. No evidence of tumor. Serum calciums normal. Celiac angiogram normal. Serum gastrin 100 picograms/ml (normal > 200, Zollinger-Ellison > 600), done by Dr. James McGuigan. This would seem to rule out Zollinger-Ellison syndrome.

Secretory Studies by Dr. Charles Richardson:

	Basal	Peak
7/16/69	6.5	40 mEq/hr
7/28/70	43.7	58
8/18/70	14.2	63

8/28/70 5-hour basal, and effect of Pathilon:

1st hour	25.7 mEq/hr
2nd hour	27.1
3rd hour	53.3
4th hour	31.9
5th hour	27.3 ←—Pathilon 20 mg IM
6th hour	5.0

9/15/70 Correlation of Parotid and Gastric Secretion:

	Basal Gastric Secretion mEq/30 min period	Right Parotid Salivary Flow ml/30 min
Period 1	17.6	3.0
2	10.1	4.0
3	17.4	0.5
4	8.0	1.0
Urocholine 5 mg subcu.		
5	7.5	20.0
6	11.2	10.0
7	8.2	10.5

Interpretation: Patient has marked basal hypersecretion, which fluctuates in severity, but is often marked, with secretory pattern of Zollinger-Ellison syndrome. Latter diagnosis unlikely because of normal serum gastrin. Salivary study indicates that parasympathetic nervous system is not overactive, since basal flow was low (while basal gastric secretion was high) and markedly increased with urocholine. The fall in gastric secretion with anticholinergic is due to general suppression of parietal cell reactivity.

The patient either has marked basal secretory drive of unknown etiology or his parietal cells are exquisitely sensitive to normal basal stimuli. A similar case study has not, to our knowledge, been reported, although others have seen cases with Zollinger-Ellison like secretory patterns without evidence for an islet cell tumor (33,34).

J.R., 48-year-old man

6/18/70 5-day history of severe epigastric pain and "hot water boiling in my throat". Upper GI showed hypertrophic gastric folds suggestive of Zollinger-Ellison syndrome, but no ulcer. Secretory studies showed severe hypersecretion (data below). Antacids q30 min. day and night were required to relieve pain. He was also treated with anticholinergics.

Patient a known diabetic since 1958, on 30 U NPH. No hypoglycemic symptoms or ketoacidosis.

Prior to the onset of GI symptoms, the patient had been under severe stress due to the death of several members of his family.

PE unrevealing. Serum calcium and gastrin normal (McGuigan). Stool fat 30 gm/24 hours, presumably due to severe hypersecretion.

Secretory data:

	6/20	7/7
Basal	24.1	15.9
Peak acid output	81.3	49.6

8/26/70 6-hr. Basal

1st	1.3
2nd	0
3rd	0.001
4th	0
5th	8.9
6th	0.003

8/28/70
5-hr. basal and histamine

1st	0.001
2nd	2.1
3rd	3.4
4th	0.02
5th	0.6
Peak	43.7

9/4/70
Basal and insulin hypoglycemia

Basal I	1.8
Basal II	0.9
Post Insulin	29.5

Hospital course and interpretation: After about 2 weeks in the hospital, the patient became asymptomatic. After 8/26/70, when it was recognized that his basal hypersecretion was markedly reduced, antacids and anticholinergics were stopped. His symptoms did not recur. Repeat studies on 8/28/70 showed that peak response was 43.7, so the fall in basal cannot be attributed to gastric atrophy or gastritis.

The study on 9/4/70 indicates that vagal fibers were still intact.

Interpretation: Marked hypersecretion of transient nature, producing gastric mucosal hypertrophy and steatorrhea. Parietal cell mass appears to be falling as basal secretion has decreased. Hypersalivation on admission suggests parasympathetic overactivity, but studies to verify this were not done. Follow-up studies under "stress interview" conditions are planned in the near future.

P.R. and C.P., 50- and 40-year-old men with duodenal ulcer, in sequential secretory study. Nothing special about history, and no explanation for falling gastric secretion during which time the patients became asymptomatic.

Secretory data

		Initial	1 month	3 months	6 months	9 months	12 months
P.R.	Basal mEq/hr	0.1	0.00	0.00	0.00	0.00	0.00
	Peak mEq/hr	24.1	14.2	9.8	3.8	13.6	7.2
	Ratio	0.04	0	0	0	0	0
C.P.	Basal mEq/hr	1.9	0.1	0.00	0.00	0.00	
	Peak mEq/hr	38.6	20.6	9.2	3.8	6.2	
	Ratio	0.05	0.005	0	0	0	

Note that basal secretion became extremely low at a time when peak secretion was still about 20 mEq/hr. Subsequently, basal secretion became zero, and the peak secretion progressively fell.

These data are compatible with (but do not prove) a falling parietal cell mass due to reduced basal secretion. If the parietal cell mass fell first, without a change in basal secretory drive, the ratio of basal/peak would not be expected to fall to such low levels. When basal secretion is persistently low, relative to peak, we anticipate that the peak will soon fall.

C.B., 52-year-old man with duodenal ulcer, in sequential secretory study. Nothing special about his history, and no explanation for rising secretion. Patient was on antacid and anticholinergic therapy throughout the study period (latter stopped 2 days before each study), and was essentially asymptomatic:

	Initial	1 month	3 months	6 months	9 months	12 months
Basal	1.9	0.5	1.9	2.3	0.3	6.1
Peak	33.0	37.0	48.0	55.2	61.8	62.0

Interpretation: Rising parietal cell mass, unable to assess mechanism.

References:

1. Marks, I. N., and Shay, H.: Observations on the pathogenesis of gastric ulcer. Lancet 1:1107-1111, 1959.
2. Davenport, H. W.: Is the apparent hyposecretion of acid by patients with gastric ulcer a consequence of a broken barrier to diffusion of hydrogen ions into the gastric mucosa? Gut 6:513, 1965.
3. Overholt, B. F., Pollard, H. M.: Acid diffusion into the human gastric mucosa. Gastroenterology 54:182, 1968.
4. Baron, J. H.: An assessment of the augmented histamine test in the diagnosis of peptic ulcer. Gut 4:243, 1963.
5. Kaye, M. D., Beck, P., Rhodes, J., and Sweetnam, P. M.: Gastric acid secretion in patients with duodenal ulcer treated for 1 year with anticholinergic drugs. Gut 10:774, 1969.
6. Checketts, R. G., Gillespie, I. E., and Kay, A. W.: Insulin potentiation of the augmented histamine response. Gut 9:683, 1968.
7. Ward, A. S., Wilkins, R. A., Cockel, R., and Windsor, C.W.O.: Duodenal inhibition of gastric secretion by osmotic agents in normal subjects and patients with duodenal ulcer. Gut 10:1020, 1969.
8. Levin, E., Kirsner, J. B., and Palmer, W. L.: Twelve-hour nocturnal gastric secretion in uncomplicated duodenal ulcer patients. Before and after healing. Proc. Soc. Exp. Biol. & Med. 69:153, 1948.
9. Cox, A. J.: Stomach size and its relation to chronic peptic ulcer. Arch. Path. 54:407, 1952.
10. Cord, W. I., and Marks, I. N.: The relationship between the acid output of the stomach following "maximal" histamine stimulation and the parietal cell mass. Clin. Sci. 19:147, 1960.
11. Doll, R., and Borch, J.: Hereditary factors in peptic ulcer. Ann. Eugen. 15: 135-146, 1950.
12. Doll, R., and Kellock, T. D.: The separate inheritance of gastric and duodenal ulcers. Ann. Eugen. 16:231, 1951.
13. Baron, J.H.: Gastric secretion in relation to subsequent duodenal ulcer and family history. Gut 3:158, 1962.
14. Grossman, M. I.: The pathologic physiology of peptic ulcer. Am. J. Med. 29: 748, 1960.
15. Mirsky, I. A., quoted in Weiner, H., et al.: Etiology of duodenal ulcer. Psychosomatic Med. 19:1, 1957.
16. Polacek, M. A., and Ellison, E. H.: Parietal cell mass and gastric acid secretion in the Zollinger-Ellison syndrome. Surgery 60:606, 1966.

17. Marks, I. N.: The effect of prolonged histamine stimulation on the parietal cell population and the secretory function of the guinea pig stomach. Quart. J. Exp. Physiol. 42:180, 1957.

18. Neely, J. C., and Goldman, L.: Effect of calciferol-induced chronic hypercalcemia on gastric secretion from Heidenhain pouch. Ann. Surg. 155:406-411, 1962.

19. Ritchie, W. P., Jr., Delaney, J. D., Barzilai, J. D., Lance, A. J., and Wangensteen, O. H.: Experimental alterations in gastric mucosal cellular populations in dogs. JAMA 197:113-117, 1966.

20. Landor, J. H., Porterfield, J. F., and Wolff, W. S.: Parietal cell response to chronic gastric secretory stimulation. SGO 122:61-65, 1966.

21. Sircus, W.: J. Royal College Surgeons 4:153, 1959.

22. Weir, D. G.: Spontaneous recovery of gastric secretion. Brit. M. J. 2:681, 1967 (June 10).

23. Waterfall, W.: Spontaneous decrease in gastric secretory responses to humoral stimuli. Brit. M. J. 4:459-461, 1969.

24. Gillespie, I. E.: Review of reference 23, in Gastroenterology 58:910, 1970.

25. Dragstedt, L. R.: Gastric secretion tests. Gastroenterology 52:587, 1967.

26. Grossman, M. I.: Dragstedt's editorial on gastric secretion tests. Gastroenterology 53:681, 1967.

27. Hunt, J. N.: Some notes on the pathogenesis of duodenal ulcer. Am. J. Digest. Dis. 2:445, 1957.

28. Hunt, J. N., Kay, A. W., Cord, W. I., and Sircus, W.: The nature of basal hypersecretion in man with duodenal ulcer, in Skoryna, S. C., Pathophysiology of peptic ulcer, J. P. Lippincott, 1963.

29. Baron, J. H.: The relationship between basal and maximum acid output in normal subjects and patients with duodenal ulcer. Clin. Sci. 24:357-370, 1963.

30. Singh, H., Goyal, R. K., Ahluwalia, D. S., and Chuttani, H. K.: Vagal influence in gastric acid secretion in normals and in duodenal ulcer patients. Gut 9:604, 1968.

31. Rune, S. J.: The indirect method for estimating the gastric acid response to normal solid food. Gastroenterology 52:137, 1967.

32. Norgaard, R. P., Polter, D. E., Wheeler, J. W., and Fordtran, J. S.: Effect of long-term anticholinergic therapy on gastric secretion, with observations on the serial measurement of peak Histalog response. Gastroenterology 58: 750, 1970.

33. Bank, S., and Marks, I. N.: Treatment of the Zollinger-Ellison syndrome. Lancet 1:51, 1966 (Jan. 1).

34. Kaye, M. D., Rhodes, J., and Beck, P.: Gastric secretion in duodenal ulcer with particular reference to the diagnosis of Zollinger-Ellison syndrome. Gastroenterology 58:476, 1970.

General Conclusions:

1) The mucous barrier theory needs more study. It would seem especially important to compare hyposecretors with duodenal ulcer (low resistance group) with hypersecretors without ulcer (high resistance group). With the large number of stomachs available via ulcer surgery, a study of the mucous lining rather than aspirated mucus seems possible.

2) The hypoxic theory is attractive because it provides a mechanism for local tissue damage, via malfunction of the A/V shunt. Since under proper conditions the resected stomach continues to secrete acid for 8 hours, and the shunts remain functional and responsive, many pathophysiological studies seem feasible.

3) Psychological studies need to be taken up again to confirm the excellent studies of Weiner, et al., and to see if hyposecretors with ulcer, and older patients (in contrast to army recruits) with ulcer, have the classic conflict that has been described. If it proves correct that hypersecretors have a specific conflict, regardless of whether or not they develop ulcer, this would seem an extremely important observation. It would, of course, fit well with the observation that normal and duodenal ulcer subjects have the same relationship between basal secretion and the ratio of basal/peak secretion rates.

4) Current concepts of gastric secretion in duodenal ulcer need to be reconsidered. Specifically, we believe that the parietal cell mass fluctuates. significantly in a significant per cent of the ulcer population and that these may be important in onset or exacerbations of ulcer, or in the spontaneous and indefinite remissions that are observed.

We also believe that the basal secretory drive has an effect on the parietal cell mass, and that previously unrecognized basal hypersecretory states are being recognized. To a large degree their recognition is possible because of the serum gastrin assay, which allows the Zollinger-Ellison syndrome to be ruled out. Much effort obviously will be needed to discover the cause of these idiopathic basal hypersecretory states, and multiple etiologies are expected. Surprisingly, little use has apparently been made of salivary flow studies to look for evidence of parasympathetic overactivity.

If these concepts prove to be true, they may resolve the argument of whether or not basal secretion is more sensitive than peak response in separating the duodenal ulcer from the non-duodenal ulcer population. Surgeons, like Dragstedt, are apt to see an ulcer population selected for basal hypersecretion, especially since basal hypersecretion is one of their criteria for vagotomy. Control groups would not be so selected, and would contain a lower per cent of basal hypersecretors. As shown in the figure which relates basal secretion to basal/peak ratio, a comparison of two such groups would lead to the conclusion that duodenal ulcer patients have a larger basal secretory drive than normal subjects. A study of unselected patients with duodenal ulcer would still show a tendency in this direction, since on average basal secretion is higher in duodenal ulcer patients than in carefully matched controls, but the differences would be less striking and probably not statistically significant.