Progress report

The pathophysiology of duodenal ulceration

That duodenal ulcer is in some way an abnormal reaction of the duodenal mucosa to acid and pepsin is the hypothesis which underlies most current views of the pathophysiological basis of duodenal ulceration and most current medical and surgical attempts at treatment. The hypothesis is accepted as a foundation for the present discussion, because the secretion of acid and pepsin by the stomach appears to be necessary for the development of duodenal ulceration, although it has not yet been proven that the exocrine secretions of the stomach are solely responsible for the pathogenesis of chronic duodenal ulcers. It is, of course, not permissible to conclude that disordered secretion of gastric juice is the cause of the ulceration from the fact that secretion of acid and pepsin is necessary for the formation of duodenal ulcer and, in any case, abnormal secretion of acid and pepsin is not demonstrable in all patients with duodenal ulcer.

The information available at present about the pathophysiology of duodenal ulceration will be analysed in terms of answers to a series of questions.

1 Is Ulceration of the Duodenum Associated with the Presence of Excessive Amounts of Acid and Pepsin in the Duodenal Bulb or Are Normal Quantities of Acid and Pepsin Producing a Pathological Reaction in an Abnormal Mucosa?

Nothing is known about the amounts of acid present in, or passing through, the duodenal bulb during the course of more than a few hours in any individual. The pH and concentration of acid in the intraluminal contents of the bulb have been measured by periodic sampling or with pH probes in studies of short duration. The studies have given conflicting results, because values derived from sampling have not matched simultaneous probe readings and for technical reasons associated with the design of the probes. More important difficulties have arisen from the need to localize the position of the tube or probe accurately, since there are very marked differences in the quantitative gradients of acid across, as well as along, the lumen of the upper duodenum. The pH of the mucosa is usually near-neutral whatever the intraluminal pH, so that there are radial gradients which are important under static basal conditions and become even more significant under the kinetic circumstances of the flow of intraluminal contents.

There are also very marked gradients of acid concentration along the duodenum. At the end of the last century, Bayliss and Starling pointed out that the first few centimetres of the duodenum differed functionally from the remainder of the duodenum and small intestine. One of the differences under steady, basal conditions consists of a steep intraluminal pH gradient, so that

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the contents of the duodenal bulb may be very acid, while the luminal contents of the descending duodenum have a pH which is nearly neutral. In this connexion, it is worth noting that the pH of water is 6.8 at 37°C. The pH is less in the presence of dissolved carbon dioxide, so that a pH of about 4.5 develops in water equilibrated with a PCO₂ of 40 mm Hg. The near neutral pH in the descending duodenum implies the presence of intraluminal bicarbonate.

Morton first noted that after a meal the contents of the duodenal bulb were more acid than normal in patients with duodenal ulcer. More detailed studies have confirmed the finding of greater acid concentration or more prolonged lowering of the pH of the luminal contents of the proximal duodenum in duodenal ulcer, both in the ‘basal’ state and after meals and during stimulation. On the other hand, the pH of the proximal duodenum was found to be not significantly different from normal in a group of patients with duodenal ulcer selected specifically because their acid-secreting capacities were normal.

One of the principal reasons why controversy and inconsistent results are to be expected in all studies of duodenal ulcer results from the difficulty in defining ‘duodenal ulcer’ and ‘normal’. It is relatively easy to define duodenal ulcer, since the presence of an ulcer can be confirmed endoscopically, radiologically, or by laparotomy. However, it is worth emphasizing that the presence of an ulcer in the duodenum does not exclude heterogeneity of the underlying pathophysiological disturbances, since a breach of the duodenal mucosa must manifest as ulceration, whatever the cause. The definition of normal is much more difficult, since no study has been reported in which all normal control subjects have been investigated endoscopically. More important, absence of overt ulceration does not necessarily imply a physiologically ‘normal’ upper alimentary tract, since some, or perhaps even all, patients with duodenal ulcer have a morphologically normal duodenal mucosa before the appearance of ulceration. It is probable, therefore, that a variable proportion of subjects who are classified as normal for the purpose of comparative investigation have one or other ‘duodenal ulcer diatheses’.

Very little is known about the significance of the secretion and activity of pepsin in the pathogenesis of duodenal ulceration, although it has been suggested that relatively more pepsin is secreted during acute clinical exacerbations of duodenal ulcer. However, the average concentration of pepsin in the gastric juice of patients with duodenal ulcer is similar to normal, both in absolute terms and in relation to acid, under basal conditions and during stimulation, so that the output of pepsin parallels the output of acid. It seems probable, therefore, that the presence of acid anywhere in the alimentary tract also signifies the presence of pepsin. The assumption requires experimental testing and quantitative evaluation, particularly in view of the possible implications for the therapeutic use of antipeptic agents.

In summary, the data available at present indicate that while there is more acid in the proximal duodenum of many patients with duodenal ulcer than in normal subjects, the duodenal concentration of acid is not invariably or always abnormal in these patients. More information is required about the changes in acid (and pepsin) content of the duodenum both in response to meals and between meals in health and disease, particularly in the form of long-term studies, in order to provide quantitative data about the degree
The pathophysiology of duodenal ulceration

and duration of exposure of the duodenal mucosa to abnormal amounts of acid, so that the relevance of duodenal bulb pH to the pathogenesis of ulceration may be properly assessed.

2 Is There Too Much Acid in the Duodenal Bulb because the Stomach of Patients with Duodenal Ulcer Secretes Too Much Acid?

Abnormal gastric hypersecretion in patients with duodenal ulcer has been so well and repeatedly documented that it has assumed a large and perhaps unsatisfactorily predominant role in the postulated pathophysiology of the duodenal ulceration. Two types of hypersecretion are usually distinguished and occur together, or separately, so that the underlying disturbances of function may be similar, or different. In some patients with duodenal ulcer, the hypersecretion appears to be 'spontaneous', since there is no obvious stimulus to secretion during the night or in the fasting state (except the mechanical effects of a tube in the stomach). The more commonly demonstrated, because more commonly measured, sort of hypersecretion represents an excessive secretory response to food or to exogenous secretory stimulants. Both types of hypersecretion involve the production of abnormally large volumes of gastric juice, containing normal concentrations of acid.

The gastric hypersecretion of patients with duodenal ulcer is statistical, in the sense that the average secretory response of patients with duodenal ulcer is greater than the average response of normal control subjects under the conditions of any particular study. The proportion of patients with duodenal ulcer whose secretory response exceeds that of all normal subjects depends partly on the secretory stimulant and has ranged from as little as 16% with ametazol to 82% with caffeine, in different groups of subjects. Comparable responses to different types of secretory stimulants within the same groups of 'normal' subjects and patients with duodenal ulcer are not available.

While it is certain, therefore, that some patients with duodenal ulcer can and do secrete more gastric juice than normal, it is also clear that a significant proportion of patients with duodenal ulcer do not differ from the 'normal' control population in gastric secretory capacity or behaviour. Hypersecretion cannot, of course, occur if the parietal cells are not functioning normally because the gastric mucosa is diseased. Functional 'gastritis', if present, may reflect the pathophysiological process underlying the duodenal ulceration or may be aetiologically quite independent, since gastritis occurs frequently in asymptomatic normal subjects and may then 'distort' the patterns of pathophysiological dysfunction associated with the duodenal ulceration. Gastritis of lesser or greater severity occurs in patients with duodenal ulcer and although the functional contribution of antral or fundic gastritis to the clinical and pathophysiological aspects of duodenal ulceration has not been studied, it has been shown that impairment of acid secretory capacity is related to the degree of fundic gastritis.

No information is available at present about the aetiological significance of gastric hypersecretion in duodenal ulcer. Thus, it is not yet clear whether the hypersecretion, when present, is the cause of the duodenal ulceration or is merely one (easily detected) facet of the pathophysiological disturbances underlying the ulceration. Conversely, it has even been suggested that the
gastric hypersecretion may be the consequence of the duodenal ulceration. For example, it has been reported that gastric secretion in patients with duodenal ulcer increases with the duration of the disease\textsuperscript{41, 42, 67} and with the presence of pyloric stenosis\textsuperscript{41, 67}. Neither view has yet been accepted because the evidence is contradictory\textsuperscript{45, 68}. Indeed, it has been shown that there is increase in the non-acid secreting mucosa of the stomach in patients with pyloric stenosis\textsuperscript{69}. Moreover, neither duration of disease nor obstruction to gastric outflow can explain the very high acid secretion which characterizes the youngest age groups of patients with duodenal ulcer\textsuperscript{70, 53, 6, 68} and it has also been suggested that high gastric secretory response may predispose to gastric retention or 'pyloric stenosis'\textsuperscript{71}.

Experimental studies in animals have demonstrated that gastric hypersecretion is associated with a high incidence of small intestinal ulceration\textsuperscript{72, 73, 74, 75, 76, 77, 78, 79}. Similarly, in man excessive amounts of gastric juice in the duodenum produce severe damage to the duodenal mucosa\textsuperscript{80, 81, 82, 83, 84} while in patients with the Zollinger-Ellison syndrome and in patients with chronic renal failure\textsuperscript{85} the more or less continuous gastric hypersecretion is associated with a high incidence of duodenal ulceration. The factors which determine the duration and level of duodenal exposure to acid that are necessary to produce human duodenal ulceration are not known.

In summary, current evidence from studies with exogenous stimulants indicates that a proportion of patients with duodenal ulcer can secrete more acid than normal. Considerable evidence is also available that many patients with duodenal ulcer do secrete more acid than normal between meals and probably also in response to food, although the latter facet of gastric secretion in patients with duodenal ulcer requires further detailed study, in view of its complexity and importance.

The relationship of the increased gastric secretory capacity to the pathogenesis of duodenal ulceration is still controversial, particularly because there are insufficient prospective long-term studies of gastric secretory capacity to permit correlation with the natural history of the disease. It is therefore still not clear whether excessive secretion of acid, when present, is the cause or the result or bears an even more complex relationship to the duodenal ulceration.

3 What is the Cause of the Gastric Hypersecretion in Duodenal Ulcer?

The currently most popular hypothesis postulates that gastric hypersecretion in patients with duodenal ulcer is due to normal or abnormal secretion by an abnormally large number of gastric secretory cells—specifically parietal cells, since chief cells have not usually been studied. Cox\textsuperscript{86} found, at necropsy, that many patients with duodenal ulcer had very large stomachs with very thick walls and many parietal cells. However, Cox's data show that although there is a preponderance of large stomachs among subjects with duodenal ulcer, the overlap with stomachs of 'normal' individuals (without duodenal ulcers) is complete. The hypothesis that the increased secretion of acid in patients with duodenal ulcer was due to an increased 'parietal cell mass' was supported by the studies of Card and Marks\textsuperscript{87}, who derived a highly significant correlation between the number of parietal cells and acid output by relating the difference between pre- and postoperative acid output to the number of parietal cells removed during gastrectomy. However, the basis of Card and Marks' com-
putation is unsatisfactory, since antrectomy reduces the secretory responsiveness of human parietal cells so that postantrectomy gastric acid output is markedly less than preoperative, even if no parietal cells are resected\(^8\). A number of subsequent studies\(^9, 10, 11, 12, 13\) have assessed the relationship between the number of parietal cells and acid secretory capacity. Unfortunately, most have been concerned with measurement of mucosal thickness and density of parietal cells, rather than total numbers of parietal cells, so that total parietal cell mass has not been measured. When acid secretion has been related to parietal cell mass after total gastrectomy, no correlation has been found\(^5\).

The postulated causes of the (hypothesized) ‘hyperplasia’ of the parietal cells in duodenal ulcer range from a primary genetic disorder to secondary causes, such as work hypertrophy and excessive trophic stimulation. The influence of hereditary factors in duodenal ulceration has been inferred from clinical studies of families\(^6, 7, 8, 9, 10\) but has not been investigated from the point of view of parietal cell hyperplasia. ‘Work hypertrophy’ of the stomach has been postulated on the basis of the observation that acid-secretory capacity is correlated with the duration of symptoms\(^11, 12\) although the converse relationship—that high acid-secretory capacity determines prolonged clinical course—has not been excluded. Work hypertrophy has also been put forward as the cause of the gastric hypersecretion of patients with pyloric stenosis\(^13, 14\) since gastric hypertrophy has been demonstrated after obstruction of the gastric outlet in rats\(^15\).

The pathogenesis of parietal cell hyperplasia has also been hypothesized to result from the trophic stimulus provided by excessive neural (vagal) activity or by excessive amounts of circulating gastrin. Abnormally high levels of gastrin have been noted in patients with duodenal ulcer (see below) and attributed to excessive antral release of gastrin, secondary to excessive vagal ‘tone’ or to prolonged antral stimulation by food, particularly when emptying of food from the stomach is retarded\(^16\). Gastrin has been shown to induce parietal cell hyperplasia in rats\(^17, 18\) but no experimental information is available about the effect of gastrin on the cellular kinetics of the human stomach. The gastric mucosa has been reported to be grossly hypertrophied in patients with the Zollinger-Ellison syndrome\(^19\) and it seems possible that the hypertrophy is the gastric mucosal response to the very high levels of circulating gastrin\(^20\) in these patients. However, no evidence has yet been presented that the high blood levels of gastrin precede and are causally related to the gastric mucosal changes. Indeed, the converse mechanism—gastric hyperplasia resulting in secondary (and tertiary) hyperplasia (and neoplasia) of the gastrin-producing cells—must also be considered, as well as the possibility that the hyperplasia of the gastric mucosal and gastrin-producing cells are manifestations of the underlying pathophysiological process. The matter could be easily resolved by prospective studies of kindreds with type I multiple endocrine adenomatosis\(^21\).

In summary, current evidence strongly suggests that increased numbers of parietal cells are responsible for the increased gastric acid secretory capacity of many patients with duodenal ulcer. However, in the author’s opinion, the evidence for ‘parietal cell hyperplasia’ is by no means conclusive and needs to be thoroughly reassessed. No evidence is yet available to account for the presence of the postulated ‘parietal cell hyperplasia’. The problems of the interrelationship of gastric hypersecretion, size of parietal cell population,
and duodenal ulceration have not yet been resolved and it is not yet possible
to decide which is the primary phenomenon and which is secondary.

4 Could the Increased Secretion of Acid in Patients with Duodenal Ulcer Occur with a Normal ‘Parietal Cell Mass’?

Recent studies have indicated that the gastric acid-secreting cells may be more
sensitive than normal to stimuli in patients with duodenal ulcer. The hypo-
thesis was put forward, originally, in connexion with the excessive ‘spon-
aneous’ secretion of acid in the basal, unstimulated state in patients with
duodenal ulcer. However, many patients with duodenal ulcer do not secrete
excessively in the basal state\textsuperscript{50,52} and basal secretory levels in duodenal ulcer
range from barely detectable to more than half the total secretory capacity,
presumably reflecting the heterogeneity of the underlying pathophysiology. It
was subsequently considered that the parietal cells of patients with duodenal
ulcer did not show increased sensitivity to stimulants, since normal doses of
stimulants were required to elicit half-maximal\textsuperscript{41} and maximal\textsuperscript{107} secretory
responses. On the other hand, recent investigation of the dose-response
characteristics to stimulants of the parietal cells of patients with duodenal
ulcer has indicated that the dose of pentagastrin required to elicit half-
maximal secretory rates is significantly less in patients with duodenal ulcer
than in normal subjects\textsuperscript{108}. The studies have not been published in full, but
confirmation and correlation with ‘spontaneous’ secretion will clearly be very
important.

What might be the mechanisms underlying the ‘hypersensitivity’ of the
parietal cells of patients with duodenal ulcer? It is theoretically possible to
explain gastric hypersecretion in terms of normal numbers of parietal cells
by postulating that the cells react more vigorously and more continuously
than normal to stimuli—more vigorously, to explain the increased secretory
capacity, and more continuously, to account for ‘spontaneous’ or ‘basal’
secretion. The hypersecretion represented by increased secretory capacity
might be due either to normal parietal cells responding to the interaction of
multiple abnormal stimuli or could be due to abnormally excessive ‘reactivity’
of the individual parietal cells, while the basal type of hypersecretion, in the
presence of normal secretory capacity, would be due to inappropriate
stimulation by normal stimuli or abnormal gastric secretory stimulants. The
possible stimulatory effects of excessive neural activity or increased circu-
lating gastrin are discussed below. Gastric stimulatory hormones of small
intestinal origin (other than gastrin) have been postulated and it is known that
cholecystokinin-pancreozymin (CCK-PZ)\textsuperscript{109,110} and under exceptional cir-
cumstances (in the Zollinger-Ellison syndrome) secretin\textsuperscript{111,112,113} stimulate
gastric acid secretion, while secretin normally stimulates pepsin secretion,
at least under experimental circumstances\textsuperscript{109,114,115,116}. Other stimulatory
hormones originating in the small intestine may still be discovered, like the
agent responsible for stimulating acid secretion in patients with portocaval
shunts\textsuperscript{117,118,119,120}. Excessive background activity of stimulatory mech-
anisms, if present, might be responsible for parietal cell hypersensitivity and
apparently spontaneous secretion, as well as increased gastric secretory
capacity. On the other hand, both types of hypersecretion could indicate
defective inhibition of the secretory cells.

There is not yet any evidence for these largely speculative theoretical
The pathophysiology of duodenal ulceration

suggestions. While augmentation of the maximal gastric secretory response can be readily demonstrated in dogs by using combinations of stimulants such augmentation (or potentiation) has not yet been established in man although the matter is controversial.

Many years ago, Dragstedt postulated that the gastric hypersecretion of patients with duodenal ulcer was due to increased vagal drive, on the grounds that vagotomy reduced the acid secretory response of the stomach and cured duodenal ulceration. It was not clear whether the increased vagal drive was promoting 'hyperreactivity' or hyperplasia of the parietal cells or increasing the antral release of gastrin, or a combination of these mechanisms. In any case, the original assumptions underlying the hypothesis of increased vagal drive are faulty, since it is not permissible to infer that intact vagal innervation is responsible for gastric hypersecretion in duodenal ulcer from the fact that vagal secretion reduces gastric secretion.

Support for the hypothesis of 'increased vagal drive' has been indirect and inferred from a number of separate (and controversial) observations. In the first place, increased vagal drive of the unstimulated stomach of patients with duodenal ulceration was thought to explain the occurrence of high ratios of basal to maximally stimulated gastric acid secretion but later studies indicated that in many patients with duodenal ulcer the increased basal secretion was strictly proportional to the increased maximal secretory capacity and was therefore assumed to reflect (hypothetical) increase in parietal cell mass, while in other patients, basal secretion was not greater than normal, despite increased gastric secretory capacity.

It has also been suggested that the increased secretion of pepsin, relative to acid, distinguishes hypersecretion due to 'predominant vagal stimulation' from that due to 'predominant gastrin stimulation', in which the ratio of pepsin to acid is much lower. The hypothesis is based on the observation that the ratio of pepsin to acid is higher after insulin (assumed to stimulate gastric secretion by vagal mechanisms) than after histamine or gastrin. It was noted that the basal gastric secretion of pepsin, relative to acid, was as great as in response to insulin in some patients with duodenal ulcer and the basal gastric hypersecretion was therefore assumed to reflect direct vagal stimulation of the parietal and chief cells.

The validity of the hypothesis has not yet been confirmed. It has been shown that the proportion of pepsin to acid increases with increasing degrees of stimulation with histamine or gastrin in man so that the low ratios in the Zollinger-Ellison syndrome may not represent a hypergastrinaemic ratio, but some disturbance of pepsin secretion, relative to acid, in this disease. It has also been shown that the ratio of pepsin to acid in basal gastric secretion is markedly variable and that the ratio is not different from normal in patients with duodenal ulcer, whether insulin or histamine are used as gastric stimulants. Detailed studies of the 'vagal responsiveness' of patients with duodenal ulcer are therefore required, particularly since vagotomy produces no change in basal pepsin secretion.

The hypothesis of abnormal vagal drive has also recently been invoked to explain both the abnormal antral release of gastrin in patients with duodenal ulcer and the abnormalities of release of small intestinal hormones (see below).

Although much attention has been devoted to the role of vagal innervation of the stomach in duodenal ulcer, very little consideration has been given to...
the role of the intramural nerves in the aetiology of the gastric hypersecretion. The cholinergic nerves of the intramural plexuses can affect the secretory response of the stomach directly, both in animals and man\textsuperscript{137,138,139} and also by reflex release of gastrin\textsuperscript{140}. Since it seems possible that the mechanical and chemical effects of food may produce abnormal reflex cholinergic activation of the acid-secreting and gastrin-releasing cells in some patients with duodenal ulcer, the functional inter-relationships between gastric distension, emptying, and the reflex stimulation of gastric secretion require further study\textsuperscript{141}. Whether other autonomic nerves (adrenergic, purinergic) are involved in the hypersecretion of duodenal ulcer, either positively through the mechanism of increased drive or negatively by failure to inhibit, is not known.

An abnormally great antral, probably hormonal, drive of the parietal cells has been postulated in patients with duodenal ulcer, particularly when vagotomy has failed to reduce acid secretion\textsuperscript{142}. Excessive, or abnormal, gastric secretory responses to infusion of meat extract into the stomach\textsuperscript{143,144,136} or mechanical distension of the antrum\textsuperscript{138} have been thought to indicate abnormal antral function in patients with duodenal ulcer, although the influence of the chemical stimulants (meat extract) has not been restricted to contact with the antral mucosa (but has necessarily also involved contact with fundic and duodenal mucosa). It has not been determined whether antral stimuli influence human gastric secretion principally through the release of gastrin or by local (short) neural reflexes. The involvement of short neural reflexes has not been studied, although the antrum is the receptor site of neural, as well as neurohormonal, reflexes, at least in animals\textsuperscript{145,146}.

A postulated morphological basis for potentially abnormal antral activity is provided by the hypothesis that the antra of patients with duodenal ulcer contain excessive numbers of G cells (which are thought to produce gastrin). The hypothesis is based on morphological and functional studies. Histological estimates have been interpreted as showing abnormally large numbers of G cells in patients with duodenal ulcer, but the estimates have only been based on measurement of the density of the G cell population in unit area of mucosa and no counts of the total numbers of G cells in patients with duodenal ulcer are available\textsuperscript{147,148}. In this connexion, it is worth emphasizing that in patients with duodenal ulceration, the size of the antrum ranges from smaller than normal\textsuperscript{149,150} to significantly larger, particularly in the presence of 'antritis'\textsuperscript{151}. The functional evidence for 'increased G cell mass' is based on the greater than normal rise in blood levels of gastrin after injection of insulin in patients with duodenal ulcer\textsuperscript{152,153}. However, the conclusion cannot yet be accepted in view of the complexity of the origins, forms, and fate of gastrin (see below). There have been no studies in which antral function has been correlated with antral size, nor has the gastrin content or formation and release of gastrin been related to antral size or numbers of G cells. It has been shown that the antral content of gastrin (as measured by bioassay of antral extracts) is not different from normal in duodenal ulcer patients\textsuperscript{154} but it is not yet possible to interpret content in terms of function.

In summary, it has not yet proved possible to define the cause of the gastric hypersecretion in patients with duodenal ulcer. It is not clear whether the hypersecretion is due to normal numbers of excessively sensitive secretory cells or to abnormally large numbers of secretory cells, which react normally or also with excessive sensitivity to stimuli. What seems certain is that both
fundic exocrine and antral endocrine parts of the stomach react excessively vigorously to all types of stimulation in some patients with duodenal ulcer. Hence an excessively great gastric response cannot be used as evidence for the primary abnormality of any one stimulatory mechanism, in the current state of our knowledge.

5 What is the Role of Gastrin in Duodenal Ulceration?

Abnormal function of the antrum in patients with duodenal ulcer has also been inferred from abnormal blood levels of gastrin. The majority of studies have shown that fasting levels of gastrin are normal in patients with duodenal ulcer\textsuperscript{155,156,157,158,159} but some reports have indicated that levels of gastrin may be abnormally elevated\textsuperscript{160,161}. Although the basal levels of gastrin are usually similar in normal subjects and patients with duodenal ulcer, significantly raised levels of gastrin are found in patients with duodenal ulcer after meals\textsuperscript{162,157,163,159,48,164} and during the night\textsuperscript{102}. Excessive secretion of gastrin may therefore be involved in the hypersecretory response of patients with duodenal ulcer to food.

The cause of the antral 'hyperreactivity' is not known. As an alternative to the postulated normal 'sensitivity' of an increased number of gastrin-secreting cells (G cell mass), it seems possible that normal numbers of G cells may be excessively sensitive to stimuli, perhaps like the postulated 'hypersensitivity' of the parietal cells, because the underlying functional disturbances are similar. It has also been suggested that the gastrin-releasing mechanisms are abnormally resistant to inhibition, because patients with duodenal ulcer should have lower basal levels of gastrin than normal\textsuperscript{165}, in view of the greater secretion of acid and presence of greater amounts of acid in contact with the antral mucosa.

Studies which have shown that blood levels of gastrin decrease following the introduction of acid into the stomach\textsuperscript{166,158} have been interpreted as confirming the inhibitory effect of acid on human antral gastrin release. However, the results of these studies cannot be interpreted solely in terms of the effect of intragastric acid on antral release of gastrin, since leakage of acid into the duodenum has not been prevented and it is known that secretin\textsuperscript{167,168,169,170} and glucagon\textsuperscript{171} can inhibit release of gastrin from the human antrum. Moreover, direct study has cast doubt on the importance of intraluminal acid for the regulation of antral release of gastrin in man, since it has been shown that low antral intraluminal pH does not inhibit the gastric stimulatory effect of antral distension\textsuperscript{138}. On the other hand, earlier studies had shown that antral acidification inhibited basal secretion of acid in patients with duodenal ulcer\textsuperscript{172}.

One factor which has not been taken into consideration in evaluating the dynamics of gastrin release in patients with duodenal ulcer is the frequent occurrence of antral gastritis in these patients\textsuperscript{178,174}, particularly since it has been shown that a diseased state of the antral mucosa significantly decreases the levels of gastrin in patients with gastritis\textsuperscript{175,176,177}.

The information about blood levels of gastrin has also been difficult to interpret, since it is known that multiple forms of gastrin, with differing biological potencies, may be present in the circulation\textsuperscript{178,179,180,181,182,183}. However, only preliminary reports are available about differences in the blood levels of the different gastrins in disease. For example, it has been briefly
recorded that there appear to be differences from normal in the immuno-reactivity of the gastrin circulating in patients with duodenal ulcer. It has also been suggested that the gastrin which is detectable in 'low normal' levels in patients with duodenal ulcer is a potent secretagogue, as assessed by bioassay. Additional information is required about the nature and biological activity of the circulating forms of gastrin in normal subjects and patients with duodenal ulcer, under different experimental and physiological conditions, before the data derived from early immunological studies can be interpreted.

Further difficulty in assessing the relevance of blood levels of gastrin relates to the interpretation of blood levels of gastrin solely in terms of production of gastrin. In the absence of information about the blood levels of the different forms of gastrin and their half life in patients with duodenal ulcer compared with normal, it is not possible to form conclusions about production or rates of release of 'gastrin'. Even more misleading is the tendency to refer to 'antral production of gastrin' despite the proven extra-antral origin of some of the circulating gastrin, particularly in patients with duodenal ulcer. Thus, the greater than normal levels of circulating gastrin after meals in patients with duodenal ulcer have been interpreted in terms of greater than normal 'antral excitability' or vagal drive to the gastrin-releasing cells in the patients with duodenal ulcer, although food elicits increase in circulating gastrin even after antrectomy. No information is available about the relative contributions to blood levels of gastrin of antral or extra-antral sources of gastrin in health or disease, or about potential abnormalities of disposal or degradation of gastrin.

The blood levels of gastrin are assumed to represent the magnitude of the 'gastrin drive' to the parietal cells, so that the abnormally sustained levels of circulating gastrin, throughout the day and the night, have been thought to explain the increased nocturnal acid secretion of patients with duodenal ulcer. The possibility has not been considered that the blood levels of gastrin reflect, rather than direct, the activity of the parietal cells. In this connexion, it has been shown in some patients with the Zollinger-Ellison syndrome that blood levels of gastrin may be high because the acid-secreting cells are overactive. For example, aspiration of acid from the stomach of patients with the Zollinger-Ellison syndrome has been shown to lower the blood levels of gastrin, while reintroduction of acid into the small intestine is associated with increase in gastrin levels. Similarly, total gastrectomy may reduce blood levels of gastrin in patients with the Zollinger-Ellison syndrome presumably because no acid passes into the small intestine.

In summary, it is not yet possible to interpret the data from immunoassay regarding blood levels of gastrin, in view of the lack of information about the relationship of changes in blood levels to changes in sites of origin and in rates of production, utilization, degradation, and excretion. The interpretation of alterations in blood levels of immunoreactive gastrin in patients with duodenal ulcer is further complicated by lack of information about the molecular and biological properties of the circulating gastrins.

6 Is There Too Much Acid in the Duodenum because Inhibition of Gastric Secretion is Defective in Patients with Duodenal Ulcer

Inhibition of gastric acid secretion is due either to the decrease or cessation of
gastrointestinal stimulation or may be mediated by activation of neural or hormonal inhibitory mechanisms.

Much information is available about the factors controlling antral release of gastrin in animals. It has been repeatedly shown, in experimental animals, that low pH of the luminal contents of the antrum inhibits the antral release of gastrin stimulated by neural reflexes and by chemical or mechanical stimulation of the antral mucosa. However, very little is known about the factors which control antral release of gastrin in normal human subjects or about abnormalities of control in patients with duodenal ulcer. On the basis of experiments in animals, gastric secretion is thought to be inhibited directly by neural and hormonal influences originating in the small intestine. In man, inhibition of gastric acid secretion has been noted when acid or fat is introduced into the small intestine. It has been suggested that in patients with duodenal ulcer, gastric inhibition is less than normal when acid is infused into the duodenum. Conversely, it has also been shown that duodenal acidification does not necessarily inhibit gastric acid secretion in normal subjects and that the gastric secretory response of patients with duodenal ulcer may be inhibited 'normally' or even more than normally. Indeed, in human subjects duodenal acidification appears to inhibit exogenously stimulated gastric acid secretion only if excessively large amounts of acid are introduced into the duodenum and it has been shown that no gastric inhibition results when a (normal) subject's own gastric juice is infused into his own duodenum. Gastric inhibition by acid or fat in the small intestine is usually regarded as being mediated by hormones and although acid secretion has been experimentally inhibited by hormones such as secretin, combinations of secretin plus CCK-PZ, and by glucagon, the inhibitory doses of the single hormones are very large and the inhibition produced by these hormones is unlikely to be of physiological or pathological significance, at least in the context of duodenal ulcer. While 'defective' inhibition has not yet been demonstrated, pathologically excessive inhibition of gastric acid secretion can occur in man, as shown by the reversible absence of secretory response to stimulants in the presence of chronically normal gastric mucosa in patients with 'pancreatic cholera'. The inhibition has been attributed to polypeptides, secreted by pancreatic islet cell tumours, but normally present in the small intestinal mucosa and therefore possibly normal gut hormones.

Neural mechanisms causing gastric secretory inhibition have hardly been studied in man, but the 'inhibition-rebound' form of the gastric secretory response to duodenal infusion of acid raises the possibility that purinergic nerves may be implicated in mediating the response, since a similar pattern of inhibition of the motor activity of the stomach appears to be characteristic of this type of autonomic innervation. The abolition of fat-induced inhibition of gastric secretion by vagotomy indicates that this type of inhibition may also be mediated by, or dependent on, vagal innervation of the stomach or small intestine.

Though experimental studies have not shown any convincing difference between normal subjects and patients with duodenal ulcer in their response to pharmacological activation of hypothetical duodenal inhibitory mechanisms, it has been postulated that other small intestinal inhibitory mechanisms may...
be involved in the hypersecretion associated with duodenal ulcer. Important recent experiments have indicated that in dogs\(^{228,229,230}\) (although not in cats) small intestinal inhibitors, under vagal control, continuously suppress gastric secretion. No information is available at present about the contribution of small intestinal inhibitory systems to the control of the normal physiological secretory activity of the human stomach, but since apparently impaired release of secretin and CCK-PZ from the small intestine has been demonstrated in patients with duodenal ulcer\(^{232}\) it has been speculated that impaired small intestinal inhibition of gastric secretion, under vagal control, may also be involved in the pathogenesis of the gastric hypersecretion in duodenal ulcer\(^{233}\).

In summary, there is no satisfactory evidence at present that inhibition of gastric secretion, originating in antrum or duodenum, is impaired in patients with duodenal ulcer. It is necessary to add that the foregoing judgement is based on the evidence derived from studying the experimental inhibition of basal gastric secretion or secretion evoked by exogenous stimulants. More careful analysis of the inhibition of endogenously stimulated gastric secretion\(^{234}\) may necessitate revision of the current views concerning the physiological and pathophysiological role of gastric inhibition arising in the upper alimentary tract. Currently of interest is the speculation about the inhibitory role of the small intestine on normal gastric function and the unconfirmed suggestion that small intestinal inhibition of gastric secretion may be disturbed in duodenal ulceration.

7 Is There Too Much Acid in the Duodenal Bulb because Gastric Contents Empty Too Rapidly in Patients with Duodenal Ulcer?

Information about the rate of gastric emptying in patients with duodenal ulcer has been contradictory\(^{235,47,141,236,237,238}\) but recent studies have shown that the majority of patients with duodenal ulcer empty both fluid\(^{239,71}\) and solid\(^{240,205,241,242,48}\) gastric contents abnormally rapidly. Indeed, acid in the duodenum increases the rate of emptying in many patients with duodenal ulcer\(^{71}\) while slowing emptying in normal subjects\(^{243,71}\). The mechanism of the reversal of the normal response is not known, but may be connected with the abnormally high partial pressure of carbon dioxide in the duodenum of patients with duodenal ulcer\(^{244}\) since it has been shown that a high \(P_{CO_2}\) in the duodenum increases the rate of gastric emptying\(^{245}\).

It is not clear whether the abnormality of gastric emptying precedes the morphological changes associated with duodenal ulceration or results from these changes. It has been shown, however, that the rate of gastric emptying during duodenal acidification is related to the acid-secretory capacity, so that patients with duodenal ulcer, who secrete more acid than normal in response to pentagastrin, also tend to empty more rapidly than normal\(^{71}\).

Some of the past controversy about alterations in the rate of gastric emptying in duodenal ulcer is due to pathophysiological heterogeneity. For example, in some patients with duodenal ulcer who secrete very large amounts of acid, discharge of fluid from the stomach is almost completely inhibited during duodenal perfusion with acid\(^{71}\). These patients, who have the clinical syndrome of pyloric stenosis, overreact to duodenal acidification like patients with achlorhydria\(^{239,71}\). The mechanisms of the duodenal hypersensitivity to acid are not known.
One of the results of the rapid gastric emptying in patients with duodenal ulcer is that gastric contents tend to be more acid than normal, owing to the excessively rapid loss of buffer from the stomach after meals\textsuperscript{239, 248, 48} (as well as to the abnormal persistence of acid secretion after passage of food from stomach into the small intestine in many patients with duodenal ulcer). The mucosa of the duodenal bulb is therefore exposed to abnormal amounts of unbuffered gastric juice, since the pH of the luminal contents of the duodenal bulb is related to the pH of the antral contents\textsuperscript{247, 8, 9}.

In summary, current information indicates that gastric emptying is often abnormally rapid in patients with duodenal ulcer. The abnormal gastric motility is responsible, at least in part, for the low duodenal bulb pH in these patients.

8 Is the Excessive Content of Acid in the Duodenal Bulb Due to Deficient Expulsion of Acid from the Duodenum?

Acid which is introduced into the duodenum disappears within the duodenum or is transferred out of the duodenum. The time course of the motor component of the response is rapid and the direction of movement is mainly towards the small intestine, although retropulsion, with reflux of gastric and duodenal contents into the stomach may be very important both under physiological\textsuperscript{248, 249} and pathological\textsuperscript{250, 251, 252, 253, 254, 255, 256} circumstances. Little quantitative information is available about the alterations in caudal propulsive motility in duodenal ulcer\textsuperscript{257, 258, 23}. Increase in the rate of flow of gastric contents through the duodenum is presumably related to a combination of the increased volume of gastric juice secreted by many patients with duodenal ulcer and to the excessively rapid emptying of the stomach. No systematic examination of the role of these two factors has yet been made. The consequent delivery of acid into the jejunum appears to be greater in patients with duodenal ulcer than in normal subjects\textsuperscript{259, 2, 258, 260}, although quantitative studies are not yet available and the relative contributions of excessive input and defective removal have not been analysed.

There is also indirect evidence for increased retrograde duodenal motor activity in duodenal ulcer, since a considerable proportion of patients with duodenal ulcer manifest an abnormal degree of duodeno-gastric reflux under experimental conditions when there is acid in the duodenum\textsuperscript{256} and in response to secretin\textsuperscript{256}. However, despite vigorous pro- and retropulsion of acid, the motor activity is not sufficient to remove the excess of acid from the duodenal bulb of many patients with duodenal ulcer. Differences in motility between the upper and post-ampullary duodenum have been demonstrated\textsuperscript{7} so that differences in pH between these two parts of the duodenum may, in part, reflect normal differences in motor pattern, perhaps aggravated by primary, or secondary, abnormality of motor function of the proximal duodenum\textsuperscript{216} so that 'stasis' of bulb contents results, or alkaline secretions fail to reflux into the bulb\textsuperscript{258}.

In summary, very little information is available at present about patterns of duodenal motility in health, so that it is not possible to assess whether significant abnormalities of motility occur in patients with duodenal ulceration.
9  Is the Excessive Acid in the Duodenal Bulb Due to Defective Removal within the Duodenum?

The most important mechanism for removing acid (and inactivating pepsin) within the duodenum consists of the secretion of sodium bicarbonate into the duodenal lumen by the pancreas, hepato-biliary system, and duodenal mucosa. It has been shown that patients with duodenal ulcer can secrete as much as or more than normal amounts of bicarbonate in response to exogenous secretin. However, despite their normal bicarbonate secretory capacity, many patients with duodenal ulcer do not respond to the experimental stimulus of acid in either duodenum or jejunum by secreting as much bicarbonate as normal subjects. The degree of impairment of the bicarbonate-secretory response to small intestinal acidification is related to the magnitude of the gastric secretory response to stimulants and the impaired response appears to improve after vagotomy.

It seems, therefore, that patients with duodenal ulcer have a small intestinal mucosa which does not respond normally to acid, either because the acid-sensing receptors are abnormal or because the neural or hormonal effector mechanisms are not functioning normally. It is interesting to note that impaired release of small intestinal hormones in patients with duodenal ulcer has been postulated in a quite different context because the response to oral glucose loads is abnormal in these patients. Moreover, the markedly increased blood levels of enteric glucagon in response to glucose after vagotomy in patients with duodenal ulcer indicate that glucagon release from the intestine is inhibited by intact vagal innervation, perhaps in a manner similar to the suggested vagal suppression of the release of secretin and CCK-PZ in response to intestinal acidification and to the release of gastrin in response to food in patients with duodenal ulcer.

In summary, it seems very likely that the secretion of bicarbonate into the duodenum is abnormal in patients with duodenal ulcer, not because the bicarbonate-secretory capacity is impaired, but because the bicarbonate response to intestinal intraluminal acid is abnormal. It is not clear at the moment whether the postulated small intestinal functional defect is primarily related to the pathophysiological processes underlying duodenal ulceration or whether the unresponsiveness to acid is secondary to the continued exposure of the small intestine to excessive amounts of acid. The presence of small intestinal dysfunction in young patients with short histories of duodenal ulceration suggests that the defect is primary, but prospective family studies are required to clarify the matter.

10  Is There Some Abnormality of the Duodenal Mucosa in Patients with Duodenal Ulceration?

Disruption of the mucosal barrier due to abnormalities of either the duodenal mucosa, or the mechanisms ‘protecting’ the mucosa against acid and pepsin, has been invoked to explain ulceration of the duodenum in patients whose duodenal bulb does not contain abnormal amounts of acid (at least during the period of study). No evidence is available that mucosal abnormalities predispose to duodenal ulceration since no prospective morphological or functional studies of the duodenal mucosa have been undertaken in high-risk subjects. The mucosal abnormalities which have been described in patients...
with established ulceration\textsuperscript{272, 273, 2774, 275} do not provide any information about the pre-ulcerative state of the mucosa.

‘Chronic duodenitis’ has been considered to represent a chronological antecedent of duodenal ulceration\textsuperscript{80} but no sequential histological or functional studies have been presented to substantiate the suggestion. It is particularly difficult to assess the significance of the relationship of duodenitis to duodenal ulceration because it seems possible that ‘duodenitis’ represents the duodenal mucosal reaction to different types of injury or disease. Thus, in addition to the duodenitis associated with gastric hypersecretion, it has been noted that chronic duodenitis is common in patients with gastric secretory impairment\textsuperscript{278}. In the latter patients, gastritis and duodenitis may have the same underlying pathophysiological basis, and it seems possible that the mucosal disease may predispose to ulceration of the stomach or duodenum, respectively. In this connexion, patients with duodenal ulcer have been described with functional abnormalities similar to those found in patients with gastric ulcer, such as normal or impaired acid-secretory responses to stimulants and normal bicarbonate-secretory responses to small intestinal acidification, but abnormal persistence of bile discharge in the presence of intraluminal acid\textsuperscript{267}. It has been suggested that such patients may be suffering from ‘gastric ulcers of the duodenum’\textsuperscript{287} on the postulated grounds that mucosal damage in the duodenum is produced by the combined action of bile salts and acid, as in the stomach\textsuperscript{277, 252, 278}. Conditions for the latter type of duodenal ulceration are not normally found in the duodenum, since intraluminal acid (and secretin) rapidly inhibits the discharge of bile into the duodenum\textsuperscript{287}.

Abnormalities of the mucosal protective mechanisms, in the form of a defective layer of mucus, have also been sought in patients with duodenal ulceration\textsuperscript{279, 260, 261}. It has been considered that the high incidence of blood group O with non-secretor status in patients with duodenal ulcer\textsuperscript{98, 262} indirectly reflects some abnormality of mucus. More specific differences between the chemical\textsuperscript{263} and physical\textsuperscript{264} composition of gastric mucus of normal subjects and patients with duodenal ulcer have also been described. However, the relevance of the blood group secretor status and the different composition of gastric mucus to the pathophysiology of duodenal ulceration has not been established, and no significant advance has been made for many years in our knowledge regarding the relationship between mucus and ‘protection’ of the duodenal mucosa against acid and pepsin.

In summary, there is only very insubstantial evidence at present that defective resistance of the duodenal mucosa is involved in the pathogenesis of duodenal ulceration. This facet of the pathophysiology of duodenal ulceration requires further study, because in many patients with duodenal ulcer the duodenal bulbar mucosa does not appear to be exposed to the potentially injurious effects of excessive amounts of gastric juice. It seems, rather, that the duodenal ulceration results during exposure of the duodenal mucosa to normal, and sometimes less than normal, amounts of gastric juice.

11 Conclusion

It can be regarded as established that the duodenal bulbar mucosa of many patients with duodenal ulcer is exposed to excessive amounts of acid. The factors which have been shown to contribute to the excessive acid content of
the bulb include excessive and inappropriate gastric secretion of acid; excessively rapid emptying of the gastric contents and defective buffering of acid within the duodenum.

It is less certainly known what proportion of patients with duodenal ulcer suffer from the different pathophysiological disturbances or what the interrelationships of the different disorders of function are. Very little is known about the mechanisms underlying the dysfunctions, although some hypotheses, such as 'increased parietal cell mass' or 'increased vagal (or gastrin) drive', have achieved popularity without sufficiently rigorous experimental support.

This review has sought to highlight our currently insufficient knowledge and represents a plea for more research into the pathophysiological basis of duodenal ulceration.

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