Progress report

Reactions to acid in the intestine in health and disease

When acid passes from the stomach into the duodenum, a series of physiological events follows, which is presumed to be causally related to the change in the contents of the small intestine. Reaction to acid in the small intestine was recognized about 150 years ago but subsequent experimental analysis was slow and caused considerable confusion. Recently, a great deal of new information has become available, particularly from the experimental use of conscious animals and purified, specific gastrointestinal hormones.

There has also been a change in emphasis, from the classical investigation of isolated reactions of individual organs, to a more detailed study of the integrated reactions of the alimentary tract to acid, as a result of which it has been found, for example, that acid elicits different patterns of reaction from different parts of the small intestine, that the response to acid involves important secretory and motor interactions, and that there are significant species differences in the reactions to acid. Recognition of these and similar patterns has helped to eliminate important sources of disagreement in earlier studies.

The present review starts with a summary of the reactions to acid manifest by the individual components of the alimentary system (Appendix), in order to provide a familiar background for the subsequent discussion. The sections which follow discuss the current views concerning the nature of the stimulus provided by acid and how that stimulus is thought to elicit responses from the alimentary tract and its accessory glands. The result is a set of integrated reactions, one of the effects of which is that acid disappears from the small-intestinal lumen. The review ends with an indication of the possible functional significance of the processes which are triggered off by entry of acid into the small intestine and describes how human disease may result in, and be caused by, disturbances of parts or the whole of the integrated reaction to acid.

Reactions to Acid

EXOCRINE PANCREAS

Earlier studies in animals showed that acid in the small intestine elicited the secretion of large volumes of pancreatic juice with high bicarbonate and low enzyme concentrations. Particular emphasis was given to the duodenum as the site of reaction to acid, since it was shown that pancreatic secretion was greatest when acid was introduced into the duodenum and became progressively smaller from lower levels of the small intestine. Recent studies in man have shown that the earlier views must be modified, because duodenal acidification is quantitatively less important in evoking pancreatic secretion than acidification of the small intestine beyond the ligament of Treitz. Similarly, in dogs it has recently been demonstrated that the duodenum and jejunum do not differ in the capacity to stimulate...
pancreatic secretion, so that the length of small intestine exposed to acid determines the pancreatic exocrine response. An unresolved controversy concerns the reaction to acid in the duodenal bulb, since it has recently been suggested that pancreatic exocrine secretion is not stimulated by exposing the first part of the duodenum to acid. In addition to the recent change in emphasis regarding the locus of action of acid, it has been shown that the pancreatic response to small-intestinal acid is not as exclusively restricted to the secretion of bicarbonate and water as suggested by the earlier studies. When large amounts of acid are infused into the duodenum of dogs and allowed to flow into the jejunum, pancreatic secretion of enzymes is stimulated. In man, the secretion of pancreatic enzymes as well as bicarbonate is stimulated when acid is introduced into the jejunum.

Pancreatic exocrine secretion may also be inhibited, particularly when large amounts of acid are introduced into the duodenum of dogs and man.

**ENDOCRINE PANCREAS**

One of the most significant recent developments in our knowledge of the physiology of the small intestine is the demonstration of complex enterodocrine interactions. For example, it has been shown that acid in the small intestine can stimulate pancreatic endocrine, as well as exocrine secretion. However, the interrelationships between acid, small intestine, and endocrine pancreas are still not completely understood and the functional significance of these observations cannot therefore be satisfactorily evaluated.

**BILIARY SYSTEM**

Although acid in the small intestine has been known to stimulate the flow of bile into the duodenum for many years, little is known about the quantitative importance of the hepatobiliary response to acid, either in animals or man. The only information is indirect and has been inferred from the complex response of the isolated biliary system to food or to parenteral hormones. These findings cannot be interpreted in terms of functional response to acid, since bile flow from the biliary tract into the duodenum is an integrated response comprising choleretic (stimulation of the secretion of bile), choledochoduodenal junctions, and of the duodenal wall. The net flow of bile into the duodenum is the resultant of these reactions, which may be activated independently and antagonistically. Both isolated choleretic and cholecystokinetic responses to small intestinal acid have been recorded in man and animals (Appendix), but there is no information about their quantitative interactions or the role played by changes in the motor activity of the biliary system. The importance of the reactions of the biliary system to acid is emphasized by the recent studies in man, which have shown that small-intestinal acidification may result in the secretion of large amounts of bile into the duodenum, but that this effect is much more frequently observed in response to jejunal than to duodenal acidification so that the juice secreted in response to acid in the duodenum is often free from bile pigment, presumably because cholecystokinesis is inhibited.
STOMACH

Ivy and McIlvain\textsuperscript{29} noted that acid in loops of canine duodenum and upper jejunum stimulated the gastric secretion of acid, although there was a long latent period between the introduction of acid and the effect on the stomach. The stimulatory effect of intestinal acid on gastric secretion has been confirmed frequently (Appendix), although recent studies have suggested that at least three different phenomena are involved. In dogs, perfusion with acid of some parts of the small intestine, particularly the distal duodenum\textsuperscript{30,31} and jejunum\textsuperscript{32}, elicits rapid increase in the secretion of acid. It has also been shown both in animals\textsuperscript{32,34,35,36} and man\textsuperscript{37,38} that increased gastric secretion of acid follows a period of inhibition of secretion, providing the inhibitory reaction to acid in the duodenum or jejunum is not too severe or prolonged. Acid in the duodenum also stimulates the secretion of pepsin in many species (dogs\textsuperscript{33,39,40}, cats\textsuperscript{41}, man\textsuperscript{38,42}) even when acid secretion is unaltered or inhibited. The functional significance of the gastric acid and pepsin secretory responses to intestinal acid is not yet known.

Many studies (Appendix) have shown that acid in the proximal duodenum inhibits gastric secretion of acid, but the functional importance of this effect is still not clear, particularly because there appear to be significant species differences in the degree of inhibition. Acid in the proximal duodenum inhibits gastric acid secretion most easily in dogs\textsuperscript{30,32,43,44,45}, while the degree of inhibition is variable and tends to be less marked in cats\textsuperscript{41,46} and man\textsuperscript{37,38,47,48}. In human subjects, the pattern of the gastric secretory responses during duodenal acidification is complex and it may be difficult to demonstrate an overall inhibitory effect, unless acidification is severe or prolonged\textsuperscript{38}.

Acid in the duodenum inhibits the emptying of gastric contents into the duodenum irrespective of the effect on acid secretion. The factors involved in the inhibition of gastric emptying by acid in the duodenum have been well defined in man by the detailed studies of Hunt and his colleagues\textsuperscript{49,49a,50}. The retention of gastric contents is related to the amount of acid introduced into the duodenum and is secondary to relaxation of the stomach\textsuperscript{51}, particularly antrum, as well as of the proximal duodenum\textsuperscript{52,53} with marked inhibition of motor activity\textsuperscript{53}, while there is associated increase in the motor activity of the distal duodenum\textsuperscript{54}, so that the stomach does not empty despite simultaneous relaxation of the pylorus\textsuperscript{55}.

SMALL INTESTINE

Acid elicits net secretion of fluid from the small intestine, with composition similar to extracellular fluid. In the duodenum, acid also stimulates the secretion of Brunner's glands in animals\textsuperscript{55}, although quantitatively the secretion of water and electrolytes from this source is unimportant compared with the pancreatic and biliary responses\textsuperscript{56}. In man, acid can be shown to stimulate the secretion of fluid into the duodenum of patients with pancreatic carcinoma with complete biliary obstruction and pancreatic achyli\textsuperscript{a57}. The significance of the small intestinal response to acid is not known, but it seems possible that local secretion of bicarbonate is largely, if not wholly, responsible for disposing of acid in the lower small intestine.

When acid passes into the human duodenum, both propulsive\textsuperscript{58,59,60} and non-propulsive\textsuperscript{54,59,61} motor activity can be recorded. The propulsive activity has been noted to correspond with progressive waves of pressure, associated with the passage of a bolus of acid through the duodenum into the
jejunum\textsuperscript{59,60}. The non-propulsive activity is represented by rapid, uniformly repetitive motor contractions\textsuperscript{59} in response to acid. There appears to be a marked difference in the motor responses of the human duodenum proximal and distal to the ampulla in response to acid, since there is often quite striking repulsion of the contents of the upper duodenum into the stomach when acid is introduced into the duodenum\textsuperscript{57,61}, while the distal duodenum responds with transient or more prolonged contraction.

**Nature of the Stimulus**

No direct information is available at this time about the nature of the stimulus provided by acid in the small intestine. The current hypotheses are therefore based on indirect evidence, inferred from the responses of one or other selected target organ to intestinal acidification. For example, it has recently been shown that stimulation of canine pancreatic bicarbonate secretion\textsuperscript{16,18,62,63}, inhibition of canine gastric secretion\textsuperscript{59}, and inhibition of gastric emptying in man\textsuperscript{49a} are all linearly related to the amounts of titratable acid entering the intestine and are not primarily dependent on the activity gradient of hydrogen ions (pH gradient) across the intestinal mucosa\textsuperscript{63}, at least at levels of pH less than 3. The significance of the role of titratable acid in this connection reflects the continual intraluminal buffering of acid both under the conditions of these experiments and under normal physiological circumstances and emphasizes the dynamic course of events in the small intestine on exposure to acid.

At pH levels greater than 3, the canine pancreatic response to acid decreases with rising pH of infusate, but is still related to the total amount of acid infused into the small intestine\textsuperscript{63}. The accompanying anion alters the response to small intestinal acid of the canine pancreas\textsuperscript{63} and also influences the inhibition of gastric emptying in man\textsuperscript{49a,50} by determining the strength and degree of ionization of the acid (that is, the proportion of the acid's hydrogen ions which are available for dissociation below pH 4.5). At pH levels greater than 2, the molecular weight of the anion becomes a significant determinant of the reaction to acid, at least as judged from the inhibition of gastric emptying\textsuperscript{60}.

Since the effects of acid seem primarily related to the titratable acid of the small intestinal contents, the magnitude of the effects is determined by the end point to which the intraluminal 'titration' of acid is carried. It has been shown that the apparent threshold for stimulation of pancreatic secretion\textsuperscript{64} and for inhibition of gastric secretion in dogs\textsuperscript{65} is pH 4.5. However, the threshold of pH below which acid elicits reactions does not appear to be uniform throughout the small intestine since the contents of the duodenal bulb are frequently acid, both in man\textsuperscript{59,66,67,68} and in animals\textsuperscript{68a,69,70}, without there being any pancreatic secretory response\textsuperscript{13,59,70}. Indeed, it has been shown that the duodenal pH must be between 1 and 2 before there is much secretion of bicarbonate in man\textsuperscript{71}, while a threshold quantity of acid (3 m-equiv/hour) must be delivered into the duodenum, even if the pH is below 2, before gastric secretion is inhibited in dogs\textsuperscript{63}. No information is available about the levels of threshold in different parts of the small intestine or about the circumstances which modify the thresholds of the reactions to acid. It is known that many other chemical and mechanical influences in the small-intestinal lumen elicit responses from the target organs similar to those
evoked by acid, but the results of the interactions of different intraluminal agents and events have not yet been investigated.

The mechanisms whereby all hydrogen ions above the threshold concentration register their presence and elicit a response is not yet known. It is of interest that the threshold of reaction of the small intestine to acid (approximately pH 4.5) is equivalent to the pH of a solution of equal amounts of acid and bicarbonate in equilibrium with a partial pressure of carbon dioxide of 40 mm Hg. Any situation which changes this equilibrium could therefore represent a potential link between the introduction of acid into the small intestine and the reactions to acid. It has been suggested that hydrogen ions may act directly by passing into the appropriate mucosal cells and producing biophysical alterations which result in the activation of the effector mechanisms (S. Anderson, personal communication). Alternatively, Hunt and Knox considered that excess hydrogen ions were titrated in the proximity of the receptor cells by means of locally produced bicarbonate, the rate of secretion of which depended on the hydrogen ion sink in the vicinity of the receptor. The residual hydrogen ions (from the carbonic acid in the receptor compartment) would then in some way stimulate the acid-sensitive receptors.

In contrast, Rune has suggested that raised tensions of carbon dioxide, generated from the buffering of hydrogen ions by bicarbonate and the subsequent dehydration of carbonic acid, might be responsible for some of the effects of hydrogen ions in the duodenum. Raised partial pressures of carbon dioxide have been employed in an attempt to reproduce the effects of acid in the duodenum, so far without success. An indirect action of hydrogen ions through a rise in pCO₂ has not, therefore, been shown to represent an important means of translating the effect of excess of intraluminal hydrogen ions.

**Mechanisms of the Response**

Two mechanisms have been invoked to explain the effects produced by acid in the small intestine.

**NEURAL**

Pavlov and pupils showed that neural activity was involved in the stimulation of pancreatic secretion by acid and subsequent reports confirmed these findings and showed that neural mechanisms were involved in the stimulation of the biliary system and inhibition of gastric acid secretion.

**HORMONAL**

The ‘neural’ hypothesis was soon supplanted by the ‘hormonal’ hypothesis when Bayliss and Starling showed that acid could produce effects (stimulation of pancreatic secretion and choleretic) when introduced into denervated loops of small intestine of dogs and that extracts of small-intestinal mucosa containing the hormone secretin could simulate the action of acid in the intestine. These studies have been confirmed and small-intestinal acid has been shown to stimulate the denervated, transplanted pancreas and inhibit the denervated stomach of dogs and, more directly, to increase the blood levels of secretin in man. The humoral hypothesis has been greatly refined by Grossman and colleagues, who have shown that pure secretin can elicit effects which are quantitatively and qualitatively similar to those produced by...
acid in the canine small intestine. However, other studies have shown that, under some circumstances, secretin does not reproduce the effects of small-intestinal acidification either in dogs, cats, or man. Moreover, the spectrum of actions of secretin cannot explain the differences between the reactions to acid and, for example, the reactions to fat in the small intestine. The discrepancies have led to the postulated release of other hormones from the small intestine, including cholecystokinin-pancreozymin, glucagon, enterogastone, and bulbogastrone. The full range of actions and interactions of these hormones is not yet known, but it seems probable that the list is incomplete and that still other gastrointestinal hormones will be found in the near future.

HORMONE-HORMONAL INTERACTION

Some of the experimental discord has been clarified recently by the finding that combinations of hormones, such as secretin and pancreozymin, modify each other's effects on the target organs resulting in quantitative and qualitative differences from the responses to the individual hormones. A result, it has been possible to reproduce the pattern of the pancreatic and biliary responses to intestinal acid in man by using a combination of secretin and pancreozymin. It has also been shown that the small-intestinal responses to acid are equivalent to the maximal, or near maximal, stimulation of the pancreatic bicarbonate and enzyme secretion in man.

While recent experimental results suggest that release of hormones is responsible for at least some of the reactions to acid, it must be emphasized that similarities in the patterns of response to small-intestinal acidification and to exogenous hormones do not necessarily prove that acid acts solely by releasing hormones from the small intestinal mucosa. It has become usual to attempt to explain reactions to intestinal stimuli in terms of hormonal dose response curves, based on the (usually unstated) assumption that if part, or more rarely the whole, of the pattern of reaction to a procedure like intestinal acidification is identical with the response to a hormone, then the mechanism by which the reaction to acidification is mediated is hormonal. Unfortunately, the target organs involved in the response to intestinal acidification have only a limited range of responses to stimuli, so that the response of single or groups of target organs does not necessarily provide information about the nature of the stimulus which elicits the response.

NEUROHUMORAL INTERACTIONS

Little is known about the role of vagal and intramural innervation in the functional response to acid, especially in man. However, it seems possible that many of the reactions to acid in the small intestine will be shown to depend to a lesser or greater extent on neural and hormonal interactions, in the same manner as gastric secretion has been shown to reflect an intimate interaction of neural and hormonal factors. Neurohumoral potentiation has been demonstrated in animals during the stimulation of pancreatic exocrine secretion and it has also been shown that innervation increases the degree of inhibition of canine gastric acid secretion in response to intestinal acid and secretin. However, it seems that the gastric secretory cells are more dependent on neurohumoral interactions for satisfactory function than either pancreas or biliary system both of which...
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respond to exogenous hormones and endogenous stimulation from the intestine after complete denervation.

Neurohumoral interactions have also been found to be very important in the regulation of the motor functions of the upper alimentary tract. For example, secretin may directly inhibit the cardiac sphincter\textsuperscript{100} and the electrical and motor activity of the stomach\textsuperscript{101} but there is evidence that innervation augments the secretin-induced motor inhibition to the stomach\textsuperscript{102}. In the duodenum, the difference in the pattern of motor response of the upper and lower parts to secretin and to acid recalls the differences in the response to vagal stimulation\textsuperscript{103}. Furthermore, the motor action of cholecystokinin on the duodenum has been shown to be dependent on the innervation of the duodenum\textsuperscript{104}. Similar neurohumoral interaction may regulate the discharge of bile into the duodenum since it has been suggested that acid in the duodenum acts through neural\textsuperscript{105,106,107}, hormonal\textsuperscript{199,108}, or neurohumoral mechanisms\textsuperscript{109,110} in evoking bile discharge.

**ACTIVATING MECHANISMS**

Little is known about the manner in which acid in the small intestine stimulates release of hormones or neural reflexes. It has been suggested, in analogy with the release of gastrin from the gastric antrum, that neural pathways are involved in the release of secretin and pancreozymin, because atropine\textsuperscript{111,111a} and local anaesthetics\textsuperscript{112,113} markedly decrease the pancreatic secretory response and the contraction of the gall bladder\textsuperscript{114} to small-intestinal acid without affecting the respective responses to direct stimulation with hormones. On the other hand, antral perfusion with acetylcholine (which is supposed to mimic local cholinergic activity) results in excellent release of gastrin from the canine antrum\textsuperscript{115,116} but acetylcholine does not elicit pancreatic secretion when applied to the canine duodenal mucosa\textsuperscript{117} and is presumed, therefore, not to release secretin or pancreozymin.

**REGIONAL DIFFERENCES IN REACTION TO ACID**

Whatever mechanisms stimulate the target organs, differences in these mechanisms presumably underlie the experimental findings that acid gives rise to different reactions from different parts of the small intestine. For example, in dogs acid stimulates pancreatic secretion both from the duodenum and from the jejunum\textsuperscript{11,12,46,118}, but gastric secretion of acid can only be inhibited by acid in the proximal duodenum\textsuperscript{90}, and, indeed, the gastric response changes to stimulation of acid secretion when the acid is introduced into the distal duodenum\textsuperscript{80} or jejunum\textsuperscript{68}.

Differences in the sensitivity to acid and in the type of reaction, particularly of the upper and lower duodenum, are still responsible for much confusion. Both in animals and in man it appears that the pH of the duodenum beyond the bulb is usually higher than pH 4.5, and frequently near neutral\textsuperscript{59,68,119}, in striking contrast to the low levels of pH in the duodenal bulb, in the fasting state\textsuperscript{66,67,68,120}, in response to food\textsuperscript{66,70,121,122,123,124}, and after gastric secretory stimulants\textsuperscript{69}. The sharp intraluminal pH gradient between the first and second parts of the duodenum has led to the suggestion that acid releases a unique hormone (bulbogastrone) from the duodenal bulb mucosa, which inhibits gastric secretion of acid but does not affect pancreatic secretion\textsuperscript{19}. On the other hand, the high pH levels (above 4.5) which have been recorded from the lower duodenum and beyond have been shown not to stimulate
significant outputs of pancreatic juice, so that it is not immediately obvious how the reactive potential of the small intestine beyond the ampulla is activated. In this connexion, experimentally observed values of near neutral pH in the lower duodenum may be misleading and may obscure the repeated, but very transient, exposure of the small intestine beyond the bulb to acid. It has been shown that when acid is delivered into the duodenum, it is rapidly moved on into the jejunum or back into the stomach so that normal duodenal motor activity combines with local buffering mechanisms to ensure that the levels of pH in the duodenum remain high, except in the bulb, in which the low pH reflects the pH on the antral, rather than duodenal, contents. The small amount of secretin which is released by the transient passage of acid through the lower duodenum into the jejunum presumably potentiates the action on the pancreas (etc) of neural reflexes and of pancreozymin, released by acid and by other food constituents. The situation may therefore be analogous to the secretion of acid by the stomach in which small, subthreshold amounts of gastrin and of neural activity potentiates to provide secretory stimulation.

Surprisingly little is known about the quantitative aspects of the reactions to acid of the intact alimentary tract. The net reaction to the physiological stimulus of a meal is not very great in dogs and it seems that neither enough motor activity nor bicarbonate secretion is stimulated to raise the pH in the lower duodenum and jejum from levels between 4 and 5 to the near neutral levels found in the fasting state.

**Fate of Acid in the Small Intestine**

Acid disappears after introduction into the duodenum, both within the duodenum itself and because it is removed from the duodenum into adjacent parts of the alimentary tract. Disposal of hydrogen ions within the intestinal lumen is brought about by buffering, mainly with bicarbonate, to form carbonic acid, which dissociates into carbon dioxide and water, both of which pass across the intestinal mucosa into the body. That buffering does occur is shown by the high partial pressures of carbon dioxide which have been observed in animals and man during the disappearance of acid within the duodenum. There is also a marked decrease in the osmolality of the intestinal contents when acid disappears, and the resultant equilibrium concentration of the intestinal contents represents the balance between the rate of formation of free water during the buffering of acid (due to clearance of bicarbonate and hydrogen ions and production of water) and the rate of diffusion of water from the small intestinal lumen.

At the level of the duodenum the bicarbonate for buffering is derived from the pancreas, biliary system, and small-intestinal mucosa, while at lower levels of the small intestine bicarbonate is secreted locally. The magnitude of the contribution from each of these sources is not known, but it has been shown that the combination of biliary and small intestinal bicarbonate can dispose of 0.44 m-equiv acid per 15 minutes for each cm of canine bowel. In human subjects, maximally about 1 m-equiv acid is removed from the lumen each minute when acid is introduced into the duodenum and allowed to pass into the remainder of the small intestine.

It has been suggested that some of the acid disappears from the intestinal lumen by diffusing across the small-intestinal mucosa. This hypothesis...
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has not been confirmed, because it has not yet been possible to distinguish between the diffusion of hydrogen ions out of the small intestine and the outward diffusion of the water which is produced by the buffering of the hydrogen ions. The potential net effect of both processes is a decrease in the acid of the intestinal contents. However, back-diffusion of hydrogen ions is unlikely to be an important mechanism for removal of acid, both because the changes in the osmolality during acid disappearance suggest that buffering is principally responsible and because there is a quite clearly defined maximal capacity for acid disposal both in man and dogs despite large residual gradients of acid from lumen to mucosa.

In addition to being buffered within the lumen, acid is removed from the duodenum by being rapidly transferred back into the stomach or on into the jejunum. It has been shown that after a meal, the contents of the human jejunum and ileum may become acid, the osmolality of the contents may decrease, or the partial pressure of carbon dioxide may rise, presumably because the acid has been rapidly spread throughout the small intestine.

While clearance of acid from the post-bulbar duodenum ensures rapid elevation of pH, the duodenal bulb behaves functionally like an extension of the gastric antrum with low pH if the contents of the antrum are acid. It is not clear why the contents of the bulb remain acid under these circumstances. In part, there appears to be insufficient secretion of buffer, since experimental administration of secretin is capable of alkalinizing the bulb of fasting dogs and man. However, even large doses of secretin only raised the canine bulb pH to an average of 4.8 during the course of a meal suggesting that insufficient secretion of bicarbonate compared with acid, persistently high intraluminal tensions of carbon dioxide, or discrete local motor effects were preventing reflux of bicarbonate into the bulb.

Functional Significance of the Reactions to Acid

One of the principal assumptions underlying the interpretation of the reactions to acid considers that acid is potentially dangerous to the small intestine, so that the reactions of the pancreas, biliary system, small intestine, and stomach to acid in the small intestine represent a complex process for preventing the deleterious effects of acid (Appendix). From this point of view, the secretion of bicarbonate provides buffer which results in the maintenance of the pH of the intraluminal contents of the small intestine at levels which do not damage the mucosa and which permit satisfactory intraluminal and mucosal digestion and absorption of food. The stimulation of intestinal motility serves to dilute the acid by spreading it through the small intestine, while regurgitation of the contents of the small intestine into the stomach reduces the acid content of the stomach. The inhibition of gastric motility and emptying limits the amount of acid to which the small intestine is exposed, and indeed, in man the amount of acid which enters the duodenum from the stomach is normally very closely related to the amount which can be disposed of in the duodenum. It also seems possible that the inhibition of pancreatic secretion and discharge of bile into the duodenum in response to excessive quantities of acid in the duodenum prevents the loss of the large amounts of pancreatic enzymes and bile salts which are secreted early during the func-
tional activity of these organs and which would be inactivated and rendered functionally useless on exposure to high concentrations of acid.

Unfortunately, there is no direct information about the amount of acid which is secreted by the normal stomach during a meal, nor about the amount of acid which remains unbuffered by food and which is delivered into the duodenum over a period of time. If these quantities are small, then the 'protective' reactions to acid in the small intestine may represent misleading interpretations of mistakenly designed experiments and of gastric hypersecretory diseases. Under these circumstances, it might also be necessary to seek alternative postulates and to suggest that acid was normally necessary for the satisfactory control of the functions of the alimentary tract. For example, it seems possible that early during the course of a meal unbuffered acid escapes into the small intestine and elicits neurohumoral reactions which prime the pancreas and gall bladder for response to the subsequent delivery of food.

**Disorders of the Reactions to Acid in Disease**

Functional disturbances of the reactions to acid can be found in human disease, but current knowledge and understanding of this important subject is rudimentary. In some instances, dysfunction is clearly caused by the underlying disease and may in turn aggravate the primary condition or result in secondary disorders. However, in the more important diseases in which abnormal reactions to acid have been found the relationship between the dysfunction and the disease is not understood.

**Disorders Caused by Disease**

Deficient reaction to acid in disease is best exemplified by patients with pancreatic exocrine insufficiency due to chronic pancreatitis or pancreatic carcinoma, who show severely impaired bicarbonate secretory responses to small-intestinal acidification²⁸,³⁷, but in whom the control of the delivery of acid into the small intestine remains intact²⁸.

Impaired bicarbonate secretory responses to small-intestinal acid are also found in patients with coeliac syndrome and are either secondary to the small-intestinal dysfunction in these patients¹¹ or due to primary pancreatic disease¹⁴². It seems probable that a pancreatic component contributes to the malabsorption of these patients.

On the other hand, an extremely vigorous reaction to small intestinal acid has been observed in patients with achlorhydria, who secrete greater than normal amounts of fluid into the duodenum⁵⁷ and empty the contents of their stomach more slowly than normal²⁸.

An entirely different pattern of functional disturbances is found in patients with severe and usually persistent hypersecretion of acid associated with the Zollinger-Ellison syndrome¹⁴³. In these patients, the contents of the duodenum and of the lower small intestine are often acid²⁴⁴ with an associated high incidence of mucosal ulceration. Some of these patients fail to show a pancreatic secretory response to secretin and pancreaticozymin²⁴⁴,²⁴⁵,²⁴⁶, a phenomenon which has been attributed to 'pancreatic exhaustion', but which presumably reflects the experimentally demonstrated inhibition of exocrine pancreatic secretion by duodenal acidification¹¹,¹⁴. It has also been noted that bile may be absent from the duodenal contents of patients with Zollinger-
Ellison syndrome\textsuperscript{114} in association with marked dilatation of the gall bladder\textsuperscript{147}. In these cases, the gall bladder is filled with fluid containing much bicarbonate\textsuperscript{147}, suggesting that the bile, formed as a result of the choleretic action of acid, has been diverted into the gall bladder instead of the duodenum. It seems probable that failure of the two main sources of supply of buffer aggravates the situation presented by the excessive load of acid in the small intestine. It also seems likely that other consequences of pancreatic and biliary dysfunction, such as defective digestion of fat, aggravates the small intestinal hyperacidification by decreasing or eliminating the fat-induced brake of gastric acid secretion and emptying.

**DISEASES ASSOCIATED WITH ABNORMAL REACTIONS TO ACID**

In patients with duodenal ulcer, the contents of the duodenum, particularly of the bulb, have been observed to be acid\textsuperscript{66,121,148,149,150,151} more frequently than in normal subjects. In duodenal ulcer, increased delivery of acid into the duodenum has been shown to be variably associated with excessive production of acid by the stomach\textsuperscript{102}, perhaps caused by an increase in the number of parietal cells\textsuperscript{153,154}; failure of acid in the duodenum to inhibit gastric secretion of acid\textsuperscript{155}; abnormalities in the regulation of gastric emptying, with greater than normal rate of evacuation into the duodenum\textsuperscript{28,161,165,156,157}; abnormally impaired secretory responses, particularly of the pancreas, to acid in the small intestine\textsuperscript{11,57,66,121,127,158}. The mechanisms underlying the observed abnormalities are not yet clear, but it seems probable that the disturbances are not homogeneous. Too little information is available at present to relate the observed dysfunction to the aetiology or natural history of the duodenal ulceration.

Patients with gastric ulcer show a different type of abnormality of reaction to acid, with persistent discharge of bile into the duodenum during duodenal acidification\textsuperscript{67}. The significance of this functional disorder is not clear, but it is perhaps related to the increased postsibal reflux of bile into the stomach\textsuperscript{159}, to which some of the gastric mucosal damage which characterizes gastric ulceration has been attributed.

**Summary**

Recent studies have emphasized that when acid is introduced into the small intestine, it evokes a series of integrated secretory and motor reactions involving the stomach, the small intestine, the pancreas, and the biliary system. In health, it seems probable that the response to acid is integrated with the responses to other components of the gastric contents after a meal, ensuring harmonious regulation of the intake, processing, and assimilation of food.

**Appendix**

**REACTIONS TO ACID IN THE SMALL INTESTINE**

Stimulation of pancreatic exocrine secretion\textsuperscript{6,7,8,9,11,12,14,16,46,57,63,64}.

Inhibition of pancreatic exocrine secretion\textsuperscript{11,16}.

Stimulation of pancreatic endocrine secretion\textsuperscript{17,18,19}.

Stimulation of bile flow\textsuperscript{20,159a,160}.
Cholerisis,\textsuperscript{8,22,161} Cholecystokinesis,\textsuperscript{11,79,114,162} Biliary tract sphincters,\textsuperscript{105,106} Inhibition of bile flow,\textsuperscript{57}.

Stimulation of gastric acid secretion,\textsuperscript{29,30,31,149} Inhibition of gastric acid secretion,\textsuperscript{13,30,31,32,37,38,40,41,43,44,45,46,65,81,155} Stimulation of gastric pepsin secretion,\textsuperscript{33,38,39,40,41,42}.

Inhibition of gastric endocrine secretion.


Stimulation of intestinal secretion,\textsuperscript{28,32,57} Brunner’s glands,\textsuperscript{55,56}.

Stimulation of intestinal motor activity,\textsuperscript{57,167a}.

REACTIONS TO SMALL-INTESTINAL HORMONES
Stimulation of pancreatic exocrine secretion,\textsuperscript{8,9,16,91,168,169,170,171,172,173} Inhibition of pancreatic exocrine secretion,\textsuperscript{173,173a,174,175}.

Stimulation of pancreatic endocrine secretion,\textsuperscript{17,19,176,177}.


Stimulation of gastric acid secretion,\textsuperscript{184} Inhibition of gastric acid secretion,\textsuperscript{21,38,40,41,77,78,81,83,84,88,95,118,173,185,186} Stimulation of gastric pepsin secretion,\textsuperscript{38,39,41,42,83,184,187}.

Inhibition of gastric endocrine secretion,\textsuperscript{188}.

Inhibition of gastric motor activity. Electrical activity,\textsuperscript{161} Motor activity,\textsuperscript{88,102,173,189,190,191} Emptying,\textsuperscript{186}.

Stimulation of intestinal secretion. Brunner’s glands,\textsuperscript{55,56,192}.

Stimulation of intestinal motor activity,\textsuperscript{110,193,194}.

EFFECTS OF ACID IN THE SMALL INTESTINE
Mucosal damage (haemorrhage, inflammation, villous atrophy, metaplasia, ulceration),\textsuperscript{145,190,196,197}.
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Mucosal functional disturbances (reduced uptake of amino acids, clearing of triglycerides)\textsuperscript{196,197}.

Irreversible denaturation of pancreatic enzymes\textsuperscript{146,198,199}.

Precipitation of bile salts and fatty acids\textsuperscript{146,200}.

Defective formation of micelles\textsuperscript{146,201}.

Defective absorption of vitamin B\textsubscript{12} (impaired binding to intrinsic factor, destruction of intrinsic factor, impaired absorption)\textsuperscript{197,202}.

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References


\textsuperscript{10}Weaver, M. M. (1927). Distribution of pancreatic secretin in the gastro-intestinal tract. \textit{Amer. J. Physiol.}, 82, 106-112.


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