Progress report

Relationship between gastric secretion and infection

Why does the stomach secrete acid? Animal stomachs are specialised organs which produce a highly acidic secretion. This is found in a wide spectrum of animals from fish to mammals. In man, acid secretion is not essential for life, or indeed for adequate digestion, as evidenced by the continued survival of achlorhydric patients with pernicious anaemia.

The physiological role of gastric acid may be summarised as follows:— (1) The initiation of protein digestion through the activation of pepsinogen. (2) The augmentation of dietary calcium and iron absorption. (3) The defence of the highly specialised absorptive and secretory cells of the lower alimentary tract from ingested organisms.

This review will concentrate on the role that gastric acid plays in the protection against ingested organisms, as well as considering the possible effects of infection on gastric secretion.

Protective role of gastric acid

Interest in this area has recently been renewed. The low pH of the intragastric environment constitutes one of the major non-specific defence mechanisms of the body. Reduction of gastric acid secretion predisposes to infection with a variety of organisms including those responsible for typhoid and non-typhoid salmonellosis, bacillary dysentery, cholera, brucellosis, giardiasis and strongyloidiasis. In addition, there are isolated reports to suggest that Clostridium difficile infection leading to pseudomembranous colitis, and infection with the fish tapeworm Diphyllobothrium latum are more likely in association with hypochlorhydria.

The protective role of gastric acidity is further emphasised by considering infection with Salmonella and the cholera bacillus. It is well recognised that previous gastric surgery is a significant risk factor for the development of Salmonella infection. This is directly related to reduction in gastric acid secretion. Elderly patients are more likely to incur severe infection with Salmonella, which is probably related to the reduction in gastric acid secretion after the age of 60. Cholera bacilli are markedly acid sensitive. Infection is more likely to occur, and to be more severe in association with reduced acid secretion.

Bacteria introduced into the stomach are destroyed within 15 minutes when the pH is 3.0 or below, but gastric juice retains some effective bactericidal activity up to pH 4.0. The bactericidal properties of gastric juice are principally because of the low pH.

The bacterial count in the stomach is normally much less than
Relationship between gastric secretion and infection

$10^5$ organisms/ml\textsuperscript{19} but is increased to well over $10^6$ organisms/ml in conditions of reduced gastric acidity.\textsuperscript{20, 21} The intragastric bacterial count is also increased temporarily when acid secretion is inhibited during treatment with H\textsubscript{2}-receptor antagonists\textsuperscript{22} or omeprazole.\textsuperscript{23} Nitrites and N-nitrosocompounds are produced in increased amounts. The exact consequences of this for human health are unclear. These compounds may be of carcinogenic potential but this has not been shown for man.

**Epidemic hypochlorhydria**

Previously healthy individuals with normal gastric secretion, as well as patients with Zollinger Ellison Syndrome, have on occasions been shown to develop a temporary but profound reduction in acid output, sometimes to complete anacidity.\textsuperscript{24–30} These observations have generally been made on volunteer subjects who were participating in gastric secretion studies, or in patients with Zollinger Ellison syndrome who were under close medical supervision with frequent measurements of gastric acid secretion. As these subjects constitute a highly selected group, the true prevalence of spontaneous achlorhydria in the community is not known.

Before the development of achlorhydria, most subjects reported non-specific symptoms of malaise, nausea, and epigastric discomfort. In some instances,\textsuperscript{25, 28, 29} achlorhydria occurred in more than one subject at the same time suggesting a possible infective aetiology. Histological features of gastritis were found in most of the subjects.\textsuperscript{25, 26, 28–30}

Hypochlorhydria has also been documented in two larger groups during the course of gastric secretion studies.\textsuperscript{31, 32} These subjects also had a mild prodromal illness before the onset of achlorhydria. This together with the clustering of cases again suggests the possibility of an infective cause. There may have been transmission of an infectious agent between individuals as in both series gastric juice was returned to the stomachs of patients after the measurement of pH with a glass electrode used for all patients. Despite extensive investigations, however, no causative agent has been identified. It is of interest to note that a retrospective examination of the gastric mucosal biopsies from some of these patients\textsuperscript{30, 31} has detected the presence of a Campylobacter-like organism.\textsuperscript{33, 34} The significance of this observation will be discussed in more detail below.

Most patients eventually recover their normal level of acid secretion, although a few remain hypochlorhydric for as long as one year, and continue to show changes of diffuse gastritis. The natural history of the condition is not yet fully understood, and it remains to be seen whether these patients will go on to develop chronic atrophic gastritis. During the period of hypochlorhydria, patients remain asymptomatic. Some have had documented malabsorption of vitamin B\textsubscript{12}.\textsuperscript{32}

A transient form of hypertrophic gastritis has been described in children.\textsuperscript{35} This is associated with reduced secretion of acid, and may resemble Menetrier’s disease of adults. A viral aetiology has been postulated for this condition. Cytomegalovirus inclusion bodies have been found in the gastric mucosal biopsy specimens from some affected children,\textsuperscript{36, 37} and high titres of antibody to cytomegalovirus have been found in the blood.\textsuperscript{37–39} One child with this condition developed hypoproteinaemia and oedema after a non-specific illness\textsuperscript{35} similar to that
Gastric campylobacter-like organisms

Bacteria resembling Campylobacter species have been isolated recently from gastric mucosal biopsies taken from individuals with active gastritis and peptic ulceration. These have been termed ‘Campylobacter pyloridis’, ‘pyloric Campylobacter’ or ‘Campylobacter-like organisms (CLO)’. They are gram negative, spiral or curved, flagellate and microaerophillic. They have been found in gastric mucosal biopsy specimens, usually from the antrum. They are generally situated below the mucus layer or in the lumen of gastric glands. An aetiological role has been postulated for them in gastritis and in relapses of peptic ulceration. In one hospital, they were isolated from 114 of 267 patients undergoing routine upper gastrointestinal endoscopy with biopsy of gastric antral mucosa. They were cultured from 88% of those patients in whom they were detected histologically. The presence of CLO is closely associated with the presence of gastritis, and they were not detected in any patient with histologically normal gastric mucosa. They were found to be sensitive to a variety of antibacterial agents including metronidazole, and also to bismuth citrate. Metronidazole has previously been found to be an effective ulcer healing agent, although its mechanism of action in this respect is unknown. It has been proposed to act through its bactericidal properties.

The observation that the cultured CLO were sensitive to bismuth citrate is of interest as chelated salts of bismuth have been used successfully in the treatment of duodenal ulcer. Healing rates which are comparable with those reported for the H2 receptor antagonists have been reported. In addition, ulcers which heal on treatment with bismuth appear to relapse more slowly than those healed on H2 receptor antagonists. Patients treated with bismuth compounds continue to show raised urinary bismuth levels for at least two weeks after cessation of treatment. Perhaps the bactericidal properties of bismuth extended for some time after initial healing are responsible for this interesting and unexplained finding. The lower relapse rates reported with bismuth compounds might be because of elimination of CLO from the stomach, whereas drugs which reduce acid secretion tend to raise intragastric bacterial counts and may even promote persistent colonisation with CLO.

It has recently been shown that CLO are transmissible between individuals. A previously healthy subject with normal gastric histology rendered himself temporarily hypochlorhydric with cimetidine and ingested a dose of CLO cultured from a patient with gastritis. This produced a mild systemic upset and a similar histological gastritis in the recipient. Unfortunately, gastric acid secretion was not monitored in this experiment. It is therefore not known if the infection prolonged the period of hypochlorhydria.
We have recently (unpublished observations) seen two patients with dyspepsia in whom diffuse superficial gastritis was found. Campylobacter-like organisms were cultured from gastric mucosal biopsies. Neither patient cleared the CLO after treatment with metronidazole or a proprietary compound containing bismuth. Both had studies of basal and pentagastrin stimulated acid output, which were essentially normal.

Apart from CLO, there has been speculation in the past about a possible infective cause for duodenal ulcer. It is known that duodenal ulcers resemble herpetic ulcers in appearance. Furthermore, it has been reported that patients with duodenal ulcer have raised antibody titres to *Herpes simplex* type I. The possibility that peptic ulceration might be the result of viral infection raises the intriguing possibility of future effective antiviral therapy for the condition. The association between infection with the Herpes virus and the occurrence of peptic ulcer is not strong, however, and any causal association will be difficult to prove conclusively because the antibody is present in up to 80% of the general population.

Possible consequences of achlorhydria

The prevalence of achlorhydria varies widely among different populations. It is generally high in developing third world nations where it often occurs in association with malnutrition. Mixed infections with enteric pathogens causing diarrhoea are a major public health problem in these countries. As well as the important considerations of hygiene and sanitation, hypochlorhydria is one of the factors which predisposes to such infections. The incidence of cholera is much higher in populations with reduced gastric acidity. It has been proposed that some infections, including typhoid, may induce achlorhydria in man. As we have pointed out, however, it is more likely that hypochlorhydria predisposes to typhoid infection and that the severity of infection is increased in patients with hypochlorhydria.

Prolonged achlorhydria may predispose to gastric carcinoma; this has been established for patients with pernicious anaemia, and probably also for postgastrectomy patients. A widely propagated hypothesis for this proposes that reduced gastric acidity leads to colonisation of the stomach with nitrate reducing bacteria, and that the resulting nitrites and N-nitroso compounds are carcinogenic. This has not been proven in man.

Marked suppression of acid secretion is generally accompanied by a compensatory increase in circulating gastrin concentrations. In man, this is most clearly shown in pernicious anaemia. Gastrin concentrations are likewise raised during treatment with potent antisecretory drugs such as omeprazole. The mild rise in gastrin concentrations produced by omeprazole does not appear to cause a rebound hypersecretion of acid on withdrawal of the drug, and may actually play a beneficial role in ulcer healing. As gastrin is trophic to the duodenal mucosa, it has been postulated that this may accelerate ulcer healing.

In toxicology studies in rats receiving very high doses of omeprazole, gastrin concentrations were found to be greatly raised. In the rat, the gastric endocrine cell known as enterochromaffin like (ECL) cell is extremely sensitive to hypergastrinaemia. Proliferation of these cells with formation of discrete local tumours has been well documented in rats treated with very high doses of omeprazole. That this effect is expressed...
through the rise in gastrin concentration is shown by the fact that ECL cell proliferation does not occur in antrectomised rats.\textsuperscript{67}

Hyperplasia of ECL cells with the formation of gastric carcinoids has been shown to occur in man in association with hypergastrinaemia. This has been found both in pernicious anaemia,\textsuperscript{68,69} and in Zollinger Ellison syndrome.\textsuperscript{70} In man, gastric ECL cell tumours found in association with pernicious anaemia appear to behave in a benign manner.\textsuperscript{71}

Omeprazole has been shown to raise gastrin concentrations in man, but this effect is of relatively small magnitude and short duration.\textsuperscript{62,63} It is unlikely that ECL cell proliferation will occur during short term omeprazole treatment for uncomplicated peptic ulcer. In patients receiving high daily doses of omeprazole, however, as in Zollinger Ellison syndrome, the process of ECL cell hyperplasia might be accelerated.

**Possible inhibitory effect of infection on gastric secretion**

Gastric acid is clearly involved in the defence against ingested organisms. There is some evidence, however, to suggest that certain infections may inhibit acid secretion.

**ANIMAL STUDIES**

Parasitic, bacterial, and viral infections have all been reported to suppress acid secretion in laboratory animals. In some instances, this is because of a direct morphological effect of the infection on the gastric mucosa. In most cases, the mechanism is not understood.

Rats infected with the parasitic cestode *Taenia taeniaeformis* develop a cystic glandular hyperplasia of mucus secreting cells of the gastric mucosa. The stomach may increase in size up to 20-fold after infection.\textsuperscript{72} Associated with this finding, there is a reduced parietal cell mass and hence a reduction in acid output. Gastrin concentrations are greatly raised in infected animals,\textsuperscript{73} presumably as a consequence of the reduced acid output. This is an example of an infection suppressing acid secretion through a morphological effect on the gastric mucosa.

Gastric or intestinal hyperplasia in the rat from other causes is generally accompanied by an increase in the parietal cell mass.\textsuperscript{74-78} The reduction in parietal cell number seen after *T taeniaeformis* infection, with the resulting decrease in acid secretion, may help facilitate the passage of the parasite through the stomach and its subsequent establishment in the intestine and liver. A similar effect has been reported for different nematode infections in other mammals including *Ostertagia* in the sheep,\textsuperscript{79} *Trichostrongylus axei* and *Habromena* sp in the horse,\textsuperscript{80} and *Nochta noctiae* in primates.\textsuperscript{81}

In ostertagiasis, it seems likely that a parasite induced host factor or a product of the parasite itself inhibits parietal cell secretion.\textsuperscript{82} *Ostertagia* occupies the stomach, however, and so could be acting locally, but without causing any demonstrable change in the histological appearance of the gastric mucosa. Another parasite of the sheep, the nematode *Trichostrongylus colubriformis*, inhabits the small intestine but also exerts a suppressive effect on gastric acid secretion.\textsuperscript{83} It has been suggested that a gastric inhibitory substance produced in the parasitised intestine acts systemically on the stomach.\textsuperscript{83} In these examples, parasitic infections cause
a reduction in acid secretion without altering gastric mucosal histology. Specific parasite derived inhibitory substances have been postulated, but their existence has not been proven.

Bacterial infection in laboratory animals is well recognised as a cause of acute ulceration in the upper gastrointestinal tract. Perforating ulcers of the stomach and duodenum are produced in guinea pigs after infection with Staphylococcus aureus.\textsuperscript{84} Postoperative wound infections in dogs lead to an increase in gastric acid secretion.\textsuperscript{85}

The opposite effect, a reduction in acid secretion, has also been observed in some animals after bacterial infection. Rats infected subcutaneously with a strain of Escherichia coli showed a significant reduction in acid output and a reduction in the number of experimental stress induced ulcers produced by restraint or pyloric ligation.\textsuperscript{86} These changes were associated with fever. Rats infected with Staphylococcus aureus did not develop fever and were not protected from ulcer formation.

Certain products of bacterial metabolism have also been shown to suppress acid secretion. In conscious dogs with denervated gastric pouches, histamine stimulated acid secretion was abolished by the intravenous administration of a lipopolysaccharide derived from Pseudomonas aeruginosa.\textsuperscript{87} Substances, which are also probably lipopolysaccharides, have been isolated from the cultures of Streptomyces bottropensis and Bacillus subtilis which suppress acid secretion in rats and reduce the incidence of stress ulcers.\textsuperscript{88,89}

Less is known about the effects of viral infection on gastric secretion. There is evidence from experiments on rabbits that certain viruses, however, particularly Vaccinia, are associated with the production of an oligopeptide in the host which can inhibit acid secretion, and which suppresses acid output when administered to other animals.\textsuperscript{90}

\section*{Studies in Man}

Bacterial infections which cause fever have frequently been associated with a marked reduction in acid secretion. Histamine fast achlorhydria was found in patients suffering from a variety of bacterial infections including typhoid, paratyphoid, pulmonary tuberculosis, bronchopneumonia, and lung abscess.\textsuperscript{91} This was reported from a region of China associated with a low natural incidence of achlorhydria.

In 106 febrile patients with infection, body temperature was positively correlated with the degree of suppression of acid secretion.\textsuperscript{92} The basal secretion of acid was reduced to approximately one third of the expected normal, and the prevalence of total achlorhydria was increased eight times. Gastric secretion returned to normal levels in 90\% of patients after eradication of the infection.

In a group of 325 patients with pulmonary tuberculosis of varying degrees of severity, there was a steady increase in the prevalence of achlorhydria with advancement of the disease.\textsuperscript{93}

It is interesting to note that William Beaumont had observed a reduction in the gastric secretion of his gastric fistula patient Alexis St Martin during a febrile illness.\textsuperscript{94} In the presence of fever, he noted that ‘...the secretions become greatly vitiated, greatly diminished or entirely suppressed...’.

It is possible that fever rather than infection per se is responsible for the suppression of acid output. A transient inhibition of gastric secretion has
been produced in man by artificially raising body temperature to 38–39°C in a heating cabinet. A similar effect has also been recorded in dogs.

There is some evidence that parasitic infections in man cause a reduction in acid secretion. Infection with the fish tapeworm Dipylidlobothrium latum is more common in association with hypochlorhydria, but there is some evidence to suggest that the infection itself may suppress acid output through an unknown mechanism. Infection with Trypanosoma cruzi, the causative agent in Chagas’ disease, is associated with reduction in basal and stimulated acid output. This may be because of the gastric parasympathetic denervation caused by the infecting organism which reduces the responsiveness of the parietal cell to physiological stimuli. Reduced gastric acid secretion has also been documented in patients infected with the hookworm Ancylostoma duodenale. This parasite is confined to the small intestine and the mechanism whereby it influences gastric secretion is unknown.

The effects of viral infection on gastric secretion in man have not received much attention, although a virus derived peptide after Vaccinia infection appears to be able to suppress acidity in laboratory animals. As nausea and vomiting are frequent and non-specific symptoms of viral infection in man, it might be expected that certain viruses would produce quantifiable changes in gastric secretion or motility. Ingestion of two strains of parovirus by human volunteers produced no alteration in either basal or stimulated acid output, but markedly slowed gastric emptying. The two viruses used do not cause any inflammation of the gastric mucosa. The situation is therefore quite different from that of epidemic hypochlorhydria in which there is diffuse gastritis.

**Hypochlorhydria and susceptibility to infection**

Both achlorhydria and infective diarrhoea occur with high frequency in third world nations. Malnutrition predisposes to chronic gastritis and reduced acid secretion. The world prevalence of achlorhydria mirrors that of enteric infection, particularly in developing nations. The combination of malnutrition and reduced acid secretion puts individuals at an increased risk of infection with enteric organisms; diarrhoeal illnesses are a major cause of morbidity and mortality in underdeveloped countries. Chronic infection with helminth parasites is also a major problem in these areas. It is estimated that about $2 \times 10^9$ people worldwide are infected with the roundworm Ascaris lumbricoides (personal communication). In view of the predilection for parasitic infection to cause hypochlorhydria in animals, chronic parasitic infection in man may also lead to reduced acid secretion. This possible association has not been adequately studied. It would be of interest to see whether primary infection with a helminth parasite inhibited acid output. If this was the case, then one of the factors predisposing to superadded enteric infection in man would be elicited.

The condition of epidemic hypochlorhydria has yet to be fully defined. It is likely to be caused by community infection with a microorganism so far unidentified. If caused by an infective agent, as seems likely, then this condition may serve as a model for the gastritis and achlorhydria in tropical countries. The finding of CLO in gastric mucosal biopsies from some of
Relationship between gastric secretion and infection

these patients\textsuperscript{30, 31} is an interesting observation but does not prove a causal relationship. It is possible that hypochlorhydria predated exposure to CLO thus allowing them to colonise and proliferate. The identification of the putative organism responsible for the phenomenon of epidemic hypochlorhydria should provide us with the first direct infective cause of reduced acid secretion in man.

The exact role of CLO in gastritis and in relapse of peptic ulcer is as yet unclear. If the hypotheses of Marshall et al\textsuperscript{34, 50} are correct, potent reduction of gastric acid may not be the optimal form of management for peptic ulcer, if this were to encourage superinfection with CLO which may in turn accelerate relapse. As gastric acid is clearly of some physiological importance in the protection of the rest of the alimentary tract, one can speculate on the optimal degree of acid suppression for the treatment of peptic ulcer.

The H\textsubscript{2} receptor antagonists have recently been prescribed as a single night time dose. This appears to give maximal suppression of acid secretion during the night with very little suppression in the daytime.\textsuperscript{103} This is an attractive concept as presumably gastric acid is less important for protection at night when the individual is not eating. In addition, it is known that duodenal ulcer patients have an inappropriately raised level of nocturnal acid secretion\textsuperscript{104} suggesting that this is when any antisecretory effect should be concentrated.

The H\textsubscript{2} receptor antagonists currently available have proved to be extremely safe drugs. Extensive postmarketing surveillance studies\textsuperscript{105, 106} have confirmed this. In a recent report,\textsuperscript{107} however, a significantly increased incidence of diarrhoea was reported for patients receiving one of these agents when compared with controls. Although the causes of diarrhoea were not stated, infection was presumed. It would be of considerable interest to know the rate of infection, and any relationship to either time of dosing or dose level. Marked suppression of acid secretion over long periods is unnecessary for the treatment of uncomplicated duodenal ulcer, and should be particularly avoided in regions of the world where there is a high incidence of enteric infection. Alternative forms of therapy are probably more appropriate in such regions. For example, in a well controlled study from India, it was shown that low doses of conventional antacids were effective in healing duodenal ulcers and in relieving symptoms of dyspepsia.\textsuperscript{108} Such treatments avoid the increased risk of enteric infection, and are more affordable in poorer countries.

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Howden and Hunt

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Relationship between gastric secretion and infection

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Relationship between gastric secretion and infection

Relationship between gastric secretion and infection.

C W Howden and R H Hunt

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