Leading article

Duodenal ulcer: does pathophysiology equal aetiology?

Most discussions about the aetiology of duodenal ulcer depict the duodenal bulb as a battlefield, on which aggressive and defensive factors wage a continuous and continuing campaign for the integrity of the bulbar mucosa. When the scales are tipped in favour of aggression, an ulcer develops. The battlefield is unique, because it is chemical warfare that is usually thought to be taking place – hence also the description of the duodenal bulb as the crucible of the alimentary tract. The so-called aggressive factor is usually considered to be gastric juice eroding, or digesting its way into (and through) the duodenal mucosa, while defensive factors are stated to include bicarbonate, which ‘neutralises’ acid and inactivates pepsin in the duodenal lumen and mucus, which acts as a barrier to acid and pepsin. In addition, the state of the duodenal mucosa is considered to be important, as duodenal ulcers may reflect presumed inadequacy of the mucosa if no other reason can be found for the ulcer.

The evidence for this internal turmoil, so often ending in defeat, is epidemiological (identifying groups of individuals at risk) and pathophysiological (indicating which individuals are at risk). The most obviously pertinent epidemiological apparent confirmation that gastric juice is noxious is both positive and derived from the high degree of association between duodenal ulceration and the gastric hypersecretion in patients suffering from gastrinomas,¹ as well as negative, because duodenal ulcers do not occur in individuals who secrete no gastric juice at all. The paper by Schulze *et al* in the present issue of *Gut* highlights the other aspect of the battle – that there are groups of individuals at risk because their defenses are defective because they secrete too little bicarbonate (as a result of pancreatic exocrine insufficiency), or because they have a diseased duodenal mucosa (duodenitis). As the authors (and many others) have pointed out, the association between duodenitis and duodenal ulcer is so controversial as to be aetiologically useless. So is (despite the report of Schulze *et al*) the association between duodenal ulcer and chronic pancreatitis because this association has also been denied.² For example, in a large number of patients with chronic pancreatitis the incidence of duodenal ulcers was 2%.³ The epidemiological evidence can therefore be summarised as showing a fairly strong (but not invariable) association between gastrinomas and duodenal ulcers, an association which, it is assumed, is based causally on the gastric hypersecretion evoked by the gastrinoma.

An alternative approach to establishing the aetiological involvement of aggressive gastric juice is experimental. After showing that gastric juice digested the legs of frogs and ears from rabbits,⁴ large amounts of

hydrochloric acid were poured into the stomachs and duodenums of dogs, without producing ulcers (if systemic acidosis was prevented), other than in exceptional circumstances.⁵ On the other hand, experimental duodenal ulcers can be produced by mimicking gastrinomas, using slow-release parenteral administration of histamine, or gastrin.⁵ Despite, however, the apparently obvious potential implications of the experimentally induced gastric hypersecretion, the precise mechanism whereby the ulcers are produced has not been defined. Experimental ulcers have also been produced by anastomosing small intestinal mucosa to gastric mucosa,⁵ although when actually transposed into the stomach the small intestinal mucosa remains intact.⁶ The anastomotic ulcers were considered to represent the effect of aggressive gastric juice on intestinal mucosa deprived of protective bicarbonate; although this explanation does not, of course, account for the failure of the aggressive gastric juice to ravage the implant. It proved much more difficult to produce duodenal ulcers by pancreatectomy (as only 1% of the operated animals developed duodenal ulcers) or by ablating the pancreatic duct⁶ so that once again the significance of the only measurable defensive factor (the secretion of bicarbonate into the duodenum) could not be shown to be important in ulcerogenesis.

Of course, the most important (alleged) evidence for the involvement of aggressive and defensive factors in the aetiology of duodenal ulceration has been derived from what are considered the pathophysiological 'disturbances' encountered in patients with duodenal ulcer. The story goes something like this: patients with duodenal ulcer have excessive amounts of acid in the duodenal bulb;⁷ attributable to excessive secretion of gastric juice⁸ as well as abnormally rapid emptying⁸ of excessive amounts of gastric juice from stomach to duodenum.⁹ The stomach secretes too much because there is an excessive mass of parietal cells in patients with duodenal ulcer.¹⁰ These parietal cells are abnormally sensitive to secretory stimuli,¹¹ perhaps because gastric inhibitory factors are not acting normally.¹² There may, in addition, be excessive stimulation of the parietal cells by abnormally large amounts of circulating gastrin¹³ both in the basal and postcibal state and also as a result of vagal activity.¹⁴ The increased amounts of gastrin are released because the number of antral G cells and the antral content of gastrin of patients with duodenal ulcer is greater than normal¹⁵ and because acid in the antrum does not inhibit release of gastrin normally.¹⁶ The excessive amounts of intraduodenal acid do not elicit sufficient, or even normal¹⁷ amounts of bicarbonate because the release of secretin from the small intestine is defective,^{18 19} in part because the threshold for secretin release is greater than normal in ulcer patients.²⁰ Add to this collection of apparently positive evidence for the aetiological importance of noxious gastric juice the negative evidence that ulcers heal and apparently remain healed if gastric secretory capacity is therapeutically reduced (surgically, or with drugs) – and one has the classical proof for what, at present, purports to be the erosive aetiology of ulcer disease.

Conceptual difficulties, however, result from a matching set of contradictory results. It has been shown that in many patients with duodenal ulcer the contents of the duodenal bulb do not contain excessive amounts of acid;²¹ that the majority of patients with duodenal ulcer do not secrete excessive amounts of acid;^{22 23} that many patients with duodenal

ulcer empty gastric contents normally or even slowly;^{8 23} that no patient with duodenal ulcer has a parietal cell mass greater than individuals without duodenal ulcers;¹⁰ that most patients with duodenal ulcer have quite normal sensitivity to secretory stimulants;²⁴ that gastric inhibitory factors in man are nebulous and, in any case, quite normal in patients with duodenal ulcer;²⁵ that basal and food-stimulated levels of gastrin are not different from normal¹³ and that the number of G cells in duodenal ulcer patients is reduced to less than normal,²⁶ while antral sensitivity to acid is also quite normal in patients with duodenal ulcer.¹⁹ It seems also, that secretin release is normal²⁰ or excessive²⁷ in patients with duodenal ulcer, so that bicarbonate secretion is actually greater than normal in these patients.²⁷ As a result of these contradictory findings the aetiological base of duodenal ulcer, derived from pathophysiological disturbances, is not quite so credible. Add to that the finding that many patients do not develop ulcers postoperatively even if gastric secretion is not impaired, or do develop ulcers when gastric secretory capacity is much reduced, and that there is no correlation between ulcer recurrence and therapeutic gastric inhibition²⁸ and it seems that the pathophysiological base of the aetiology of duodenal ulceration crumbles and disappears.

In an attempt to rescue something from the debris it has been suggested that one, or a few, of the above pathophysiological disturbances alone may determine the development of duodenal ulcers. That is, patients do not need to manifest all, or even more than one of these disturbances before ulcers develop. This hypothesis proposes that ulcer disease reflects pathophysiological heterogeneity – in other words, whatever apparent disturbance of function one happens to find, that particular dysfunction is somehow implicated in the genesis of the ulcer disease and if one does not find anything, then (presumably) lack of defensive factors – which are unmeasurable, like mucus synthesis or secretion – must be responsible.

I think that it is time to call a halt. Pathophysiological disturbances, like the gastric hypersecretion which occurs in one sixth to one third of patients with duodenal ulcer, are changes from the usual physiological situation and that is all they are. There is no evidence whatsoever that these variant reactions are anything other than that, or that they are in any way ulcerogenic. Indeed, these pathophysiological disturbances may be merely a consequence of the disease and it is not impossible to conceive that some may even reflect a defensive reaction associated with the development of a duodenal mucosal lesion. To take the argument further, there is really no evidence that there are any endogenous aggressive factors or that gastric juice is ever aggressive towards normal alimentary mucosa. That being so, there are normally no defensive factors, either.

What alternatives do we have for the aetiology of duodenal ulcer? We do know as fact, that there are exogenous duodenal ulcerogens in the form of chemicals and probably also of infective agents. For example, aspirin produces duodenal ulcers in a considerable proportion of patients.²⁹ Derivatives of nitriles almost invariably produce duodenal ulcers when administered to experimental animals and we are ubiquitously exposed to these chemicals.³⁰ Moreover, it has recently been shown that some patients with duodenal ulcer have very high titres of antibodies to herpes simplex virus, type I,³¹ suggesting that infection with this type of virus may have been the cause of the duodenal ulcers.

But it might be argued, what about the significance of the therapeutic effects of the new gastric inhibitory anti-ulcer drugs? I have discussed previously³² the example of urogastrone. This peptide, isolated from urine, was found to exert powerful gastric secretory inhibition.³³ As a result it was used to treat the duodenal ulcers of patients with gastrinoma.³⁴ It was shown subsequently that urogastrone was identical with another peptide, called epidermal growth factor (EGF).³⁵ Epidermal growth factor promotes the healing not only of alimentary ulcers³⁶ but of all sorts of other ulcers and wounds³⁷ because it stimulates wound repair. Epidermal growth factor was then shown to promote resistance of the mucosa to injury,³⁸ to stimulate the production of repair-promoting factors³⁹ and, even more interestingly, to exert an antiviral effect.⁴⁰ When it was subsequently shown that cimetidine⁴¹ and carbenoxolone-like agents⁴² also has antiviral effects it was obviously no longer permissible to assume that cimetidine, or any other drug, necessarily healed ulcers by reducing gastric secretion or, as in the case of carbenoxolone, by somehow promoting mucosal defence. Indeed, it is probably safest at present to conclude that we do not know how our therapeutic regimes – medical, or surgical – heal ulcers, because we do not know the aetiology of ulcers.

We can, however, make some guesses which may be testable. Schulze *et al* describe in this issue of *Gut* how they biopsied the duodenum at two sites in all their patients. So do many other endoscopists, because duodenal biopsy is quite safe and surprisingly does not result in more duodenal ulcers. Surprisingly, because if the duodenal intraluminal contents were aggressive in these patients, one would expect traumatic lesions like biopsy ulcers to be converted into proper clinical ulcers. As the biopsy lesions heal rapidly, it seems not only that the duodenal luminal contents are not aggressive but that the main problem with duodenal ulcers is their failure to heal. For example, we have found that ulcers may persist asymptotically for many weeks, or months in an apparently unchanged manner,⁴³ rather like varicose ulcers.

Why do not the duodenal mucosal lesions which present clinically as ulcers heal normally? We know very little about mucosal healing and factors which promote and retard this process. I have summarised some of the available information (in preparation). Very briefly, mucosal wound healing depends on the complex interactions of mucosal and interstitial cells with circulating and locally-derived peptides and other factors, which stimulate the proliferation, movement across the mucosal defect and differentiation of the mucosal cells and supporting mesenchymal cells. Many of the interactions are potentiating ones – such as the stimulus to proliferation produced by peptide growth factors – for example, fibroblast growth factor and epidermal growth factor – and proteases – for example, thrombin and trypsin. It is easy to speculate how defective repair might occur. To mention just one possibility – fibroblast growth factor is a fragment of myelin basic protein and is released from injured peripheral myelin.⁴⁴ The extraordinary anatomic discreteness of duodenal ulcers might, therefore, reflect a local scarcity of nerves in the mucosa, with failure to release sufficient repair factor after mucosal damage. And so on.

I conclude that it is incorrect to assume that the pathophysiological disturbances associated with duodenal ulcers reflect aetiological mechanisms. We must determine why ulcers do not heal, because failure of

normal mucosal repair seems to me the aetiological basis of duodenal ulceration.

K G WORMSLEY

*Department of Therapeutics
Ninewells Hospital
Dundee
Scotland*

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