Gastric ulcer and regurgitation gastritis

Experimental and clinical data have incriminated excess gastric acid secretion as an important factor in the development of duodenal ulcer. On the other hand, gastric ulcer is characteristically associated with normal to low levels of acid secretion, and mucosal resistance factors have been invoked to explain the pathogenesis.

The purpose of this report is to summarize the evidence favouring the hypothesis that regurgitation of duodenal contents into the stomach causes gastritis and an attendant decrease in mucosal resistance to ulceration.

Recent experimental results from our laboratory support this proposition. The concept of regurgitation gastritis is not original with us but has received inadequate attention.

Four lines of evidence favour the proposed hypothesis. (1) Gastric ulcer is invariably accompanied by gastritis. (2) Individuals with gastric ulcer have greater than normal regurgitation of duodenal contents into the stomach. (3) Exposure of normal gastric mucosa to intestinal contents leads to gastritis. (4) Gastritis increases the susceptibility of the mucosa to ulcer formation.

Gastric Ulcer and Gastritis

Cruveilhier, in 1862, pointed out the association of gastric ulcer and atrophic gastritis. Konjetzny observed that gastric ulcer is invariably surrounded by inflammatory changes, and noted further that the mucosa in an ulcer-bearing stomach is diffusely abnormal. He proposed the dictum that gastric ulcer never develops in normal mucosa. Magnus correlated gastroscopic and histological appearances of stomachs removed for treatment of peptic ulceration. Thirty per cent of the specimens excised for gastric ulcer had diffuse gastritic changes in the body mucosa. None of the stomachs resected for duodenal ulcer demonstrated such an abnormality.

Hebbel made a thorough study of the relationship of chronic gastritis to gastric ulcer. Of 15 resected stomachs, 12 demonstrated moderate to severe gastritis involving the entire antrum in addition to the immediate region of the ulcer. The diffuse distribution of histological changes suggested to him that gastritis was a primary process rather than the result of the ulcer. Stomachs seen at necropsy from subjects with no known gastric or duodenal disease showed gastritic changes in only 18% of specimens. Guiss and
Stewart\(^8\) reaffirmed that stomach ulcers were invariably surrounded by gastritis. When ulcers were located in the corpus of the stomach, rather than the antrum, there was gastritis in the body mucosa remote from the immediate vicinity of the ulcer.

In no case of gastric ulcer did DuPlessis\(^{10, 11}\) find the antrum to be free of gastritis and in no instance did the changes involve less than 40% of the total antral area. More than half the total area of the body mucosa was affected in 37 of 61 specimens (61%). In every case the gastric ulcer occurred in an area of gastritis. This study supported the observation of Ball and James\(^{12, 13}\) that the higher the ulcer in the stomach, the greater the extent of chronic gastritis and diminution in parietal cells. The latter authors also observed that gastric contents at night were generally neutral in patients with an ulcer of the body of the stomach, whereas patients with antral ulceration demonstrated at least some degree of nocturnal gastric acid production, suggesting again that more extensive mucosal injury is found with ulcers located in the corpus.

Capper\(^{14}\) and his colleagues approached the question from a functional point of view. Patients undergoing operation for ulcer disease were given histamine shortly before the stomach was opened. The pH of the gastric mucosa was mapped directly using a glass electrode. The size of the area not secreting acid varied greatly from one subject to another. The mean area of the alkaline mucosa was more than twice as great in patients with gastric ulcer than in patients with duodenal ulcer or in normals. Every gastric ulcer was found to lie in an area incapable of secreting acid.

To summarize, there is general agreement that gastric ulcer is always accompanied by antral gastritis. The fact that the ulcer does not occur in normal mucosa is widely accepted. Although observations regarding the extent of gastric changes in the corpus associated with gastric ulcer are less consistent, it seems fair to state that an ulcer occurring in the body of the stomach is usually associated with diffuse gastritis in that portion of the organ.

**Duodenal Regurgitation**

Evidence that abnormal quantities of duodenal contents regurgitate into the stomach in gastric ulcer victims has been obtained in human studies. James and Pickering\(^{15}\) pointed out that bile staining of the gastric contents is a more frequent occurrence in individuals with gastric ulcer than in normals. DuPlessis\(^{31}\) measured bile acid conjugates in gastric aspirates. Normal individuals were found to have low concentrations of bile acids in overnight gastric collections whereas patients with duodenal ulcer had somewhat higher concentrations and those with gastric ulcer showed considerably larger amounts.

Rhodes and his group have recently reported a technique in which subjects were given an intravenous dose of\(^{14}\) C-tagged bile salts. Gastric juice was aspirated and the concentration of secreted radioactive bile salts measured, this value serving as an index of regurgitation of duodenal contents through the pylorus into the stomach. Patients with gastric ulcer were found to have significantly greater quantities of bile salts in the gastric contents than patients with duodenal ulcer or normal stomachs.

Capper\(^{17}\) devised a qualitative test for pyloric regurgitation. A small tube was threaded into the duodenum and barium injected. No duodenal gastric reflux could be seen in 15 normal controls whereas 19 of 29 patients (66%) with gastric ulcer had gross reflux. Beaumont\(^{18}\) had observed a century earlier
that bile appeared in the stomach of Alexis St. Martin during 'violent passion' but that 'bile is never present in the gastric organ in health'.

In summary, available evidence suggests that patients with gastric ulcer have excessive regurgitation of duodenal contents through the pylorus into the stomach. Anatomical deformity of the pylorus or duodenum may enhance pyloric incompetence. The mechanism of this motor malfunction is yet to be elucidated.

**Intestinal Juices and Gastritis**

Early suggestions that the contents of the small intestine exert a toxic effect on human gastric mucosa came from observations in patients with gastro-intestinal anastomosis. Benedict\(^9\) made systematic gastroscopic examinations of 50 patients following partial gastrectomy with an end-to-side gastro-jejunostomy (Billroth II reconstruction). Forty-five of the 50 patients had gastroscopic and/or histological evidence of gastritis in the residual stomach. Biopsies of the mucosa after partial gastrectomy were taken under fluoroscopic control and evaluated histologically by Johnston.\(^9\) Eight patients with proven marginal ulcer showed inflammation around the stoma but the gastric mucosa in areas distant from the stoma was normal. On the other hand, the majority of patients without stomal ulcer had diffuse atrophic gastritis involving the entire residual stomach. These observations suggest that the gastric atrophy due to regurgitation of intestinal contents into the stomach may provide some protection against stomal ulcer.

Van Geetruyden\(^41, 42\) has reported extensive studies concerning the effects of intestinal contents upon the gastric mucosa. Following partial gastrectomy with Billroth II reconstruction in human subjects, he measured the secretory capability of the residual gastric pouch and found a progressive diminution in its ability to secrete acid, coincident with progressive gastritis.

Animal experiments have provided more direct evidence of the capacity of intestinal contents to induce gastritis. Using dogs, Lawson\(^49\) constructed gastroduodenostomy (Billroth I) and gastrojejunostomy (Billroth II) anastomoses with distal gastrectomy. The latter allows ready reflux of intestinal contents into the stomach whereas with an end-on gastroduodenal anastomosis peristalsis tends to minimize reflux. The animals were sacrificed after 100 days. In the dogs with Billroth I reconstructions, gastritis was limited to an area within 2 cm of the anastomosis. With Billroth II reconstructions, however, gastritic changes extended halfway up the residual gastric pouch.

Ritchie and his colleagues\(^8\) demonstrated that the parietal and chief cell populations of the residual gastric pouch after antrectomy with a Billroth I type reconstruction are unchanged for periods up to one year following the procedure. However, after a Billroth II reconstruction, there was a progressive diminution in the numbers of parietal and chief cells and a progressive increase in cells secreting mucus. The characteristic changes of atrophic gastritis were most severe within 3 to 5 centimetres of the gastrojejunostomy.

Byers and Jordan\(^44\) implanted vascularized patches of gastric body mucosa into the wall of the gallbladder in dogs. After a year the mucosa was histologically normal, indicating that bile alone was incapable of inducing gastritis. They argued that an acid milieu might be essential to the development of the lesion.

We\(^5\) have reported a series of experiments in which tubes of gastric wall were constructed from the greater curvature of the dog stomach, pedicled on the short gastric vessels, interposed at various site in the gastrointestinal
tract, and biopsied at intervals. Exposure to jejunal contents led to rapid and profound mucosal changes consisting of round-cell infiltration, the appearance of mucus cells deep in the gastric crypts, the diminution of parietal and chief cells, and cystic dilatation of the glands. Exposure of gastric body mucosa to ileal contents had a similar effect. The parietal cell mass after six months of exposure to intestinal contents was so reduced that it could not be quantitated. On the other hand, tubes of body mucosa exposed to pure bile demonstrated no diminution in parietal cell density, although proliferation of surface epithelial cells was seen. In another preparation, the gastric tube was exposed to pure pancreatic juice. Here the morphological changes were consistent with those seen following exposure to whole jejunal contents, but were milder and slower to develop.

Gastritis and Resistance to Ulceration

Lawson\textsuperscript{25} constructed explants of antral or body mucosa on the abdominal wall of dogs. After one month of exposure to air the mucosa was devoid of parietal cells and exhibited a dense inflammatory infiltrate. The explants were then anastomosed back into the stomach wall. Shortly after reimplantation the centre of the mucosal patch ulcerated. \textit{Left in situ}, the ulcers healed and the mucosa returned to histological normality.

Ritchie and Delaney\textsuperscript{4} have carried out a similar experiment, explanting patches of dog gastric corpus onto the abdominal wall. When atrophic gastritis had developed, the patch was reimplemented into the stomach. After a week to allow healing, 10 animals were given 14 days of histamine-beeswax injections as an acid secretory stimulant. Ten control animals received no drugs. All of the control dogs demonstrated persistent atrophy of the mucosal patch for at least 21 days following reimplantation and none developed gastric ulceration. On the other hand, eight of the 10 dogs given histamine developed ulcers confined to the atrophic mucosal patch. The conclusion from both studies is clear: atrophic mucosa is more sensitive than normal to the corrosive action of acid peptic juice.

Discussion

The motor abnormality that leads to excessive regurgitation of duodenal contents into the stomach is not understood. Garrett and Summerskill\textsuperscript{26} studied motility in a series of patients with gastric ulcer and found the propulsive peristaltic waves in the antrum significantly less vigorous than in normal controls.

If regurgitation gastritis is, in fact, the sole basis for gastric ulcer, one would expect to see such a lesion developing frequently in individuals whose pyloric function is destroyed or bypassed by pyloroplasty or by gastro-enterostomy. Such is not the case. Gastritic changes seem to be a prerequisite of, but not the sole cause, of gastric ulcer. Undoubtedly there are other, poorly defined factors that reduce the resistance of the mucosa to the corrosive action of gastric juice. Following gastric resection or vagotomy, acid secretory capacity is likely to be reduced below a critical level such that it is insufficient to ulcerate even damaged gastritic mucosa.

The role of acid secretion in the development of regurgitation gastritis is unclear. Bile alone definitely does not cause the complete lesion. From our experiments it appears that elements of the pancreatic juice play a more important role. Pancreatic enzymes function optimally in the range of normal
intestinal pH and intragastric acidity precludes their activity. We would propose that pancreatic enzymes induce mucosal damage during periods when the gastric pH is nearly neutral. The compromised mucosa is then susceptible to acid peptic injury during periods of low pH. The observation that patients with a gastric corpus ulcer usually secrete no acid during the night is consistent with the proposal that regurgitated intestinal enzymes exert their injurious effects on the gastric mucosa during the hours of sleep.

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References