has been observed in gastric cardia mucous cells in individuals with neither evidence of esophageal metaplastic epithelium nor symptoms or signs of gastroesophageal reflux disease (16).

In conclusion, Barrett's esophagus is defined histologically by its phenotype, similar to that observed in incomplete intestinal metaplasia of the stomach, with both goblet cells and intermediate metaplastic mucous cells. However, it may be difficult to distinguish between short segment Barrett's esophagus and carditis with intestinal metaplasia and there is a need for other markers in this situation.

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Intestinal metaplasia

N. Ectors

Gastrointestinal Pathology Unit, K. U. Leuven, Belgium.

Gastric adenocarcinomas are subdivided into two main histological types with different epidemiological characteristics. The intestinal type of gastric cancer is preceded by a chain of phenotypical changes including *Helicobacter pylon* infection, chronic gastritis, atrophy, intestinal metaplasia and dysplasia. For the diffuse type of gastric cancer no similar precursors have been described.

I-l. pylon acquisition is the main cause of chronic gastritis in humans. The infection causes chronic active inflammation of the gastric mucosa in the majority of infected patients. In up to half of infected subjects, chronic gastritis progresses to atrophic gastritis and intestinal metaplasia. Various mechanisms are triggered that may contribute to the multistep pathogenesis of gastric cancer. Such mechanisms include inflammation-related cascades involving cytokines, free radical reactions, growth factors and their receptors. A novel member of the epithelial growth factor family, cripto, has been shown to be overexpressed in 35% of gastric cancers and is also seen in intestinal metaplasia (1). Numerous other factors may also play a significant role in this process, including overgrowth of bacteria in the hypochiorhydric or achlorhydric stomach, a high dietary intake of salt, nitrates or nitrites, a low intake of vitamins or micronutrients and an inherited genetic instability. The interplay of these factors may affect the cell genome and thus further influence progression towards gastric neoplasia. The molecular biology of gastric cancer has revealed a spectrum of gene errors that vary in type and extent between different histological types of cancer as well as between individual cases. The proposed pathway for the development at the genetic level of poorly *versus* well-differentiated gastric cancer reveals interesting differences (1). There is now evidence that the intestinal metaplasia or the gastric epithelium in atrophic gastritis reveals signs of the abnormal expression of various regulatory genes. Translocated promoter region-met rearrangements have been shown to occur in the earliest stage identifiable in the sequence, *i.e.,* in superficial gastritis, and K-ras mutations are associated with intestinal metaplasia (2). Thus, the mechanisms leading to mutation of the genes in epithelial cells may be triggered very early in the *H. pylon* gastritis sequence and atrophic gastritis and intestinal metaplasia may result from these processes.

It is likely that the nature of the disease complicating chronic *H. pylon* infection is determined by host and environmental factors while bacterial factors determine the magnitude of the risk of developing such disease. The pathogenesis of atrophy is still in part hypothetical. The rate at which atrophy develops has been addressed by investigators in different countries and has recently been summarized by Kuipers *et at.* (3). A range from 1.2-3.3% for the annual rate of development in populations is found as a whole. Conditions characterized by low rates of gastric acid secretion seem to be associated with a higher annual rate of development of atrophy. Furthermore, patients infected with cagA+ strains are almost four times more likely to develop antral intestinal metaplasia than cagA— patients (4).

Reversibility of a number of histological lesions can be achieved through *H. pylon* eradication. Reversibility has been shown in only the first step of the carcinogenesis sequence *i.e.,* in chronic superficial gastritis. Only limited, contradictory data are available on the potential reversibility of atrophy and intestinal metaplasia. Recent data would tend to suggest irreversibility. Forbes *etal.* (5) followed up 22 duodenal ulcer patients with failed *H. pylon* eradication and 32 duodenal ulcer patients with successful *H. pylon* eradication for a mean of 7.1 years. Glandular atrophy remained unchanged in both groups while the presence and severity of intestinal metaplasia was similar in both groups both initially and after follow-up. In a large prospective study, Van der Hulst *et at.* (6) investigated the course of atrophy and intestinal metaplasia after eradication in relation to cagA+ *H. pylon* strains. None of the 122 patients showed changes in the degree of atrophy and intestinal metaplasia after short-term follow-up or after follow-up for up to 18 months. Satoh *et at.* (7) con-

firmed these findings in a small group of patients. It appears that destruction of the glandular basement membrane and the immediately surrounding sheath of supporting cells prevents orderly regeneration. When applying a strict definition of atrophy, as proposed by Genta (8), it is highly unlikely that cure of *H. pylon* infection will result in *restitutlo ad integrum i.e.,* glandular parenchyma regeneration and functional recovery. Few studies have given indications that intestinal metaplasia may reverse. Genta et *al. (9)* have shown in a small but detailed study that intestinal metaplasia regresses.

In conclusion, the mechanisms leading to mutation of the genes in epithelial cells may be triggered very early in the *H. pylon* gastritis-gastric cancer sequence. Atrophic gastritis and intestinal metaplasia may result from these processes. Moreover, these changes would seem to be the point of no return.

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Metaplasia in the ileal reservoir

N. Shepherd

Dept. of Histopathology, Gloucestershire Royal Hospital, Great Western Road, Gloucester, UK.

Introduction

Restorative proctocolectomy with heal reservoir, known as ileal pouch-anal anastomosis in North America, has become a leading surgical procedure for patients with ulcerative colitis and familial adenomatous polyposis (FAP) who require total colectomy. The operation is very popular, particularly because it restores continuity by anastomosis of the heal reservoir to the anorectal junction, thus obviating the need for a permanent stoma. The creation of the pelvic heal reservoir has provided pathologists with a whole new field of study. Not unsurprisingly, the heal reservoir acts as a neorectum and hence morphological changes familiar to pathologists in the rectum also affect the pouch (1).

It has been recognized for many years that the mucosa of the pouch, in the majority of patients, undergoes varying, in some cases profound, morphological change, accompanied by chronic inflammatory change (2-5). While patients with an initial diagnosis of FAP do show such morphological changes, the features are often much more pronounced in ulcerative colitis patients (3, 6). Indeed, studies have demonstrated that individual patients show consistency of these changes, in time, and that it can be predicted which of these groups the patient falls into within 6 months of establishment of the functioning reservoir (7, 8). One such patient group, comprising about 10-20% of ulcerative colitis patients, show the most profound morphological abnormalities, with more advanced chronic inflammatory and villous atrophic change and it is this group who suffer from pouchitis. This enigmatic condition, which requires fulfillment of clinical, endoscopic and histopathological criteria (6, 9), is the most important long-term complication of the operation.

True pouch metaDlasia or not

The combination of villous atrophy together with crypt hyperplasia creates a morphological appearance reminiscent of large bowel mucosa: O'Connell *et al.* (2) first termed this phenomenon 'colonic metaplasia". These changes probably result from an adaptive response of the ileal mucosa to the altered intraluminal environment, especially stasis and alterations in fecal flora (10). Similar alterations are seen in the ileal pouches of experimental animals (11). The pathological changes (and endoscopic abnormalities) are particularly concentrated in the posterior and inferior parts of the pouch, suggesting that contact with static fecal residue is a major determinant of these changes (12). Despite this, no consistent changes have been demonstrated in bacterial flora, although an inverse relationship between villous atrophy and volatile fatty acids suggests that anaerobic bacteria may have a protective role and intramural aerobic facultative bacterial counts have been found to be elevated in patients with pouchitis (4, 6).

The evidence for a form of colonic metaplasia is supported by mucin histochemical studies that have demonstrated a change from small intestinal type sialylated mucin to highly sulfated colorectal-type mucin in a high proportion of cases (3, 5). The mucin change is independent of the original diagnosis, occurring in both ulcerative colitis and FAP patients. The alterations in mucopolysaccharides have also been shown by the use of sophisticated biochemical techniques, in particular the 35S-3H glucosamine dual labeling method, which demonstrates the increased sulfation of both intracellular and secreted large intestinal-type mucus in the pouch (13). The evidence for colonic metaplasia in the reservoir mucosa is further substantiated by the acquisition of immunoreactivity for putative colon-specific monoclonal antibodies and lectins (12, 14, 15). There may be further colon-type features in terms of proliferative compartment organization and electron microscopy, although these cannot be regarded as specific to colonic mucosa (16).

While there is evidence for the acquisition of certain colonic phenotypes in the ileal reservoir mucosa, some studies have cast doubt as to whether the changes represent true and complete colonic metaplasia. For instance, all reservoirs retain evidence of small intestinal mucosal differentiation, specifically disaccharidase activity and a small intestinal-type supramucosal mucin barrier (5). Furthermore, our studies have indicated that, while a high proportion of reservoirs will demonstrate a colonic phenotype, only one-half will demonstrate more than one of these phenotypes (12). For