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. pylori infection will result in *restituto 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. pylori 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.

**References**


**Metaplasia in the ileal reservoir**

N. Shepherd

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

**Introduction**

Restorative proctocolectomy with ileal 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 ileal reservoir to the anorectal junction, thus obviating the need for a permanent stoma. The creation of the pelvic ileal reservoir has provided pathologists with a whole new field of study. Not unsurprisingly, the ileal reservoir acts as a neo-rectum 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 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 metaplasia 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 intra-luminal 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 colo-rectal-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 3SS-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
this reason, we have proposed that colonic metaplasia may not be complete in the reservoir mucosa and that colonic phenotypic change may be a more appropriate term (12).

Colon phenotypic change is a common and widespread feature of the reservoir mucosa. Less common is an epithelial change from small intestinal-type mucosa to that resembling antral-type gastric mucosa. This nonspecific response of intestinal epithelium to ulceration has highly characteristic morphological and immunohistochemical features and has been termed ulcer-associated cell lineage (17). Ulcer-associated cell lineage is seen in a small proportion of reservoirs and in this situation is a useful marker of previous severe active inflammation and ulceration, especially of previous pouchitis (16).

Possible significance of metaplastic change

The precise relationship between colon-type “metaplastic” changes and inflammation in the reservoir remains unclear, and this is particularly so with active inflammation and pouchitis. If there is true colonic metaplasia in the reservoir, even focally, then one could envisage that ulcerative colitis could recrudesce in the heal reservoir. Indeed such a thesis remains the most plausible explanation for the pathogenesis of pouchitis (6, 18). There are many clinical, immunological and pathological parallels between pouchitis and ulcerative colitis. For instance, most accept that pouchitis is essentially a disease of ulcerative colitis patients although there is one “rogue” report of pouchitis occurring in a FAP patient (19). Ulcerative colitis patients show more inflammatory change in their reservoirs than FAP patients (3). Like ulcerative colitis, pouchitis has a strong negative association with smoking (20), is closely associated with extraintestinal manifestations of inflammatory bowel disease, particularly primary sclerosing cholangitis (21, 22) and responds to therapy similar to that used for ulcerative colitis (18). The most contentious facet of the ulcerative colitis theory is the extent or importance of colonic phenotypic change in the mucosa. As already indicated, current evidence would suggest that colonic metaplasia is not complete in the reservoir: it is this area of pouch mucosal pathophysiology that demands further research.

Neoplastic potential in the pouch is a controversial topic. Both dysplasia and carcinoma have been described in the pouch. Neoplastic change in the reservoir has been principally demonstrated arising from remaining rectal mucosa (the cuff) at the lower aspect of the reservoir (23-25). Because of this, many surgeons advocate the removal of all potentially neoplastic (and inflammatory in ulcerative colitis) rectal mucosa in both ulcerative colitis and FAP patients. Colon phenotypic change in ileal mucosa, in combination with inflammatory change and associated epithelial hyperplasia, at least suggests the potential for increased neoplastic risk of the ileal mucosa in the pouch.

In the experience of most groups, dysplasia and carcinoma in the ileal pouch mucosa are extremely rare (26). However, workers from Huddinge, Sweden (8, 27) have intensively studied patients over many years with multiple endoscopies and biopsies and have demonstrated relatively high rates of dysplasia in ulcerative colitis patients: in their studies about 10% of pouch patients develop the most florid inflammatory changes with severe villous atrophy. It is this group that is subject to pouchitis and 71% of patients in this group have had dysplasia, including one with high-grade dysplasia. These studies suggest, at least, that there is potential for neoplastic change within the heal mucosa of the pelvic ileal reservoir in patients with ulcerative colitis. For management purposes, it would seem that the highest risk is with those patients with the most advanced pathological changes, who are those most likely to develop pouchitis. As this patient group can, seemingly, be identified within 6 months of ileostomy reversal, it would seem that these patients should be selected for the most comprehensive surveillance, although all patients should be in surveillance programs until we know more of the long-term outcome for the pelvic pouch.

Currently, there must be a balanced attitude toward neoplastic risk in the pouch. Dysplasia has only been described from one center and others’ experience is that neoplastic change in native ileal mucosa is exceedingly rare. One conundrum of the pelvic ileal reservoir is its dissimilarity, in terms of pouchitis and, ostensibly, neoplastic risk, with Kock’s continent abdominal reservoir. In the latter it has been shown that, in the majority of patients, the ileal mucosa returns almost to normality when the reservoir has been established for 20 years (28). Why the presence of the anal mechanism should have, apparently, such a great influence on long-term inflammatory, metaplastic and neoplastic potential is perplexing. Remaining rectal cuff and differing alterations in the microenvironment would seem possible explanations but investigations are certainly inconclusive. The development of the pelvic ileal reservoir has created a unique in vivo model for ulcerative colitis in pouchitis and an uncertain neoplastic potential. The contribution of metaplastic changes to the pathogenesis of ileal reservoir mucosal pathology remains uncertain. This facet of pouch pathology demands more research.

References

Metaplasia in the pancreas

J. Luttges

Dept. of Pathology, University of Kiel, Germany.

Metaplastic and hyperplastic changes of pancreatic epithelium affect almost exclusively cells of the duct system. The major types of such changes are squamous metaplasia, mucin cell hyperplasia, papillary hyperplasia, and adenomatoid hyperplasia. They occur in normal, disease-free pancreatic parenchyma as well as in association with carcinomas and chronic pancreatitis. All types, preferentially those of the mucin cell type, harbor K-ras mutations at codon 12, the rate varying from about 6% in the normal pancreas to 50% in tumor-associated tissue. However, since there is evidence that these lesions are evenly distributed in the normal pancreas and since they do not show a preponderance in the head region, the preferential site of ductal adenocarcinomas, their role as a tumor precursor should perhaps be reconsidered. Only lesions with dysplasia harbor additional mutations, such as those of the p53 gene or the p16 gene and only these can be regarded as true tumor precursors. Compared with other organs, the role of metaplasia and hyperplasia of the ductal epithelium in the tumorigenesis of pancreatic cancer has not yet been defined and a sequence of stepwise mutations has yet to be discovered.

General remarks

More than 90% of metaplastic and hyperplastic changes occur in the ductal system. For acinar cells, only focal acinar transformation has been described. This has also been termed acinar adenomatous hyperplasia or acinar cell dysplasia, although this alteration is not related to any neoplastic changes of the pancreas and has been reported in various frequencies (1). The duct epithelium is assumed to be the site of origin of ductal adenocarcinomas. Therefore, interest has focused on epithelial changes that might represent tumor precursor lesions. According to the World Health Organization (WHO) (2), four major types are distinguished: mucinous cell hyperplasia, papillary cell hyperplasia, adenomatoid hyperplasia, and squamous metaplasia. Only the latter lesion is of nonmucinous cell type, and is preferentially observed in association with mechanical disturbances of the duct system due to prolonged stenting (2, 3) or with certain types of chemotherapy (4). It does not appear to be related to the development of pancreatic carcinomas. All of the other lesions are of mucinous cell type. Interest has focused on these lesions and studies have been undertaken to determine their distribution in the organ and possible genetic mutations, such as the K-ras or p53 mutations, which are the most common mutations in manifest carcinoma.

Duct lesions in normal pancreatic tissue

The distribution and frequencies of the different duct lesions in the normal pancreas could give a clue as to which lesions and sites are high-risk for the development of carcinomas. The large studies by Sommers (5), Cubilla and Fitzgerald (6), Kozuka et al. (7), Mukada and Yamada (8) and Kk-ppel et al. (9) have indicated that metaplastic and hyperplastic duct changes occur most frequently in the head of the pancreas, the preferential site of carcinomas. However, in these investigations often only one histological slide was evaluated per organ; hence the conclusions must be interpreted with caution. Systematic investigations of sections from the head, corpus and tail by Stamm (10) and by our group (submitted for publication) have revealed that duct changes are evenly distributed throughout the entire pancreas and do not share the same distribution as carcinomas. Nevertheless, they increase beyond the age of 40 (5-7). They can even harbor a K-ras mutation at codon 12, as Tada et al. (11) and our group have shown. Lesions that harbor the K-ras mutation do not, however, preferentially occur in the head of the pancreas. Therefore, other mutational events involving in particular the lesions in the head region seem to be necessary for tumor progression.

Duct lesions in the tumor-associated pancreas

In many organs, precursor lesions have been identified in the vicinity of the established tumor and they provide information on the development of the carcinomas. For the pancreas, several studies on carcinomas (6, 7, 9) have indicated that mucinous cell hyperplasia is the most frequent type of lesion in these organs, followed by papillary hyperplasia, adenomatoid hyperplasia and squamous metaplasia. Molecular analyses have revealed high frequencies of...