Enteropathy-type intestinal T cell lymphomas (EITCL) are a recognised complication of coeliac disease (CD). A recent survey confirmed that non-Hodgkin lymphomas, although rare, are the main cause of mortality in CD. The mechanisms favouring the development of EITCL in CD patients but not in other chronic inflammatory bowel diseases remain elusive, but mounting evidence points to a profound disturbance in intraepithelial lymphocyte (IEL) homeostasis, leading to the emergence of lymphoid malignancies. A link between IELs and EITCL was first advocated in 1988 by Spencer et al, who observed that most EITCL expressed the CD103 IEL marker. Two complementary observations suggested that EITCL derive from a reactive T cell population present in the intestine of CD patients: thus the same T cell clonal rearrangement was detected by Murray et al in EITCL and in the adjacent non-tumoral flat mucosa, and by Ashton-Key et al in non-lymphomatous ulcers of ulcerative jejunitis and in lymphomas, which later developed in these patients. Patient work in refractory sprue (RS) provided a missing link between IELs and lymphomas in CD.

RS is a coeliac-like enteropathy, primary or secondary resistant to a strict gluten free diet (GFD). Several conditions underlie villous atrophy resistant to GFD (Cellier et al, in preparation), but the majority of RS complicate CD and are associated with massive expansion of IELs with normal cytology but clonal T cell receptor γ (TCRγ) rearrangements and abnormal phenotype. The malignant nature of IELs in RS was demonstrated by the frequent association of RS with ulcerative jejunitis (30%), and the outgrowth of EITCL sharing the same clonal identity and phenotype after several months or years in approximately 20% of cases. RS can thus be regarded as a “cryptic or low grade T cell lymphoma” derived from IELs, and draws a link between IEL hyperplasia, characteristic of CD, and EITCL. In some CD patients however, EITCL develop directly without this first intermediary step.

The report of seven new patients by Farstad and colleagues suggests that CD30 allows the early detection of overt lymphoma. Firstly, they detected some CD30+ blast-like IELs and lamina propria cells away from the tumours in their three cases of EITCL. Secondly, in one patient with RS without overt lymphoma, they found that CD30+ IELs were however observed in another RS patient with rapid severe outcome, whereas a third patient with some CD30+ IELs was improved by parenteral nutrition and a GFD. Finally, the patient with many CD30+ IELs did not benefit from one attempted cure of CHOP. These observations illustrate the difficulties in predicting outcome and in propounding an appropriate treatment in RS patients. Apart from CD30, other immunohistochemical markers may help to detect transformation from low to high grade proliferation, such as proliferation markers or p53 detected by Murray et al on small lymphocytes in the bowel adjacent to EITCL. Nevertheless, as in patient No 3 reported by Farstad et al, none of these markers may be useful in predicting untractable malabsorption in the absence of overt lymphoma. Functional analysis of abnormal IELs in RS may identify criteria predictive of their aggressiveness for the mucosa or new targets for therapy, a pressing need given the lack of current efficient treatment for severely sick RS patients and the poor prognosis of EITCL. Insight into the mechanism(s) disturbing IEL homeostasis in CD may help to decipher the links between inflammation and lymphoid malignancies and to design treatments able to prevent or cure these rare but most severe complications of CD.
Irritable bowel syndrome and the enteric nervous system

Infection and irritability

R Lea, P J Whorwell

A proportion of patients with irritable bowel syndrome report an apparent association between the onset of symptoms and a dysenteric illness

Chaudhary and Truelove were amongst the first to recognise that a proportion of patients with irritable bowel syndrome (IBS) report an apparent association between the onset of symptoms and a dysenteric illness. The concept of "post-dysenteric IBS" (PD-IBS) has now been widely accepted of symptoms and a dysenteric illness. However, careful questioning of these patients sometimes, but not always, suggests that they may have had a "forme fruste" of the disorder before their infection, raising the possibility that diarrhea per se is important. It is also well known that the use of antibiotics often results in diarrhoea, and there is reason other than dysentery.

Psychosocial factors are known to be important in IBS. Several studies, including that of Neal and colleagues, which specifically relate to PD-IBS have shown that the risk of developing persistent symptoms following dysentery is related to the presence of psychopathology. Although gastroenteritis may lead to the presence of psychopathology.
physiological changes that predispose to IBS, there is evidence that an adverse psychosocial milieu is necessary for the condition to fully develop. This is perhaps not surprising as it is now well recognised that stress can affect the immune, and hence the inflammatory response. Similarly, stress may increase intestinal permeability, an observation that may be particularly relevant as increased gut permeability has been demonstrated in some patients with PD-IBS.

It would seem reasonable to assume that whatever the triggering factor, an inherited predisposition for IBS might be necessary. This is suggested by the observation that IBS tends to cluster within families, although this could also be explained by environmental factors and indeed, similarities in health related behaviour have been observed between close relatives of those with IBS. Nevertheless, twin studies have shown an increased prevalence of IBS in mono compared with dizygotic twins, which might support a genetic background, but a study involving mono and dizygotic twins separated at birth would be required in order to reach a firm conclusion. Laboratory evidence also provides some support for the concept that inheritance is an important factor in the development of IBS. Studies on cytokines, which are known to be involved in the modulation of intestinal inflammation, have shown that mice lacking the interleukin 10 gene develop a spontaneous form of chronic enterocolitis, and that patients with ulcerative colitis are more likely to have genotypes associated with a lower production of interleukin 10. Similarly, a significantly reduced prevalence of the “high producer” gene for interleukin 10 has been reported in a group of unslected patients with IBS.

It is almost 40 years since Chaudhary and Truelove wrote their classic paper identifying the PD-IBS subgroup. We now know that female sex, younger age, prolonged duration of the initial illness, and psychological comorbidity appear to be important risk factors, and that sufferers usually have the diarrhoea predominant form of the condition. However, there is still much to learn, and emerging technologies will undoubtedly aid this process.

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Colorectal cancer

Top down or bottom up? Competing management structures in the morphogenesis of colorectal neoplasms

N A Wright, R Poulson

Modifier genes may influence the severity, or adenoma number, of familial adenomatous polyposis in humans through tumour initiation rather than progression

One of the earliest tumour suppressor genes to be identified was APC. Germline mutations in APC are found in familial adenomatous polyposis (FAP) and second hits lead to the development of often many hundreds of adenomas in the colon and rectum, some of which progress to cancer if untreated. Many sporadic adenomas, and their ensuing carcinomas, show APC mutations, and FAP remains an important paradigm for the commoner sporadic form. Thus recent studies from the Tomlinson laboratory show a very close linear relationship between the macroscopic—or naked eye—count of adenomas in excised FAP colons and the count made microscopically from adenomas occupying one crypt (the unicryptal or monocryptal adenoma, Fig 1) upwards. Such a close relationship strongly indicates that progression from microadenomas to macroscopic size is essentially random, that variation in disease severity (number of adenomas) results from differences in the number of microadenomas rather than disease progression, and importantly, that the selective advantages provided by different APC mutations act on tumour initiation rather than progression. A paper in this issue of Gut, also from the Tomlinson laboratory, analyses the effects of putative modifier genes: the severity of the disease was related to the site of the mutation, as might be expected, but first degree relatives showed polyph counts which were more similar than more distant relatives [see page 420]. These observations indicate that modifier genes influence the severity of FAP, again through tumour initiation. Furthermore, the finding of a constant microadenoma density as the colon is traversed suggests that initiation of FAP adenomas...
are spontaneous events rather than environmentally produced, which of course has considerable potential implications for sporadic adenomas.

These observations underline the pivotal early events in colonic carcinogenesis: establishment of the mutant clone, its evolution to a microadenoma, and its development into a tumour recognisable by the naked eye. The molecular events associated with these stages are clear in FAP a second hit in the APC gene is sufficient to give microadenoma development. But a further recent article from the Vogelstein laboratory has drawn on some earlier morphological studies to challenge contemporary concepts of how such mutant cells establish themselves and develop into an adenoma. Struck by the appearances in some early non-FAP adenomas (fig 1), dysplastic cells were seen only at the orifices and luminal surface of colonic crypts. Shih et al determined loss of heterozygosity (LOH) for APC, and nucleotide sequence analysis of the mutation cluster region of the APC gene was applied to microdissected well orientated histological sections of these adenomas. Not surprisingly perhaps, half the sample showed LOH in the upper portion of the crypts and most of these had a truncating APC mutation. Those cases without LOH showed a truncating mutation, again confined to the dysplastic epithelium at the crypt apex. Moreover, these cells showed intense proliferative activity, with nuclear localisation of β-catenin, supporting the presence of an APC mutation in these apical dysplastic cells. Several earlier morphological studies have drawn attention to the same appearances, including those in FAP in which the crypt divides, passes to the top of the crypt and proliferates, or transforms in situ at the top of the crypt. Both concepts lead to expansion of the clone in the intercrypt zone [from Shih and colleagues]. (G) How mutated clones expand in the colorectal epithelium by crypt fission.

Figure 1  (A) A monocryptal or unicryptal adenoma. (B) A three dimensional reconstruction of a unicryptal adenoma (inset) from serial sections, showing the adenoma in blue. Note that the adenomatous epithelium extends to the base of the crypt. (C) The mechanism of crypt fission in the normal colon whereby a crypt divides into two by this fission process. (D) A larger adenoma showing expansion by basal fission and budding. (E) Lateral migration at the margins of an adenoma, with adenomatous epithelium invading crypt territories (reproduced with permission from Shih and colleagues, copyright 2001 National Academy of Sciences, USA). (F) “Top down models” of adenoma morphogenesis where either a single cell incurs APC inactivation, passes to the top of the crypt and proliferates, or transforms in situ at the top of the crypt. Both concepts lead to expansion of the clone in the intercrypt zone [from Shih and colleagues]. (G) How mutated clones expand in the colorectal epithelium by crypt fission.
colon in ulcerative colitis—“top down” by lateral migration or “bottom up” by crypt fission, or both? Which management structure prevails will have considerable implications for gut biology.

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Top down or bottom up? Competing management structures in the morphogenesis of colorectal neoplasms

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