Allelic variation in Helicobacter pylori: progress but no panacea

Helicobacter pylori colonisation in the stomach is associated with increased risk for the development of peptic ulcer disease and non-cardia gastric adenocarcinoma. However, the incidences of these diseases vary in different parts of the world, and these rates have been changing over the past century. It now is clear that the mere presence of H pylori is insufficient to account for this variation. Alternative hypotheses to explain differing outcomes include variation in bacterial strains, in host related factors, or in the particular interactions governing the long term equilibrium between H pylori strain populations and the colonised host. In this issue, Kidd et al (see page 499) explore whether H pylori strain differences are related to illness occurrence in South African patients undergoing endoscopy. Why was such a study undertaken?

Despite overall conservation of most genes, H pylori are a highly diverse bacterial species. Their population structure indicates that they are freely recombining, which tends to eliminate clonal or allelic variation. Yet, in accordance with previous work, Kidd et al found that important clonal differences exist, even within the single geographical locale studied. Three important allelic differences are the presence or absence of the cag island, the m1 or m2 alleles of vacA, and the independent s1 and s2 alleles of vacA'; s1 can now be divided into s1a, s1b, and s1c. Although the boundaries of these alleles are not fully defined and probably shift, their very existence, against the strong pressure between particular interactions governing the long term equilibrium, indicates that they are freely recombining, which reflects the summation of all the particular allelic variations. The key to understanding H pylori related diseases is likely to be the interaction term between host genotype, host environment, and gastric microbial populations. I have hypothesised that the age at which H pylori is acquired, and the multiplicity of different organisms colonising the stomach have important bearing on gastric microecology, and thus, ultimately, on disease risk. Nevertheless, those looking for simple answers about the relations of H pylori and disease undoubtedly will be disappointed; the complexity likely is older than the human race. However, the challenge is great, and the clinic is our laboratory. Clinical researchers, microbiologists, experimental pathologists, and mathematicians each can contribute to solving the puzzle.

Conflict of interest: M J Blaser holds patents relating to H pylori genotypes, serology, and vaccines.

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Short bowel, short answer?

The paper by Jeppsen et al (see page 559) shows that glucagon-like peptide-2 (GLP-2) concentrations are low in patients lacking an ileum and colon. This is not an unexpected finding as the L cells that produce GLP-2 are situated in the ileum and colon. GLP-2 is an enterocyte specific growth hormone that in mice causes small and large bowel villus/crypt growth and increases small and large bowel length and weight. In mice it also reduces body weight loss and restores mucosal integrity after dextran-induced colitis. In pigs it reduces gastric antral motility. As it stimulates mucosal growth and/or enzyme activity, GLP-2 is produced by the L cells of the ileum and colon, slows gastric emptying and small bowel transit. Peptide YY, which like GLP-2 is produced by the L cells of the ileum and colon, slows gastric emptying and small bowel transit and may be responsible for the “ileal” and “colonic” brakes. Peptide YY serum values are high in patients with a retained colon and low in patients with a jejuno-colic anastomosis. Thus peptide YY may be responsible for part of the functional adaptation that occurs in patients with a retained colon; however, it is unlikely to induce structural changes.

A distal ileal/colonic peptide with glucagon-like immunoreactivity has been recognised for many years and termed enteroglucagon. However, the molecular structure of enteroglucagon was originally unknown and serum concentrations were derived by subtracting pancreatic glucagon concentrations from total glucagon-like immunoreactivity. Enteroglucagon producing tumours were associated with mucosal hyperplasia and enteroglucagon was thought to be responsible for the ileal adaptation that occurred after a jejunal resection. GLP-2 is likely to be the most important mucosal growth stimulating hormone. Its consists of 33 amino acids and its structure is highly conserved throughout all mammalian species (only one amino acid different in the rat). It has been synthesised and its receptor characterised. As it stimulates mucosal growth there is the possibility of giving it to patients with a short bowel to promote adaptation, or to adults or children with intestinal damage (e.g. from ischaemia, irradiation, chemotherapy, severe coeliac disease, necrotising enterocolitis or congenital microvillus atrophy).

When the jejunum is resected, the remaining ileum undergoes both structural and functional adaptation. Structural adaptation is apparent as the bowel increases in length of bowel. Functional adaptation may be the result of structural changes, a slowing of transit rate or intracellular molecular events (e.g. increased transport and/or enzyme activity). Patients with a short bowel commonly encountered in clinical practice do not have a retained ileum; they have either a jejuno-colic anastomosis or a jejunostomy. There is no convincing evidence in humans that the remaining jejunal mucosa can adapt structurally in either of these situations; however, patients with a retained colon do show evidence of function adaptation.

The clinical problems experienced by the two types of patient with a short bowel are different. Both have problems with nutrient absorption; however, patients with a jejunostomy also lose large amounts of water and sodium from their stoma. This is because of loss of normal daily intestinal secretions (about 4 litres/24 hours), rapid gastric emptying and rapid small bowel transit. If a patient has less than 100 cm jejunum remaining and a stoma he/she is likely, as a minimum, to need long term parenteral saline. This requirement does not reduce with time. Patients with a retained colon do not have these problems and, owing to functional adaptation, nutrient absorption usually improves with time. To explain the differences between the two types of patient, measurements of various gastrointestinal hormones have been made with interest focusing upon those produced by the ileum and colon. Peptide YY, which like GLP-2 is produced by the L cells of the ileum and colon, slows gastric emptying and small bowel transit and may be responsible for the “ileal” and “colonic” brakes. Peptide YY serum values are high in patients with a retained colon and low in patients with a jejuno-colic anastomosis. Thus peptide YY may be responsible for part of the functional adaptation that occurs in patients with a retained colon; however, it is unlikely to induce structural changes.
Pseudo-obstruction in children: transplant or wait?

With advances in immunosuppression intestinal transplantation has emerged as a viable option for patients with chronic intestinal failure and life threatening complications. With a one year graft survival rate of around 60% over the past few years, the current situation compares favourably with the pre-1990 results when 30% survival rates were achieved (data from the Intestinal Transplant Registry: www.lhsc.on.ca/itr). At the 7th Meeting of the European Intestinal Transplantation Study Group (Brussels, 1998), one year survival rates up to 80–90% were reported by some very experienced centres.

In children, chronic intestinal pseudo-obstruction is often a primary disorder, either congenital or acquired. Secondary pseudo-obstruction is related to various systemic diseases and is more common in older patients. According to the pathological findings, the primary disease is classified as neuropathic, myopathic, or idiopathic if no specific pattern is recognised. The disease always involves the small bowel and may occur in any other (or all) regions of the digestive tract. Signs and symptoms of obstruction, but without anatomical obstruction being evident on conventional imaging, dominate the clinical picture. The first symptoms may appear as early as the neonatal period or later in life and range from occlusion and complete intolerance to food to recurrent abdominal pain and constipation.

Chronic bacterial intestinal overgrowth and chronic central venous access for parenteral nutrition can be associated with infectious episodes, which in turn can result in the development of life threatening problems in the context of gut failure (mostly progressive liver disease and/or central venous access problems). Sigurdsson et al propose a reasonable approach—patients who do not present with cholestasis or hepatic dysfunction should be managed conservatively. These patients should benefit from the best appropriate care, minimising the risk of progressive liver disease and preventing line infections. This strategy adheres to the current consensus guidelines: transplantation should be avoided by adequate medical management but patients who develop complications (cholestasis, portal hypertension, vascular access problems) should be referred for transplantation.

Earlier referral and thus registration of patients while still in reasonable health may help to decrease both pre- and post-transplant risks. In a recent study, early referral for liver transplantation led to better results which in turn had a positive effect on patient selection.

Bueno et al reported that a bilirubin concentration above 3 mg/l, a prothrombin time of more than 15 seconds or bridging fibrosis at liver biopsy were significantly related to poor outcome. Also, 80% of the children under 1 year of age when referred for transplant assessment died within two years. Thus, patients should be referred to transplant centres as early as possible before liver dysfunction or portal hypertension has developed, or at least before complications occur. Then, after a full evaluation of the patient's condition, the appropriate management strategy should be discussed with the referring team, including the option for possible future transplantation and its ideal timing.

Early referral and early interactive management between local and transplant centres is essential if the general outcome of patients in potential need of bowel replacement is to be improved.

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Screening for colorectal cancer: the heart of the matter

All screening interventions have the potential to do harm and screening by faecal occult blood testing (FOBT) is no exception. The harm arises not from the test itself, although the psychological impact is not negligible, but mainly from the investigation and treatment of test positives. The benefits of FOBT have been studied extensively and it seems that among those who comply with biennial testing, colorectal cancer mortality is significantly reduced and that the reduction is greater when the test is used annually. But there is a price to pay. Firstly, there is the anxiety engendered by performing the test itself and the greater anxiety induced in those who are found to be positive requiring further investigation. Although this has been shown to be short-lived, lasting mainly until the completion of diagnostic investigations, cumulatively it might be expected to affect around 10% of those complying with the test biennially over 20 years.

Secondly, there are the well documented complications associated with colonoscopy, which is considered the gold standard for the diagnostic workup of test positives. Overall mortality rates are reported to average around 0.02%, varying between 0 and 0.06%. Perforation can be expected in 0.3% and haemorrhage in around 1% of people undergoing polypectomy. A variety of other complications have been reported, the most serious of which are cardiovascular. Finally, there is the significant morbidity associated with the surgical treatment of colorectal cancer and large adenomas, with published 30-day mortality rates varying between 1 and 8%.

Based on the promising findings of the randomised trials, pilot studies of FOBT screening are about to start in two sites in the UK in preparation for possible implementation in a national screening programme. These studies aim to examine feasibility and acceptability rather than efficacy and adverse effects. Therefore the paper in this issue reporting on the adverse effects of screening in the Nottingham study is timely. Robinson et al (see page 588) specifically tackle three issues raised by Ahlquist in a paper questioning the wisdom of implementing screening by FOBT. Ahlquist argues: (1) that false negative results falsely reassure patients, leading to delayed diagnosis and poorer outcome; (2) that colonoscopic mortality compounded over several years could counter any gains in reducing deaths from colorectal cancer; (3) that true positive FOBT results may lead to overdiagnosis and treatment of asymptomatic colorectal cancers which might have an innocuous natural history, perhaps leading to a shortened lifespan. To counter the first point, Robinson et al show that there is no difference in the stage at diagnosis in interval and control cancers, suggesting that false negative FOBTs probably do not delay diagnosis. In response to the second point, they show that there were no colonoscopy deaths although their perforation rate (5 of 1474, 0.3%) was exactly as that reported by Ahlquist. Moreover, they restrict their analysis only to baseline colonoscopies even though those who were found to have adenomas were entered into a colonoscopic surveillance programme. If we assume that the 40% of patients undergoing colonoscopy who were found to have adenomas underwent an average of two more colonoscopies, this approximately doubles the exposure of the cohort to colonoscopy.

One point not tackled by Robinson et al was the observation by Ahlquist that, in the Minnesota study, the reduction in colorectal mortality was precisely offset by an increase in mortality from cardiac ischaemia. An increase in cardiovascular deaths, of similar magnitude to the reduction in colorectal cancer mortality, was also observed in the Danish study. The non-colorectal cancer mortality rate was also increased in Nottingham, more than offsetting any reduction in deaths from colorectal cancer, therefore it would have been of interest to have examined deaths from ischaemic heart disease in Nottingham (table 1).

Table 1 Proportion of deaths due to various causes by screening arm in randomised trials of faecal occult blood testing

<table>
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<th>Control</th>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kronborg and colleagues2</td>
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<td>30996</td>
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<tr>
<td>Mandel and colleagues3</td>
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CRC, colorectal cancer; IHD, ischaemic heart disease.

See article on page 588
HCV in hepatic failure

Despite the identification of hepatitis C virus (HCV) as an aetiological agent of blood borne non-A, non-B (NANB) hepatitis a decade ago, its role in fulminant NANB hepatitis is still uncertain.1 In the West, HCV is only infrequently associated with NANB fulminant hepatitis. Thus, in studies from the USA, positive serum HCV RNA was reported in none of 15 cases by Wright and colleagues2 and in only two (12%) of 17 cases by Liang et al.3 Similarly, none of the 23 and 30 NANB cases in the French and English series, respectively, was positive for HCV infection.4 In contrast, the prevalence of serological markers of HCV infection in NANB fulminant hepatitis is much higher in the Oriental countries. In an early study from Japan, Muto et al found that seven (58%) of 12 patients with NANB fulminant hepatitis were anti-HCV (anti-C100–3) positive; findings which were later confirmed by Yangi et al who reported detectable serum HCV RNA in 43% (3/7) of cases of NANB fulminant hepatitis.7 In Taiwan—geographically close to Japan—HCV RNA was detected in 45–50% of patients with NANB fulminant hepatitis8 and in the Republic of China, more than 50% of patients with various types of fulminant viral hepatitis had anti-HCV.9

The cause of this discrepancy between findings in the West and East is uncertain. Views of the pathogenesis of fulminant viral hepatitis suggest that an aggressive early host immune response to the virus is the cause of massive hepatocellular necrosis. Levels of the causative virus in the serum and liver may be high before the “peak” of liver damage and due to immune clearance, the viral load could be below the detection limit of currently available assays when the patients are first seen at the time of severe liver damage.10 Hence, in the absence of serial serum samples, in particular those preceding the patient’s admission to hospital, early HCV viraemia may have been missed. In many series the diagnosis has been based on the presence of anti-HCV rather than HCV RNA in the serum and unlike HCV RNA, anti-HCV is usually not detectable for two to three months after the initial exposure and infection. With the short time course of illness, patients with fulminant hepatic failure may not survive long enough to develop detectable anti-HCV in the serum. In most of the studies tackling the issue of HCV aetiology in NANB fulminant hepatitis, serial serum samples during and after the illness are lacking. However, in a recent study by an NIH group, the level of HCV viraemia, as measured by branched-chain DNA assay, increased in parallel with serum alanine aminotransferase concentrations and the degree of hepaticcellular necrosis, indicative perhaps of a direct cytopathic effect of the virus.11 Accordingly, a single negative test for HCV RNA, by PCR, in a patient with fulminant hepatitis would rule out HCV as the cause. This finding certainly requires further validation.

As the various HCV genotypes have geographical preferences: 1b in Oriental countries and 1a in the USA, another possibility would be that the differences between East and West in fulminant NANB hepatitis are related to distinct HCV genotypes. This possibility was explored in the prospective study reported in this issue by Chu et al (see page 613). One hundred and nine consecutive HCV RNA positive patients with acute hepatitis admitted to a Taiwan hospital were investigated. Eleven patients (10.1%) developed fulminant hepatic failure but no correlation could be detected between the occurrence of fulminant hepatitis and HCV genotype. Other viral factors such as HCV viral load and coinfection with hepatitis G virus (HGV) were also investigated and were not found to be related to the occurrence of a fulminant course. One shortcoming was the lack of cases with genotype 1a in the current series which could have weakened the significance of the findings. In a recent human-to-chimpanzee transmission experiment, the same HCV strain, genotype...
HBV infection and even displace HBsAg from serum.  

One important finding in the study by Chu et al was the presence of concomitant chronic hepatitis B virus (HBV) infection, as defined by positive HBV surface (HBsAg) and negative IgM anti-HBV core (HBc) antigens in nine (82%) of 11 subjects who developed fulminant hepatic failure compared with only 30/98 (31%) of those with non-fulminant acute HCV hepatitis (p<0.05). This is in keeping with a study from France which showed that eight (47%) of 17 HBsAg positive patients with fulminant hepatic failure were also HCV RNA positive, although on no occasion in that series was HCV infection alone demonstrable. Furthermore, Wright et al detected HBV DNA by PCR in the liver specimen from six of 12 patients with “NANB” fulminant hepatic failure treated by transplantation who had negative HBV serological markers and undetectable serum HBV DNA in the serum by PCR. It has also been shown that acute hepatitis C infection in patients with chronic HBV can suppress markers of HBV infection and even displace HBsAg from serum.  

Hence, in some instances of HCV superinfection of HBV carriers or concomitant dual infection, HBV serological markers may not be detectable and the severe liver damage may be attributed to HCV alone. It is also possible that without the co-factor of HBV infection—much more likely in areas of high prevalence as in the East—HCV will less frequently be the cause of fulminant hepatic failure. Whatever the inter-relation between HCV and HBV infection in the East, it is clear that in the West there is still a significant percentage of cases of fulminant hepatic failure from presumed viral hepatitis where no markers of hepatitis viral infection can currently be identified.

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