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Landscaper seeks remunerative position

R J PLAYFORD

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**Landscaper seeks remunerative position**


**Abstract**

Juvenile polyposis syndrome (JPS) is an inherited genetic defect resulting in production of multiple hamartomas, some of which subsequently develop into carcinomas. About 30% of these patients are known to have a heterozygotic defect in the SMAD4 gene that codes for a mediator of transforming growth factor beta signalling. The loss of one of the two normal SMAD4 alleles is not thought to be sufficient to induce hamartomas but requires the additional loss of the residual normal allele as a secondary event. In patients with JPS, the hamartomas were thought to result from loss of the second normal allele in stem cells that produced stromal cells and equally importantly, that the overlying epithelium continued to have one copy of the normal allele. On this basis, the subsequent development of carcinoma of the epithelium was considered to be due to the epithelial cells being positioned in a highly abnormal microenvironment (“soil”, hence landscaper theory). In this paper, Woodford-Richens et al used fluorescence in situ hybridization (FISH) directed against the SMAD4 gene to probe individual cells of the polyps to determine which had lost both copies of SMAD4. They found that cells of the stroma and epithelium, but not the inflammatory infiltrate, had lost both alleles. A complicated theory involving “cross talk” between a normal overlying epithelium and an abnormal stroma does, therefore, not have to be invoked to explain why the epithelial cells subsequently undergo malignant transformation. In addition, the finding of identical secondary genetic defects in both the epithelium and stroma of the hamartomas suggests that they originate from the same stem cells and not from distinct lineages as previously thought.

**Comment**

In 1998, Kinzler and Vogelstein proposed a hypothesis that expanded the limited data available from known specific genetic defects into a general mechanistic process underlying malignant transformation of the gastrointestinal tract. In this model, classic tumour suppressor genes such as APC function as “gatekeepers”, preventing, in the case of APC, the translocation of β-catenin to the nucleus where it complexes with Tcf-4 and induces, inter alia, expression of c-myc, with ensuing increased cell proliferation and selection. Secondly, DNA repair proteins such as MLH1 and MSH2 act as “caretakers” of the genome, correcting mismatches in potentially important genes and thus preventing their inappropriate expression. Finally, in a series of diseases as disparate as inherited polyposis syndromes such as juvenile polyposis syndrome (JPS), and acquired conditions such as ulcerative colitis, changes in the stromal component of the lesions—the clonal stromal component of the hamartomas of JPS and the inflammatory infiltrate in ulcerative colitis—result in an altered terrain for epithelial cell growth which increases cancer susceptibility (the “landscaper” hypothesis or effect). In this model, it is envisaged that mutations in the stroma of the hamartomas in some way modulate epithelial cell proliferation through epithelial:mesenchymal interactions or epithelial damage (fig 1) while the cocktail of cytokines secreted by the inflammatory infiltrate have similar effects on the colonic epithelium in ulcerative colitis. The detailed molecular processes underlying this epithelial:mesenchymal “cross talk” remain to be elucidated although several examples have now been demonstrated. For example, large...
fold gastritis is a premalignant gastric condition that involves Helicobacter pylori colonisation causing an increase in cytokine (interleukin 1β) production by the inflammatory infiltrate. This in turn stimulates hepatocyte growth factor production and release by mesenchymal cells, resulting in increased epithelial proliferation due to the released hepatocyte growth factor binding to c-met receptors on epithelial cells. In conditions such as these, a general stimulation of proliferation may allow subpopulations of cells with genetic defects to expand. Alternatively, the constituents of the inflammatory cocktail, such as nitric oxide, free radicals, and the cytokines themselves, may result in direct genetic injury. In addition, modulation of cytokine and growth factor production might influence cell growth and cell-cell interactions via mechanisms such as E-cadherin downregulation and β-catenin signalling.

While the jobs of the “caretaker” and “gatekeeper” appear safe, at least for the moment, a recent paper by Woodford-Richens and colleagues has made the position of the “landscaper” if not redundant at least tenuous. Epithelial malignancies are increased in incidence in both JPS and ulcerative colitis. The “landscaper” effect was coined to explain the apparent paradox of a stromal lesion—the hamartomas of JPS—predisposing to an epithelial malignancy: the abnormal stromal environment affects the development and growth of epithelial cells. JPS is one of several hamartomatous polyp syndromes which include Peutz-Jeghers syndrome and Cowden’s syndrome, all of which show multiple polyps in the gastrointestinal mucosa, with cystically dilated glands and a cellular stroma composed of smooth muscle, fibroblasts, and myofibroblasts. The spectrum of organ specific malignancies in these syndromes is wide, with Peutz-Jeghers syndrome predisposing to breast, cervix, and gastrointestinal cancers, Cowden’s syndrome to thyroid and gastrointestinal tumours, and JPS to carcinomas occurring in the intestine and stomach. The molecular pathology of these lesions is now being studied: in Peutz-Jeghers syndrome, the polyp epithelium shows clonal allelic loss at the LKB1/STKII locus (encoding a serine-threonine kinase) on chromosome 19p13.4, and carcinomas arising in Peutz-Jeghers Syndrome show loss of this wild-type allele, strongly favouring evolution from hamartomas to carcinoma. Moreover, hamartomas, and both adenomas and carcinomas in Cowden’s syndrome, show loss of heterozygosity at the PTEN/MMAC1 locus on chromosome 10q23.3, indicating that further loss of the wild-type allele induces growth of the hamartoma with occasional progression to carcinoma, in the classical tumour suppressor gene mode.

In JPS, germline mutations in the SMAD4, or DPC4 gene on chromosome 18q21.1, are seen in a proportion of cases. Most SMAD4 mutations produce a truncated protein that inactivates its function as a cytoplasmic mediator in the transforming growth factor β signalling pathway. SMAD4 appears to act as a classical tumour suppressor (gene) in the colon and pancreas, and importantly, a high incidence of colorectal cancer has been reported in a large JPS kindred, linked to 18q21.1, with mutation in SMAD4, further suggesting that SMAD4 acts as a tumour suppressor gene in JPS.

Using microsatellites, Woodford-Richens and colleagues have demonstrated that JPS polyps containing a constitutional mutation often lose the wild-type SMAD4 allele, strongly suggesting that somatic loss of this allele is the first somatic mutation, inducing the growth of the hamartoma. Thus hamartomas in JPS resemble colonic adenomas, rather than primarily stromal lesions as previously thought. Furthermore, FISH showed loss of SMAD4, not only in epithelial cells but also in stromal fibroblasts and pericytial myofibroblasts, but not in lymphocytes.

These findings indicate that the epithelium in JPS polyps is clonal and somewhat surprisingly, this clonality is shared by a component of the stroma, suggesting that the precursors of these lesions are laid down very early in development, before epithelial:mesenchymal differentiation in the intestinal anlage, with later clonal expansion. Alternatively, the mutation could occur later in life as a stem cell with plasticity of a greater degree than is usually considered. Certainly other neoplasms with multiple lineages, such as hamartomas in tuberous sclerosis and mixed Mullerian tumours which contain both epithelial and mesenchymal elements, appear clonal.

This brings the epithelium into sharp focus in the formation of the hamartoma and its progression to carcinoma. Thus in JPS, and also possibly in other hamartomatous lesions such as Peutz-Jeghers syndrome and Cowden’s syndrome, the development of epithelial malignancy is likely to be due to direct progression of the epithelial component. Therefore, although the previous suggestion of complex epithelial:mesenchymal interactions remains a possibility in the causality of malignant development of JPS, invocation of Occam’s razor dictates that the most “straightforward” mechanism (involving the minimum number of assumptions) should be considered to be the most likely. There is no need therefore to incriminate the “landscaper” hypothesis: in these lesions, job flexibility or retraining to the “gatekeeper” career pathway seems more appropriate. Whether or not openings are available for landcapers in other terrains, such as the inflamed colon of patients with ulcerative colitis, remains to be seen.
Ulcerative colitis is more strongly linked to chromosome 12 than Crohn's disease

LETTERS TO THE EDITOR

Editor,—Lesage and colleagues reported failure to detect linkage to the IBD2 locus on chromosome 12 in a panel of 95 families with two or more relatives affected by Crohn's disease (Gut 2000;47:787–91). Linkage of inflammatory bowel disease (IBD) to this region was first detected in a panel of 160 families containing multiple cases of Crohn's disease, ulcerative colitis, or both.1 Lesage et al justify the study of Crohn's disease families alone on the grounds that "genetic heterogeneity in susceptibility cannot be ruled out", and they imply that studying the Crohn's disease subgroup of IBD should thus maximise their chance of successful replication. We concur entirely that genetic heterogeneity is important, and we have recently reported strong evidence that it does indeed apply to chromosome 12.2 However, our study of 367 multiply affected families suggested a significantly stronger contribution of this locus to ulcerative colitis than Crohn's disease.3 The difference between the linkage results for ulcerative colitis (LOD 3.01) and Crohn's disease (LOD 1.66) reached statistical significance in two separate tests for heterogeneity. In the light of these results, the validity of the exclusion map drawn by Lesage et al is undermined. The exclusion map was based on an assumed locus specific $\lambda_c$ of 2.0, but this value was derived from a panel containing Crohn's disease, ulcerative colitis, and mixed pairs.4 Given the evidence for a substantially stronger contribution to ulcerative colitis than Crohn's disease, it is likely that the true $\lambda_c$ value for this locus with regard to Crohn's disease is much less than 2. Thus the contention that Lesage et al can exclude a contribution of IBD2 to Crohn's disease susceptibility is probably not valid. As pointed out in the accompanying editorial, simulation studies have demonstrated that lod scores can be expected to vary, particularly when the study population is relatively small.5 Furthermore, the implication that a panel of 157 affected relative pairs should provide sufficient power to detect linkage if this locus is contributing to disease susceptibility is at marked variance with the power calculations derived by Suarez et al, Mandal et al, and others.6

In many respects, the surprising feature is that IBD2 has been replicated in as many as five independent panels.7 The datasets that have failed to detect linkage at this locus have all contained predominantly or exclusively Crohn's disease cases.8 Although IBD2 probably does contribute to Crohn's disease susceptibility, the effect is likely to be weak and thus would require very large panels of multiply affected families to have a realistic expectation of replicating (or excluding) the linkage result.

It is our view that attempts at fine mapping IBD2 probably have the greatest chance of success and of offering new insights into genes or individuals with ulcerative colitis, which appears to be significantly more strongly linked to this locus than Crohn's disease.

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References


Reply

Editor,—In 1996, Satsangi et al reported a positive linkage between inflammatory bowel disease (IBD) multiplex families (including Crohn's disease (CD), ulcerative colitis (UC) and mixed families) with a locus (called IBD2) located on chromosome 12. The attributable risk in siblings (s) of this IBD2 locus was calculated to be 2. In a recently published study in the journal, we failed to demonstrate a positive linkage on chromosome 12 using an independent panel of 95 CD multiplex families (Gut 2000;47:787–91). This result was different to the previous report and we proposed several explanations for the observed discrepancy.

The first explanation may be lack of statistical power in our replication study. We investigated a similar number of affected relative pairs (n=157, all CD pairs) compared with the first linkage analysis (n=186, 81 CD pairs, 64 UC pairs, and 41 mixed pairs). Because linkage tests may exhibit large fluctuations when applied to family sets of similar size for complex genetic disorders, we tested if a gene with a $\lambda_c$ of 2 was compatible with our observation and we were able to reject the hypothesis. We thus concluded that genetic heterogeneity may occur in Caucasian family panels for IBD susceptibility. Parkes et al have recently demonstrated that this genetic heterogeneity may be related to phenotypic heterogeneity. In their proposed susceptibility model, UC is more tightly linked to IBD2 than CD. This study confirms our conclusion that there is genetic heterogeneity in familial IBD. As expected, this heterogeneity may be in part reduced by an adequate phenotype classification, as done from a methodological point of view, Parkes' report demonstrates that working on homogeneous phenotype groups may be preferable than pooling several phenotypes for linkage studies. Considering CD and UC families as separate subgroups, Parkes et al suggested that the IBD2 locus has only a marginal role in CD susceptibility. This conclusion is in complete accordance with our demonstration that the relative risk attributable to IBD2 in CD multiplex families is low.

In practice, it is difficult to know what is the weight of this IBD2 locus in both CD and UC. A line of evidence, including the above mentioned reports,1 and a large collaborative work performed on more that 600 multiplex IBD families clearly suggests that the role of the IBD2 locus is weak in CD families. In contrast, its role in UC is difficult to estimate to date. In their recent work, Parkes et al pooled previously investigated families from UK and US panels.7 Because these families were a priori known to be positively linked to IBD2, this study provides a biased estimate of the role attributable to IBD2. Further works using unselected family panels are required to answer this question.

Interestingly, the IBD1 locus has been postulated to play a major role in UC and to be less important in CD.9 However, in their recent report they would be postulated that IBD1 is a CD susceptibility locus and IBD2 is a UC gene. Some truth may reside in this assertion. However, a line of evidence including analysis of family data10 suggests that UC and CD have common familial risk factors and does not allow a simple dichotomic classification of UC and CD genes. Many additional steps, including gene identification, are now required before we can understand the underlying genetic model for IBD which will certainly be confirmed as a complex genetic disorder.

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References

Intestinal permeability: the cellubiosemannitol test

EDITOR,—I should like to bring to your attention a conceptual error in the paper by Daniele et al (Gut 2001;48:28–33) regarding the cellubiosemannitol test. The authors suggest that improvement in cellubiose mannitol ratio reflects improvement in permeability from the use of oral glutamine. However, only mannitol excretion improved significantly with glutamine; cellubiose excretion remained unchanged. As the authors explain in their methods section, it is the increased cellubiose excretion that reflects increased permeability, not the decrement in mannitol excretion. Therefore, modifications in sugar transport induced by 5-fluorouracil (5-FU) reflected only an absorptive, not a permeability, nature. The conclusion remained unchanged. As the authors suggest in their methods section, it is the increased cellubiose excretion that reflects increased permeability, not the decrement in mannitol excretion. Therefore, modifications in sugar transport induced by 5-fluorouracil (5-FU) reflected only an absorptive, not a permeability, decrease. The decrement in mannitol excretion parallels the decrement in D-xylose excretion, probably reflecting decreased transcellular passage of the test sugars induced by 5-FU and improved with glutamine.

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Reply

EDITOR,—I thank Dr Craig for raising this issue but I do not see any conceptual error. The apparent inconsistency that he points out in our paper (Gut 2001;48:28–33) is due to the controversy surrounding transcellular permeation of mannitol, as well as of other monosaccharides. While transcellular permeation of mannitol is well known, its use for osmotic shrinkage of membrane vesicles and as an extracellular fluid marker suggests that, at least in part, mannitol diffuses through the intercellular tight junctions. Thus it seems justified talking of permeability for mannitol. One of the reasons for its use in combination with cellubiose is the different molecular sizes of the two probes: the smaller size of mannitol allows its passage through the small tight junctions of the villi while the larger cellubiose passes through the larger tight junctions of the crypts. Further, we did find an increase in cellubiose excretion after fluorouracil (5-FU) that was in part prevented by oral glutamine. Although this difference did not reach statistical significance, overall the data indicate increased intestinal permeability after 5-FU, partially prevented by oral glutamine.

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Evaluation of the role of CFTR in alcohol related pancreatic disease

EDITOR,—In up to 30% of patients with idiopathic pancreatitis (IP) a mutation of at least one or both alleles of the cystic fibrosis transmembrane conductance regulator (CFTR) gene can be identified.1,2 The study by Malats et al (Gut 2001;48:70–4) addressed the question of whether CFTR mutations, possibly together with environmental factors such as alcohol, may be associated with chronic pancreatitis or pancreatic cancer. The vast majority of the pancreatic patients (86.4%) investigated by Malats et al were diagnosed as having alcoholic pancreatitis (AP), and 75.4% of the cancer patients were daily drinkers. The authors found no statistically significant difference in the prevalence of delta-F508 (0%; 2.4%) and the 5T allele (10.5%; 5.5%) in the AP or cancer groups compared with the expected prevalence in the general population. The lack of a positive association of both delta-F508 and the 5T allele with AP is neither surprising nor argues against involvement of CFTR variations in the development of AP, considering the following. In cystic fibrosis (CF), the degree of correlation between CFTR genotype and CF phenotype varies between clinical components but is highest for pancreatic involvement.1 CFTR mutations can simplify be divided into “severe” and “mild” with respect to the degree to which mutations impair CFTR function.2 Approximately 85% of CF patients suffer from pancreatic insufficiency (PI) while ~15% are pancreatic sufficient (PS). Generally patients with two “severe” mutations as well as is associated with at least one “mild” mutation (fig 1). In CF, pancreatic insufficiency is rather frequent in PS patients but not in PI patients. Today, more than 850 CF mutations have been reported to the CF Consortium (http://www.genet.sickkids.on.ca/cftr). The deletion delta-F508, accounting for about 70% of mutant CF alleles worldwide and approximately 53% in Spain, studied by Malats et al, is responsible for severe functional loss of CFTR function. Further studies including the prevalence of an abnormal CFTR allele in AP have been published as full papers.1,3 Pooling these four studies, one or two mutant CFTR alleles were detected in 9/217 (4.1%) patients with AP. But the detection rate varies between 0% and 8.5% depending on the sensitivity of the screening method to detect an abnormal CF allele in the corresponding population (53–94%). None of the studies revealed a positive association of the 5T allele with AP or IP. Compared with the general population, delta-F508 was significantly more frequent in British and US Caucasian, but not in Australian or Spanish AP patients. Up to now no environmental or genetic cofactor was identified in patients with mutant CFTR alleles associated IP, suggesting that impairment of CFTR function alone may not be enough to induce pancreatitis.3,4,5,6 On the other hand it may be speculated that patients with an abnormal CFTR allele, who develop pancreatitis in conjunction with alcohol abuse, may be characterised by a higher residual CFTR function, which by itself is not capable of inducing pancreatitis. Therefore, to delineate the genetic background of pancreatic disease in AP it seems to be more appropriate to investigate this prevalence of uncommon mild variants (“atypical mutations”) in large cohorts of AP patients than to test for the more common (“severe, typical”) mutations of the CFTR gene in small patient groups. It has to be considered that the test kits for CFTR mutations often used in routine screening are usually designed to detect the more severe CF mutations. This would result in missing a substantial number of patients with CFTR mutations, as suggested by preliminary data on more comprehensive genetic testing in patients with ICP.

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Reply

EDITOR,—We agree with the view of Ockenga et al that from an ideal research perspective a complete analysis of the cystic fibrosis transmembrane conductance regulator (CFTR) gene should be performed for cases of pancreatitis before a definitive statement on...
the role of this gene in chronic pancreatitis can be made. However, it is well known that 18–30% of patients with CFTR related disorders (congenital bilateral absence of the vas deferens and bronchiectasis) have only one CFTR mutated allele.1,2 Thus despite our study being based on only the two most common CFTR mutations (F508del and 5T), these two alterations should suffice to rule out or confirm a potential role of CFTR in patients with chronic pancreatic diseases. Furthermore, complete analysis of CFTR in the general population has led to the identification of amino acid variants of yet unknown clinical and functional consequences, as it has been shown for patients with asthma.3 As we proposed in our paper (Gut 2001;48:70–4), only the design of large studies specifically addressing these issues in target and adequate control populations and a comprehensive molecular analysis of CFTR will answer the question on the role of this gene in chronic pancreatic disease.

We first described the strong correlation between obesity and serum TNF- α in 1998.4 Adipose tissue synthesises a number of proinflammatory cytokines.4 The negative correlation found in the Adelaide study is surprising given the findings in larger studies of non-NASH subjects, and may be due to the small study numbers and not correcting for modest alcohol intake.

Alcohol consumption is considered a risk factor for the development and progression of liver disease in patients with fatty livers. We previously showed a strong negative correlation between any alcohol consumption and serum TNF-α levels in a general population sample.5 Moreover, consumption is known to suppress TNF-α production by monocytes, thereby suppressing post-transcriptional TNF-α production.6 Furthermore, alcohol also has effects on TNF-α function mediated via high density lipoprotein (HDL). Alcohol enhances HDL levels by stimulating lipoprotein lipase activity in adipose tissue.7 HDL not only inhibits TNF-α release from macrophages8 but also protects certain cells against TNF-α induced damage.9

If TNF-α is important, then modest alcohol intake should be protective via suppression of TNF-α. This raises the possibility that TNF-α is not important in early steatohepatitis.

In defining patients with NASH, alcohol consumption must be rigorously excluded. In the Adelaide study, 10 of 22 patients drank up to 20 g of alcohol per day; however, even modest amounts of alcohol have effects on TNF-α levels and function.

The known interaction between alcohol and obesity in the pathogenesis of fatty liver and steatohepatitis suggests that investigators must look to factors other than TNF-α in studying the early pathogenesis of this condition. In the same way that altered cytokine homeostasis has been implicated in alcoholic liver disease, NASH is probably caused by changes to more than one proinflammatory cytokine. Interleukin 6 (IL-6) is a proinflammatory cytokine, a hepatocyte stimulator, and inhibitor of hepatic apoptosis. It has been suggested that hepatic steatosis is due to the rate of hepatocyte apoptosis becoming insufficient to match the rate of hepatocyte proliferation. IL-6 induced liver regeneration may render the liver more susceptible to the effects of other insults. Unlike TNF-α, serum IL-6 shows a positive correlation with both obesity and alcohol intake (fig 1).10 So far IL-6 has not been studied in the aetiology of NASH.

Future studies examining the link between TNF-α and NASH will need to rigorously control for alcohol consumption and assess many other aspects of the inflammatory cytokine network.

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Reply

EDITOR,—Our recent paper found increased small bowel bacterial overgrowth (50% versus 22%) and twofold increased systemic levels of tumour necrosis factor α (TNF-α) in patients with non-alcoholic steatohepatitis (NASH) compared with control age and sex matched subjects (Gut 2001;48:206–11). Poullis and Mendall question the finding of elevated TNF-α levels in blood in NASH subjects and quote their own work of elevated TNF-α levels in obese subjects.1 There was no correlation between TNF-α levels and obesity in our study whereas their study showed a correlation with obesity. How can this be explained? The question comes down to whether TNF-α is being produced predominantly in adipose tissue or in the liver, and which of these contributes to elevated systemic levels. At the moment this cannot be resolved. TNF-α will need to be investigated in liver biopsies and TNF-α levels sampled from the hepatic vein (not entirely impossible). The same should be done in animal models of obesity. In the meantime, it would be important to ascertain what proportion of obese patients have unrecognised NASH and whether this could explain the elevated TNF-α levels in obesity. Several lines of evidence suggest TNF-α is upregulated in the liver in alcoholic liver disease and presumably this is reflected in serum levels. We doubt therefore whether a low (<20 g/ day) consumption of alcohol reduces systemic TNF-α levels but this could be formally studied. We have re-examined our data and found that there is no difference in mean TNF-α levels between those who


Figure 1 Relationship between the cytokines tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6), and obesity and alcohol. BMI, body mass index.

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reported no alcohol consumption and those who drank alcohol. Finally, we would also comment from our recent work that shows that the C\textsuperscript{13}-D-xylose/H\textsubscript{2}-CH\textsubscript{4} breath test is only positive in 60–69% of cases of small bowel bacterial overgrowth, mostly because it depends on bacterial overgrowth being present on the day of testing. Thus small bowel overgrowth may have contributed even more to NASH than indicated in our paper.

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We are in the throes of a revolution in the printing world, the ramifications of which cannot be accurately foreseen but are certainly as likely to have as dramatic effect on global culture as did Johann Gutenberg's invention of printing in the 15th century. Maybe we should all be pleased that we are living right in the middle of the revolution in communications technology. It is an endless source of fascination to listen to those who just a few years ago could not distinguish a RAM from a ROM, now feeling free to wax lyrical to all within earshot about the latest bit of “state of the art” technology that they own. How good it is to be at the cutting edge of information technology.

Yet, maybe not everyone is head over heels in love with IT. While the medical and particularly the academic community are keen to grasp all the opportunities, there must be many publishers who are rather fearful about what the future might bring. For them, like for almost all of us, change brings uncertainty. But it is not good to question technological progress in the UK just now. We have a modernising government and its leader is fond of saying that he is proud of his country’s past, but he does not want to live in it!

So what will modernisation bring to the publishing world. A whole generation is now being brought up to look upon the personal computer as the main means of communication. Conventional correspondence is now sneeringly dismissed as “snail mail”. Maybe daily newspapers will hang in there a bit longer but what is the future of medical journals?

All of these thoughts were going through my mind as I read this book, the first edition of which was published six years ago. The sheer range of what can now be done interventionally through an endoscope is quite breathtaking. There is a series of essays on therapeutic endoscopy nearly all of which are of very high quality indeed. The publisher, WB Saunders, has served the editors very well. I think this book has been most beautifully produced—the illustrations are generally very fine and the reproduction of colour photographs is quite superb. This is a book that should be read by every trainee.

Yet there is a problem. It is something of a truism that medical textbooks are out of date before they are published. Of course that is always true, even in an area such as this where the pace of technological progress out speeds the publishing schedule. However, the problem here is rather deeper. In many ways, this book is a manual. It is full of helpful tips on “how to do it” and it is very good on pitfalls and how to avoid them. The problem is that the medium of a textbook just cannot be the way of the future for this sort of book. As most of the neologisms in the IT language, multimedia is a fairly ghastly word, nevertheless one just feels there ought to be a CD or DVD to go with the book.

Whether anybody will be publishing books like this in five years time is anyone’s guess—but I wouldn’t bet on it. Doubtless trees will be happier but in any case the present publishers state proudly in a preface that their policy is “to use paper manufactured from sustainable forests”. Jolly good of them too!

**NOTES**

Sir Francis Avery Jones British Society of Gastroenterology Research Award 2002

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2002 Award. Applications (TWENTY COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 2001 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Birmingham in

**CORRECTIONS**

An error occurred in the Science @lert article by Playford RJ (Out 2001;48:594–5). The text and reference 1 refer to the author “Kinlzer” and not “Kinzlker”. Professor Playford apologises for the incorrect spelling.

The authors of Gut 2001;48:816–20 have notified the journal of a computational error they made in figure 2. The correct figure is printed here.

The line of text that describes the figure, under the heading “intrahepatic cholangiocarcinoma” on p817, should now read, “There was, on average, a 12-fold increase in AspMR per 100,000 population in ages 45 and above, with larger increases at older ages and in women (fig 2A, B)”. The authors apologise for this error, and wish to point out that all the rest of the data are correct, and this does not change the findings reported upon in the paper or the interpretation.
March 2002. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2001.

Hopkins Endoscopy Prize 2002
Applications are invited by the Endoscopy Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2002 Award. Applications (TEN COPIES) should include:
- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

An applicant need not be a member of the Society. The recipient will be required to deliver a 20 minute lecture at the Annual meeting of the Society in Glasgow in March 2002. Applications (TEN COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2001.

Falk Symposium No 123: VI International Symposium on Inflammatory Bowel Diseases
This Falk Symposium will be held on 3–5 September 2001 in Istanbul, Turkey. Further information: Falk Foundation e.V., Congress Division, Leinenweberstr. 5, PO Box 6529, D-79041 Freiburg, Germany. Tel: +49 761 15 14 0; fax: +49 761 15 14 359; email: symposia@falkfoundation.de

Falk Symposium No 124: Medical Imaging in Gastroenterology and Hepatology
This Falk Symposium will be held on 28–29 September 2001 in Hannover, Germany. Further information: see Falk Symposium No 123 above.

9th Asian Conference on Diarrheal Diseases and Nutrition
This meeting will be held on 28–30 September 2001 in New Delhi, India. The organisers hope the meeting will promote meaningful and effective collaboration among individuals/institutions towards control of the major health problems in Asia, particularly those affecting women and children. Further information: Professor M K Bhan, Coordinating Secretary, Centre for Diarrheal Disease and Nutrition Research, All India Institute of Medical Sciences, New Delhi. Tel: +91 11 6963822; fax: +91 11 6862662; email: ascodd2001@rediffmail.com

VI Congress of the International Xenotransplantation Association
This congress will be held on 29 September to 3 October 2001 in Chicago, USA. Further information: Felicissimo & Associates Inc., 205 Viger Avenue West, Suite 201, Montreal, Quebec, Canada H2Z 1G2. Tel: +1 514 874 1998; fax: +1 514 874 1580; email: info@ixa2001chicago.com; website: www.ixa2001chicago.com

Falk Symposium No 125: Cytokines in Liver Injury and Repair
This Falk Symposium will be held on 30 September to 1 October 2001 in Hannover, Germany. Further information: see Falk Symposium No 123 above.

Falk Symposium No 126: Hepatocyte Transplantation
This Falk Symposium will be held on 2–3 October 2001 in Hannover, Germany. Further information: see Falk Symposium No 123 above.

EASL Single Topic Conference
The EASL Single Topic Conference “Liver fibrosis: from basic science to clinical targets” will be held on 12–13 October 2001 in Florence, Italy. Organisers: Massimo Pinzani (University of Florence) and Detlef Schuppan (University of Erlangen-Nuernberg). The aim of the conference is to provide the latest information on this key area of hepatology and to translate the current knowledge into clinical terms. It is directed at both the expert in the field and the general hepatologist. Further information: Massimo Pinzani, Dipartimento di Medicina Interna, Università degli Studi di Firenze, Viale GB Morgagni, 85, I-50134 Florence, Italy. Tel: +39 055 4277845; fax: +39 39 055 417123; email: m.pinzani@dfc.unifi.it

Falk Symposium No 127: Autoimmune Hepatitis
This Falk Symposium will be held on 30 October 2001 in Hanover, Germany. Further information: see Falk Symposium No 123 above.

42nd Annual Conference of the Indian Society of Gastroenterology
This conference will be held on 23–29 November 2001 in Lucknow, India. The programme includes two pre-conference symposia (on gastrointestinal motility and scientific communication, on 23 November), a one day postgraduate course or CME (24 November), and an endoscopy workshop (28–29 November). Further information: Dr S R Naik, Department of Gastroenterology, SGPGI, Lucknow 226014, India. Tel: +91 522 440700 or 440800, ext 2400; fax: +91 522 440078 or 440017; website: www.sgpgi.ac.in/conf/isg2001.html

41st St Andrew’s Day Festival Symposium on Therapeutics
This will be held on 6–7 December 2001 in Edinburgh, UK. Further information: Ms Eileen Strawn, Symposium Co-ordinator. Tel: +44 (0)131 225 7324; fax: +44 (0)131 220 4393; email: e.strawn@rcpe.ac.uk; website: www.rcpe.ac.uk

14th Intensive European Course of Digestive Endoscopy
This course will be held on 17–18 December 2001 in Strasbourg, France. Further information: Michele Centonze Conseil, 6 bis rue des Cendriers, 75020 Paris, France. Tel: +33 1 44 62 68 80; fax: +33 1 43 49 68 88; email: mail@m-centonze-conseil.com