PostScript

LETTERS

Should we remove all lesions at colonoscopy?

The study by Hurlstone and colleagues (*Gut* 2004;**53**:376–80) is commendable in raising the awareness of flat and depressed colonic neoplasia. However, I am surprised at the high rate of severe dysplasia reported in their study. Of their 170 lesions, 19% harboured high grade dysplasia. This high rate of severe dysplasia is particularly surprising as the study reported on diminutive colorectal lesions.

Large numbers of small adenomas develop as we grow older. According to autopsy studies, over 30% of the population over the age of 50 years have small adenomas.[1] With the use of dye spraying and magnification, these lesions can be found in up to 50% of asymptomatic patients attending for colonoscopy.[2] As only 5% of the population develop colorectal cancer, clearly the great majority of small adenomas never grow, advance, or turn cancerous. This conclusion is supported by studies reporting a lower than 1% risk of high grade dysplasia in small adenomas.[3–5]

Further studies have reported on the risk of high grade dysplasia in adenomas of all sizes. In our own series from Leeds,[6] high grade dysplasia was found in 9.5% of neoplastic lesions of all size ranges. Similarly, Tsuda and colleagues[7] reporting on colorectal adenomas in Sweden found high grade dysplasia in an average of 7.8% of lesions. Saitoh and colleagues[8] reported on neoplasia in a North American population and found high grade dysplasia in 9% of all lesions. Konishi and colleagues[9] published the findings from the University Hospital in Tokyo and reported high grade dysplasia in 10.1% of adenomas. The corresponding value from the National Cancer centre in Tokyo(personal communication) is high grade dysplasia in 10.4% of all neoplastic lesions (excluding invasive cancers). Kiesslich and colleagues[10] reported a 7.5% risk of high grade dysplasia in a German population. In all studies, the risk of high grade dysplasia increased with the size of the lesion.

If Hurlstone *et al* are correct in their conclusion that one in five diminutive adenomas harbour early cancer, we face the huge task of harvesting all colonic lesions. If their findings are incorrect, the reader who attempts to remove all small colonic polyps will be wasting time, resources, and putting patients at risk unnecessarily.

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Author's reply

We thank Dr Rembacken for his interest in our paper and agree with his observation regarding the high prevalence of high grade dysplasia (HGD) in the study cohort (*Gut* 2004;**53**:376–80). Multiple factors may account for this finding. Importantly, case mix in comparable studies is variable. Our study cohort included 233 patients (90%) who were undergoing colonoscopy for polyp surveillance, post surgical cancer surveillance, or investigation of iron deficiency anaemia. This cohort is markedly different to that of the initial Leeds prevalence study[1] and that of Saito's group[2] who included only 22% of patients with a previous history of colorectal polyps but did not include patients undergoing postoperative surgical surveillance or those with suspected colorectal neoplasia. Additionally, patients with hereditary non-polyposis colon cancer were excluded from the analysis in both Jaramillo's[3] and Tsuda's[4] study. Our cohort included four patients who fulfilled modified Amsterdam criteria for hereditary non-polyposis colon cancer syndrome, all of which were germline mutation positive. This is a high risk colorectal cancer group who are known to develop flat right hemicolonic lesions, which may favour a de novo neoplastic pathway and demonstrate early submucosal invasion despite diminutive luminal appearances.[5–7] Thirty per cent of diminutive adenomas with foci of HGD were identified in this group.

Chromoscopic techniques used also vary between studies and may alter detection of diminutive and flat colorectal lesions. In the studies of Rembacken and colleagues,[1] Jaramillo and colleagues,[3] and Tsuda and colleagues,[4] selective chromoscopy was used following detection of subtle mucosal changes. Such techniques may fail to diagnose some diminutive lesions, which rarely demonstrate the characteristics of fold convergence, focal vascular net loss, or other focal mucosal architectural changes.[8] Furthermore, Saito's chromoscopic method differed significantly from that of our design where all patients received mucosal chromoscopy of the left colon with progression to pan-mucosal chromoscopy only if left sided lesions were apparent.[2] Hence flat adenomas and carcinomas that are known to cluster within the right hemicolon and may not be associated with synchronous left sided lesions could have been underrepresented using this study design.[9 10] Furthermore, Mitooka's study design differed again using ingested indigo carmine dye capsules.[11]

Dr Rembacken is however correct to conclude that resection of all diminutive and flat colorectal lesions are not required. In our study, although increasing the total number of adenomas detected, a significant number of hyperplastic lesions were detected using pan-chromoscopy, with 86% being present within the rectosigmoid. These data confirm the observation of Brooker and colleagues[12] and indeed that of our initial prevalence study[9] where 93% of flat hyperplastic lesions were present in the left colon.

High magnification chromoscopic colonoscopy has also been shown by our group and others to have a high sensitivity and specificity at differentiating between hyperplastic lesions and adenomas.[13–16] Hence the additional use of magnification chromoscopy may lower the histopathological burden of insignificant biopsies and attenuate overall procedure related risk by excluding insignificant lesions from inappropriate endoscopic resection.

In conclusion, pan-chromoscopic colonoscopy versus targeted chromoscopy proved beneficial in our randomised controlled trial using a cohort of patients assuming a high risk of colorectal neoplasia and may help better stratify overall colorectal cancer risk in this group. Kiesslich *et al*, using pan-chromoscopy for the detection of intraepithelial neoplasia in longstanding chronic ulcerative colitis, have noted similar observations,[17] data validated by our group.[18] The implications of these data are therefore significant as interval cancers are known to occur despite intensive colonoscopic follow up.[19 20] No data exist regarding the applicability of this technique when used in the setting of diagnostic colonoscopy in low-moderate risk colorectal cancer cohorts. Further studies are required to assess the efficacy of chromoscopy as an adjunctive endoscopic tool in this group. This is particularly relevant given the imminent introduction of a Nationwide Colorectal Cancer Screening Programme in the UK where economic, endoscopic, histopathological, and man power issues are scarce but pivotal to a successful programme.

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Liver fibrosis: natural history may be affected by the biopsy sample

We read with great interest the article by Ryder and the Trent Hepatitis C Study Group (*Gut* 2004;**53**:451–5) addressing the issue of fibrosis progression in untreated patients with chronic hepatitis C. After examining a large series of paired liver biopsies (median inter-biopsy interval 2.5 years), the authors concluded that even in patients with a ''histologically mild'' presentation, chronic hepatitis C is characterised by progressive fibrosis. Histological assessment of liver fibrosis in chronic liver diseases is an area of interest to us and we wish to raise a methodological issue concerning Ryder's study.

While many attempts have been made to standardise non-invasive tests for predicting liver fibrosis, biopsy sampling is currently considered the standard reference for grading and staging chronic hepatitis. Biopsy sampling error and sample size have proved the major sources of bias in liver fibrosis assessment and both variables should be taken into account when the outcome of histology guides patient management decisions.

Two studies[1 2] have recently demonstrated that the traditional concept of ''adequate liver biopsy sample'' (core biopsy 1.5 cm long and/or containing 4/5 portal tracts) is no longer acceptable. Both studies consistently demonstrated that the stage of disease is underrated in biopsy samples shorter than 2–2.5 cm and/or thinner than 1.4–1.2 mm. More recently, a well designed study by Brunetti and colleagues[3] showed that fine needle biopsies also underestimate the stage of chronic hepatitis C, as revealed by large needle biopsies. The critical factor in staging fibrosis is the number of complete portal tracts included in the sample, the range of 11–15 complete portal tracts being the minimum requirement for a reliable histological assessment.[1] In practice, this means that when paired biopsies are used to assess fibrosis progression, biopsy size and/or number of complete portal tracts has to be comparable in the two samples considered: any progression or regression of fibrosis may be biased due to the inconsistent size of the paired liver biopsy samples (that is, initial small versus larger follow up biopsy, or large initial versus smaller follow up biopsy).

In the Ryder study, the threshold for adequacy was the presence of more than five portal tracts and the authors did not say whether the paired biopsies were comparable in terms of the number of portal triads. Fibrosis regression (10%) was interpreted as ''presumably'' being due to ''a combination of observer error and sampling variation''. We agree that this is a possible interpretation of ''regressive'' fibrosis but we would suggest that a similar interpretation should also be considered for ''progressing'' fibrosis.

Our concern is of some practical importance as Ryder's study demonstrates that fibrosis progresses, in less than three years in 33% of untreated hepatitis C patients (including those with persistently normal alanine aminotransferase). This means that the strategy that excludes subjects with mild disease from treatment (as recommended by current guidelines) needs to be reconsidered.

The size of liver biopsy samples is feasibly one of the clinical variable pertaining to in vivo studies and it would be unreasonable to disregard liver biopsies that fail to fulfil current adequacy criteria entirely. None the less, the considerable bias that ''inadequate'' biopsy material can introduce makes it necessary to pay more attention to ensure an exhaustive description of the analysed samples (too often neglected in the ''Methods section'' of otherwise valuable articles). This methodological recommendation applies both to pathologists involved in clinical trials and to manuscript reviewers.[4]

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Author's reply

Drs Guido and Rugge make important points about the interpretation of liver biopsy if the sample is small.

Our study (*Gut* 2004;**53**:451–5) was accepted for publication before the Colloredo article was published in the *Journal of Hepatology* and we would agree that the standards for accepting a liver biopsy as adequate have changed in the light of their data.

With respect to our study, we can confirm that the median number of portal tracts per biopsy was 15 in the second biopsy that showed regression with no biopsy having less than 11. Analysis of size and portal tract number in the groups of patients who progressed, remained stable, or regressed showed no difference. In particular, the second biopsy sample in ''regressors'' contained a higher median number of portal tracts than the index biopsy. Using the criteria established by Brunetti *et al*, only six biopsies from the whole cohort would have been characterised by them as inadequate, and omitting these patients from the analysis does not alter the results.

We therefore feel that the biopsy size in our study was adequate and the conclusions remain valid.

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Ultrastructural changes in enterocytes in subjects with Hashimoto's thyroiditis

We have recently described[1] mucosal ultrastructural impairments, such as height and thickness of microvilli, space between microvilli, and thickness of tight junctions, in non-coeliac type 1 diabetic patients after a

preliminary report of an alteration in intestinal mucosal permeability (IP) evaluated by the lactulose/mannitol (LA/MA) test.[2 3]

Therefore, in the ''aetiological'' classification of autoimmunity based on initiating factors,[4] the category of diet induced diseases could be expanded to include type 1 diabetes and, perhaps, other endocrine autoimmune diseases.

Thyroiditis is the most frequently associated autoimmune endocrine disease with type 1 diabetes. Moreover, type 1 diabetes and Hashimoto thyroiditis present similar pathogenetic mechanisms of cellular damage, a cell mediated autoimmunity induced by Th1 cytokines. However, mucosal intestinal morphology and function have not yet been studied in autoimmune thyroiditis patients. Hence we investigated intestinal mucosal ultrastructural morphology and IP in a group of patients with autoimmune thyroiditis. The study was approved by the local ethics committee.

Fourteen patients (12 females and 2 males; mean age 33.2 (SD 10.2) years) and 23 controls (12 females and 11 males; mean age 27.9 (SD 8.01) years) were enrolled into the study after giving written informed consent.

The diagnosis of autoimmune thyroiditis was based on the following criteria: plasma autoantibody TPO positive at high titre and a typical thyroiditis ultrasound pattern. All patients were in euthyroidism (normal FT3, FT4, and TSH plasma levels without hormonal therapy). Mean duration of known disease was 5.2 (2.5) years. All patients were negative for the presence of antigliadin antibodies IgA and IgG, antiendomysium antibodies IgA, as well as antihuman transglutaminase IgA following a gluten rich Mediterranean diet. Type 1 diabetes mellitus was excluded according to the 1997 American Diabetes Association criteria, and none of the participants had a family history of diabetes mellitus. Other intestinal and endocrine diseases were excluded through clinical and, when indicated, laboratory evaluation. Food or other allergies were excluded. None of the subjects reported gastrointestinal signs or symptoms, or was a habitual smoker, abuser of alcohol, or regularly took non-steroidal anti-inflammatory drugs.

Only four of 14 patients and nine of 23 age matched controls consented to undergo standard oesophagogastroduodenal endoscopy, and biopsy specimens were collected from the distal portion of the duodenum. Biopsies were then processed for standard histological examination by light microscopy (LM), after staining with haematoxylin and eosin, and for transmission electron microscopy (TEM) analysis.

The following enterocyte parameters were measured in a blinded fashion by two different pathologists: height of microvilli, thickness of microvilli, space between two adjacent microvilli in the same cell, and total thickness of the tight junction. The value expressed for each of the above parameters represents the mean of eight such measurements. TEM analysis was performed with a ZEISS EM 109 Transmission Electron Microscope.

At LM, all four intestinal biopsies from thyroiditis patients showed a normal histological pattern. In particular, intraepithelial lymphocytes were within the normal range (Marsh grade = 0: <30 lymphocytes per 100 epithelial cells). TEM showed some alterations, particularly evident on the apical side of enterocytes where rarefaction and partial disappearance of microvilli were observed (fig 1).

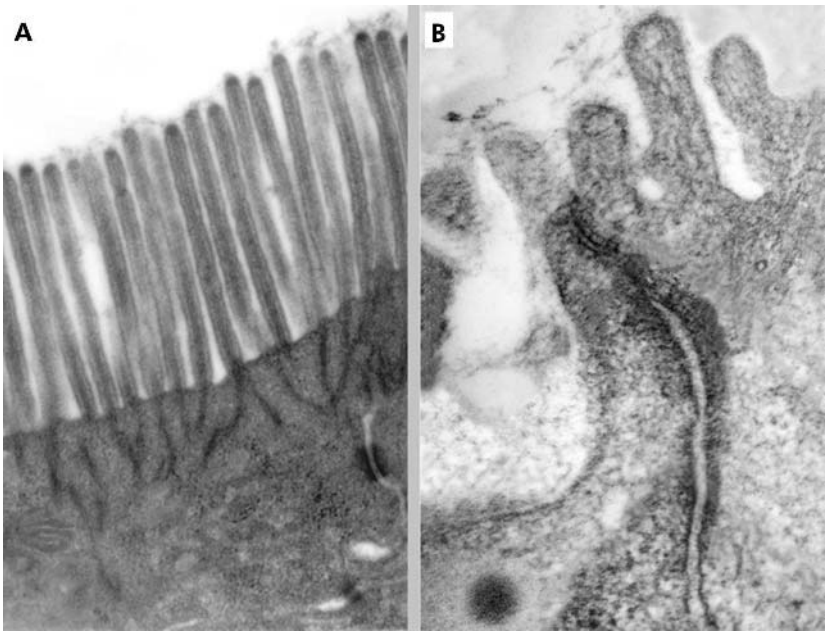

Figure 1 (A) Transmission electron microscopy (TEM) of a normal duodenal mucosa in a sample from a healthy control subject. Both microvilli and the visible tight junction (TJ) are normal with respect to thickness and height. Original magnification: 24 000×. (B) TEM micrograph showing features of adjacent enterocytes in a mucosal sample from a thyroiditis affected patient. TJ complexes are characterised by dilated intercellular spaces; some microvilli are also visible, clearly shorter and thicker than normal. Original magnification: 60 000×.

Among the four parameters investigated, the space between two adjacent microvilli and the thickness of microvilli were significantly different in patients compared with controls (0.045 (0.019) *v* 0.024 (0.006) μm ($p = 0.012$); 0.132 (0.012) *v* 0.098 (0.036) μm ($p = 0.032$), respectively; *t* test for independent samples). Moreover, mean height of the microvilli and mean thickness of the tight junctions were different in the two groups, although these differences were not statistically significant (thyroiditis patients *v* controls 1.18 (0.16) *v* 1.33 (0.23) μm ($p = 0.224$); 0.031 (0.005) *v* 0.023 (0.010) μm ($p = 0.114$), respectively). Therefore, these findings suggest some alterations in the morphology of the enterocytes of patients with Hashimoto's thyroiditis that make them much more similar to type 1 diabetic subjects[1] than to controls.

To investigate if these morphological findings were related to functional mucosal alterations, similarly to type 1 diabetes, IP was evaluated by the LA/MA test in all subjects. After an oral load, the percentage of sugar probe recovery from urine was measured. The ratio %LA/%MA is commonly referred to as the IP index. Detection and measurement of the two sugar probes in urine was performed by high performance anion exchange chromatography coupled with pulsed amperometric detection, as described previously.[5] LA/MA values were significantly different in thyroiditis patients compared with controls (0.024 (0.018) *v* 0.014 (0.06) ($p = 0.022$); *t* test for independent samples). Increased LA/MA values are consistent with impaired IP in subjects with chronic autoimmune thyroiditis compared with controls. These functional data further support the ultrastructural observations.

These original findings are similar to impairments previously observed in non-coeliac type 1 diabetes. This novel observation suggests that endocrine autoimmune diseases with similar autoimmune mechanisms of cellular damage show impaired intestinal morphology and function. Thus a pathogenetic role for mucosal intestinal damage at the onset of such diseases can be proposed. Further investigations are necessary to confirm this hypothesis.

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BOOK REVIEWS

Inflammatory Bowel Disease: From Bench to Bedside, 2nd edn

Edited by S R Targan, F Shanahan, L C Karp. Dordrecht: Kluwer Academic Publishers, 2003, £219, pp 903. ISBN 1 40200 713 2

Few diseases can lay claim to four large multiauthor textbooks in addition to numerous more concise handbooks and monographs. This is certainly unique in gastroenterology where inflammatory bowel disease (IBD) has attracted eager basic scientists, clinicians, and the pharmaceutical industry with a frenzy of translation from bench to bedside. The concept of ''boundary less'', so effectively developed by Jack Welch as the CEO of General Electric Co, aptly describes current IBD research, where geneticists, epidemiologists, immunologists, microbiologists, and molecular biologists interact seamlessly with gastroenterologists, physicians, health economists, and nurse specialists.

Three additional questions posed in this second edition, over and above those posed in the first edition, hold the textbook together very well. These are stated by the editors as: (a) Based on understanding derived from a wide range of animal models, are Crohn's disease and ulcerative colitis different expressions of the same disease or are they discrete entities? (b) Do infectious agents have a role in the aetiology or pathogenesis of inflammatory bowel disease? (c) Where is research taking us and how will it change the management of inflammatory bowel disease?

Section 1 covers epidemiology and laboratory research, and in addition to the usual journey through genetics, immunology, animal models, and microbial interactions, contains useful chapters on the effect of inflammation on intestinal function and systemic consequences, as well as intestinal healing and repair. Brief description of the new cytokines interleukin (IL)-20, IL-21, IL-22, and IL-23 are provided, as well as interesting molecules expressed on intestinal epithelial cells such as the CD1 family of proteins. Some key immune cells are perhaps less well covered than expected, such as dendritic cells. Nevertheless, the first section should get all readers up to speed in basic scientific aspects of IBD research.

''The bedside'' covered in section II is probably the greatest strength of the book. The chapters covering clinical aspects are uniformly written with superb insight and analysis, and are more than a mere representation of established facts. The endoscopy section suffers from a lack of colour photographs but the imaging section is very well illustrated. Medical and surgical managements are comprehensively covered and illustrate how rapidly these are changing. Paediatric perspectives are provided. Management options are discussed at a very practical level but provide enough scientific background necessary for wise application. This makes the textbook very accessible for all practising gastroenterologists managing IBD. Keeping in mind the intended readership, the book also provides valuable chapters on microscopic colitis, intestinal ischaemia, diversion colitis, pseudomembranous colitis, and infectious colitis, all conditions that may be mistaken for IBD.

The final section attempts to answer the last question posed above, and discusses the enormous pace of translation and the challenges of such a rapid pace of development. Genomics, phenomics, and proteomics will all strive to target a limited pool of patients, and prioritisation based on science rather than pharmaceutical expediency is a major challenge. Altering the natural history of IBD is here to stay and one wonders whether the third edition will be in a position to describe the cure. This book must be considered an essential acquisition for all medical libraries, institutional or departmental, and in addition should be on the shelves of researchers and clinicians dealing with IBD. IBD currently almost fulfils Voltaire's quotation—''The multitude of books is making us ignorant''—but this certainly is one book on the subject worth having. It is comprehensive but not encyclopaedic, a tribute to editorial discipline.

S Ghosh

Inflammatory Bowel Diseases

Edited by J Satsangi, L Sutherland. London: Elsevier, 2003, £99.99, pp 792. ISBN 0 443 07121 7

In pure quality of production terms, this is clearly the ''Ferrari'' among all multiauthored books on inflammatory bowel diseases (IBD). Lavishly illustrated in colour and printed on glossy pages, this is a beautiful book to thumb through. The authorship is very international and therefore somewhat variable in style. Some chapters unpredictably lack a useful ''conclusion'' section, not made up by the very brief bullet points at the beginning of each chapter. Following a brief historical perspective, the arrangement is traditional and comprehensive, dealing successively with pathogenesis, clinical presentation and diagnosis, medical and surgical treatments, and complications and clinical problems. The intestinal complications section deals only with abdominal fistulising Crohn's disease and omits other intra-abdominal and intestinal complications dealt with in the surgical treatment section.

The pathogenesis section covers genetics, immunology, epithelial barrier, animal models, and implications of pathophysiology for clinical management. However, this section is roughly about one fifth of the book and for a basic scientist looking for an exhaustive reference source, somewhat limited in scope. The clinical section is however extensive and superbly illustrated. The chapter on endoscopy is especially pleasing with a wide range of photographs and a detailed treatise, but capsule endoscopy is missing. The two chapters on imaging are somewhat overlapping and repetitive and could have been separated along the lines of barium radiology, computed tomography, magnetic resonance imaging, and emerging techniques. Somewhat surprisingly, biological therapies come under selected topics in therapy. Given the importance of infliximab in current management, this might have been given a separate ''anti-tumour necrosis factor'' chapter, although there is some repetition, with infliximab also being discussed in the primer of current therapies chapter. The surgical treatment section is magnificent but spoiled by inappropriate headers in places, such as ''Complications of port access'' spilling over into later pages. Quality of life issues probably should have come earlier in the clinical section rather than as the last chapter, and are somewhat superficially dealt with. Pharmacoeconomic aspects are not extensively dealt with, given that these will become progressively important issues in the era of expensive therapies.

Overall, one cannot but marvel at the encyclopaedic breadth and scope of this book and this is a must have for all institutional libraries. The index is not particularly user friendly, and a search could not find ''dendritic cells'' or ''bile acid malabsorption''. For a book dealing with inflammatory bowel *diseases*, the absence of a substantial chapter on microscopic colitis may be considered an omission although it is briefly covered in the differential diagnosis.

''Some books are to be tasted, others to be swallowed, and some few to be chewed and digested: that is, some books are to be read only in parts, others to be read, but not curiously, and some few to be read wholly, and with diligence and attention'', Sir Francis Bacon. It may be a daunting task to read this book wholly with diligence and attention but it is a marvellous advertisement for IBD. An individual gastroenterologist would probably like to refer to this book from the institutional library rather than own one. Like a Ferrari, owning one may not be the most practical way to travel every day.

S Ghosh