To perform or not to perform liver biopsy: an alternative view

I would like to thank Joy and Scott for their comments in their letter in response to my review (Gut 2002;51:9-10).1 I entirely agree with their view that ultrasound is highly specific and sensitive for the diagnosis of fatty liver. However, I do not feel that the presence or absence of fatty liver is the issue here. It is established that approximately 30% of patients with fatty liver who have significant fibrosis will go on to develop chronic liver disease and cirrhosis, with all its complications, including hepatoma.2 The purpose of histological sampling is not to confirm the presence of fatty liver but to see whether fibrosis and other abnormalities are present, putting the patient at risk of developing chronic liver disease. This issue was addressed in a recent article by Saadeh and colleagues3 who compared patients with non-alcoholic steatohepatitis (NASH) and those with steatosis (non-alcoholic fatty liver disease (NAFLD)) alone. The authors evaluated the role of various radiological modalities, including ultrasound, computed tomography, and magnetic resonance imaging, in the role of distinguishing between NASH and the less aggressive forms of NAFLD. Their conclusion was that none of the radiological modalities detected the presence of hepatocyte ballooning, Mallory’s hyaline, or fibrosis, which are the important features in the diagnosis of NASH. The study showed that ultrasound had high sensitivity and specificity for the diagnosis of severe steatosis but it confirmed that ultrasound had no predictive value in the diagnosis of fibrosis or cirrhosis.

On the basis of this article together with earlier studies, I can find no basis for the conclusion reached by Joy and Scott that ultrasound is a reasonable alternative to liver biopsy for patients who have abnormal liver function tests with no diagnostic serology.

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PostScript

References
1 Joyce D, Scott BB. To perform or not to perform liver biopsy: an alternative view. Gut 2003;52:610.

Non-medical treatment of GORD

The interesting comment of Heading (Gut 2002;50:592-3) on the work by Fibe et al needs to be completed by considering the anatomical factor in the study of gastrointestinal reflux disease (GORD) before advocating any non-medical appropriate treatment (fundoplicator, Stratten procedure, Gastropexis, etc). The multiple controversies arising from all non-medical proposed treatments, with contradictory results, are due to the complete neglect of delineating the gastrointestinal junction (CEJ) and the shape of the angle of HIS, and the role of the anatomical factor in selecting the correct candidate for successful non-medical treatment.

The new generation of gastrointestinal specialists, who come after the endoscopy era, are not aware of the radiology of the gastrointestinal tract, particularly when we need to have the anatomical configuration of the CEJ.

Gastric physiology and junction motility are the next step in evaluating any case of GORD. Ignoring the anatomical shape of the CEJ is behind the various conflicting results that we are hearing at medical meetings devoted to GORD.

Improving the study of the anatomical feature of the junction, which is very variable from person to person, is the first step in evaluating any proposed treatment of GORD, medically or surgically.

Applying the devices (Plicator, Stratten procedure, etc) without studying the anatomy of the junction is behind any side effects of these proposed procedures.

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Association between K469E allele of intercellular adhesion molecule 1 gene and inflammatory bowel disease in different populations

We read with interest the article by Matsuzawa et al showing an association between the K469E allele of intercellular adhesion molecule (ICAM)-1 gene and inflammatory bowel disease (IBD) in a Japanese population (Gut 2003;52:75-8). The ICAM-1 gene lies on chromosome 19p13, previously implicated in determining susceptibility to IBD, and codes for a surface glycoprotein that belongs to the immunoglobulin superfamily. ICAM-1 plays an important role in the trafficking and activation of leucocytes and is upregulated in the inflamed mucosa of IBD patients. Matsuzawa et al found that the allelic frequency of K469 was significantly higher in both Crohn's disease (CD) and ulcerative colitis (UC) than controls. While Braun et al showed an association between R241 allele and UC, independently of ANCA status. The G241R polymorphism of the ICAM-1 gene was also investigated in these studies, and IBD patients were stratified by antineutrophil cytoplasmic antibody (ANCA) status. In particular, Yang et al found a significantly increased frequency of the G241R polymorphism both in ANCA negative UC and ANCA positive CD patients' while Braun et al showed those obtained in Caucasians patients.

We also searched for the K469E mutation in 42 consecutive Italian IBD patients (31 males, mean age 36 (14) years), 17 with CD and 25 with UC, and 227 ethnically matched controls. Our preliminary results (see table 1), although obtained in a limited number of patients, are in contrast with the findings of Matsuzawa et al (Gut 2003;52:75-8) and confirm those obtained in Caucasians patients. The possible explanation (for such a discrepancy) in results is the influence of the different geographic distribution of the genetic mutation. Japanese patients with IBD have a genetic background that differs from Western patients, as also demonstrated recently for the NOD2/CARD15 gene polymorphisms. Indeed, several studies have reported an association between CD and NOD2/CARD15 mutations in Caucasians but not in Japanese cohorts.

These data indicate that there may be significant genetic heterogeneity between different ethnic and racial IBD populations and environmental factors may play a leading role in the pathogenesis of IBD. Thus, environment interactions represent a crucial event in the pathogenesis of IBD that they cannot be considered as distinct entities.

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Table 1 Allelic frequencies of the E/K469 ICAM-1 polymorphism in Italian patients affected by IBD, and in controls

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=227)</th>
<th>IBD (n=42)</th>
<th>UC (n=25)</th>
<th>CD (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allelic frequency (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E469</td>
<td>45</td>
<td>45</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>K469</td>
<td>55</td>
<td>55</td>
<td>54</td>
<td>56</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn’s disease; ICAM, intercellular adhesion molecule.
Authors’ reply

We would like to address the possible cause of the inconsistency of the ICAM1 alleles, which associated with inflammatory bowel disease (IBD), between Japanese (K469) (Gut 2003;52:75–8) and German White popula-
tion.1

Inconsistency of the associated alleles with a certain complex genetic disease among eth-
nic groups has been repeatedly described in the literature of the field of the study of the eth-

ic groups. The marker association between ulcerative colitis and HLA-IBD1*0301 in a Caucasian population but with HLA-IBD1*0301 in the Japanese has been reported in many studies. Such allele inconsis-
tencies were also observed in the HLA-B, HLA-DOB, and DQB alleles.2-4

Three explanations have been considered for these inconsistencies.1 Firstly, the marker genes (HLA genes) themselves may not be the primary disease causing genes in this region but are in linkage disequilibrium with one or more primary responsible genes located in this region. Also, in different popu-
lations there may be different linkage disequi-
libria. This explanation seems to fit with the inconsis-
tencies of ICAM1 allele association.

The second explanation is that there may be genetic heterogeneity in the allele associ-
tions in a certain gene. Recently, the existence of a population specific disease predisposing mutation (DPM) in NOD2 to Crohn’s disease (CD) has been suggested conferring risk for inflammatory bowel disease on chromosomes 16p. Proc Natl Acad Sci U S A 2002;99:321–6.2


Eosinophilic oesophagitis: treatment using Montelukast

I read with interest the paper by Attwood and colleagues (Gut 2003;52:181–5) on eosin-

philic oesophagitis (EO). According to the authors, the distinct clinical syndrome of EO is not usually seen either as a component of gastro-oesophageal reflux disease or as a vari-

ant of eosinophilic gastroenteritis (EG). The diagnostic hallmark of EO is oedynaphagia and the diagnosis is always his-
tology dependent (>20 eosinophils/high power field) (Gut 2003;52:181–5). In the pediat-
ric setting, the condition is widely recogn-
ised but the adult EO may escape diagnosis due to general lack of awareness of the condi-
tion. In this respect, the paper by Attwood and colleagues (Gut 2003;52:181–5) is a valuable contribution towards understanding the com-

plexity of eosinophilic oesophagitis.

The pathophysiology of EG or EO may be similar to that of asthma. Asthmatic patients demonstrate increased production of cysteinyl leukotrienes during acute asthma attacks.5 Cysteinyl leukotrienes have potent chemotactic properties for eosinophils and play an important role in the pathophysiology of asthma.6

In EG, accumulated eosinophils cause se-

vere tissue damage characteristic of EG. Cysteinyl leukotrienes, along with cytokines interleukin 5 and 3 and granulocyte macrophage-colony stimulating factor play a role in the recruitment of eosinophils into the tissue causing the damage.4

No controlled treatment trial for EG or EO exist. Limited results have been achieved with oral cromolyn, ketotifen, and other antihista-

amines. Oral corticosteroids are effective but long term use is complicated by side effects.7 Montelukast is a leukotriene receptor an-
tagont (LTRA) which actively and selectively blocks the leukotriene D4 (LTD4) receptor. Because LTD4 is both a potent eosino-
phil-attractant and chemotactic factor for eosinophils, this may provide the rationale for treating a patient with EG or EO with a LTRA. The first reported case of successful Montelukast treatment for an young EG patient was published in 1999.1 Montelukast was originally licensed in the UK for use in asthma.8 There has been some concern regarding association between the use of LTRA and Churg-Strauss syndrome (CSS) in asthma.9 CSS is a rare form of eosinophilic vasculitis associated with asthma. This syndrome has previously been associated with the use of Zafirlukast.10 The Committee on Safety of Medicines has reviewed 12 reports of CSS and pulmonary eosinophilia possibly associated with Montelukast.11 There are other reports of Montelukast induced CSS in asthma patients’ literature. Attwood and colleagues (Gut 2003;52:181–5) observed nausea in four patients and perigast-

ria in one in the Montelukast group but there was no mention of CSS. In the previous report of Montelukast therapy in EG, it was shown the Montelukast did not increase eosino-

philia (TE) or symptoms in a patient with severe EG complicated by oesophageal stricture. In another report, Montelukast reduced peripheral eosinophilia with no report of CSS.11

In Attwood et al’s paper (Gut 2003;52:181–5), treatment with Montelukast for a median

www.gutjnl.com

References


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References


period of 14 months in eight patients out of a cohort of 12 patients with EO did not change the density of TE. However, subjective improvement was seen in seven patients with swallowing difficulties in Attwood's series, one of eight patients on Montelukast. LTRAs are a useful therapy for EO. While anti-leukotriene drugs are generally safe and effective for most patients, from the asthma experience I conclude that clinicians need to be vigilant of any development of CSS in all patients with eosinophilic oesophagitis undergoing treatment with Montelukast. I agree with the authors that further randomised control trials are required to assess the full benefits of Montelukast therapy in EO.

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References
1 Bisgaard H Pathophysiology of the cysteiny1 leukotrienes and effects of leukotriene receptor antagonists in asthma. Allergy 2001;56(suppl 66):7–11
4 Sampson A, Holgate S. Leukotriene modifiers in the treatment of asthma. BMJ 1999;316:1257–8

Effect of a rapid access flexible sigmoidoscopy clinic on the yield of early stage rectal cancer
We read with interest the debate on population based endoscopic screening for colorectal cancer (Gut 2003;52:323–6). While we agree that the case for population screening is compelling, we believe that Macaee and Scholefield’s statement that “earlier diagnosis is unlikely to occur through increased awareness or patient education alone” is unnecessarily pessimistic.

We have recently had the opportunity to audit the impact of a dedicated rapid access flexible sigmoidoscopy clinic established in the endoscopy department of Dewsbury and District Hospital in January 1997. General practitioners were invited to use a proforma to refer patients to the clinic who were over 40 years old and had presented with a history of a recent change in bowel habit, rectal bleeding, or iron deficiency anaemia. Following initial consultation using a structured history form and clinical examination, flexible sigmoidoscopy was carried out by a consultant surgeon or a nurse endoscopist. If significant pathology was encountered, biopsy material was obtained and further investigations and management were planned as appropriate.

During the period January 1993 to December 1999, 167 patients underwent surgery for histologically confirmed adenocarcinoma of the rectum. Introduction of the dedicated rapid access flexible sigmoidoscopy clinic occurred 48 months into this audit period, with 87 patients treated before the introduction of the clinic period 1 and 80 patients after (clinic period 2). Comparison of the groups of patients treated before and after reorganisation of the colorectal service demonstrated significant differences in several important clinical variables, with early stage tumour stage, complete circumferential margin clearance, and absence of visible residual tumour following excision all commoner in the later period (table 1).

There are several possible factors that may have contributed to the observed clinicopathological differences in the two time periods, including increased public awareness of suspicious symptoms, decreased embarrassment about reporting these symptoms, and increased GP education. Creation of a fast track flexible sigmoidoscopy clinic may also have contributed to the improved patient outcomes observed in our institution, and we believe that the debate around screening for colorectal cancer should take into account the improving results of the investigation of asymptomatic colorectal disease. Not to do so may prevent the improvement of service provision in the hospital sector and is unnecessarily nihilistic.

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Detecting the risks of osteoporotic fractures in coeliac disease
The recent report by Thomason and colleagues (Gut 2003;52:518–22) which failed to detect a significant increase in fractures experienced by treated coeliacs might reassure many patients and physicians. However, this study, and the accompanying commentary by Compston (Gut 2003;52:459), need full and critical assessment before changes in practice are adopted and coeliacs are no longer targeted to be screened for osteoporosis.

It is not surprising that no significant increase in fracture could be detected in this population of well treated coeliacs, given previous findings. The American Gastroenterology Association recently reviewed studies of osteoporosis in gastrointestinal diseases, including coeliac disease, according to standard levels of evidence.1 All such studies have shown low mean bone mineral density (BMD) around the time of diagnosis of untreated coeliacs, with a pooled analysis showing very low bone mass (age and sex adjusted z scores below –2) in 40% in the spine and 15% at the hip. However, many reports, including our own,1 have shown normal or near normal mean values after treatment. This reflects the great improvement in BMD2 and calcium absorption3 which occurs when enteropathy is reversed with a gluten free diet. The real issues are how to recognise previously undiagnosed cases, and how to identify potential patient subgroups who might still be at risk due to suboptimal treatment.4

The study also did not have sufficient power to detect any increase in those fractures most typical of osteoporosis which have a high prevalence late in life.5 Such fractures typically include vertebral collapse and deformity, causing significant morbidity, but which commonly are undiagnosed unless looked for radiologically. In a 50 year old woman, there is a 32% life time risk of subsequent vertebral fractures.6 However, these were not recorded in either coeliacs or controls in this study, indicating that the questionnaire method employed led to marked under-reporting. Femoral neck (hip) fractures, the most serious complication of osteoporosis, have a population incidence of less than 1% by the age of 65 years but approaching 20% by the age of 90 years. In this study, only about one third of coeliacs were aged over 65 years and only

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**Table 1** Association between treatment before [clinic period 1; 1993–96] and after [clinic period 2; 1997–99] the introduction of a dedicated rapid access flexible sigmoidoscopy clinic and the clinicopathological characteristics of rectal adenocarcinomas

<table>
<thead>
<tr>
<th>Clinic period 1</th>
<th>Clinic period 2</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>69.9</td>
<td>69.0</td>
</tr>
<tr>
<td>ASA</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>A</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Admission</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Emergency</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>Treatment</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Curative</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>Palliative</td>
<td>56</td>
<td>66</td>
</tr>
<tr>
<td>CRM</td>
<td>Positive</td>
<td>18</td>
</tr>
<tr>
<td>Dukes'</td>
<td>A</td>
<td>10</td>
</tr>
<tr>
<td>B-D</td>
<td>77</td>
<td>49</td>
</tr>
</tbody>
</table>

CRM, circumferential resection margin. Not all patients had their tumours resected.

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one-tenth (n=20) over 75 years. Approximately 400 cases and controls would be needed in a prospective study to detect a 50% increase in risk from 20% to 30% with 80% power. Hence the ability of this study to detect a significant life time increase in fracture risk in the minority of coeliacs who are suboptimal treated is clearly limited. Much larger groups are needed in a prospective study which includes radiologic ascertainment of vertebral fractures.

A relevant comparison can be made with the large US Study of Osteoporotic Fractures Research Group where over 9000 women older than 65 years of age were studied. In 1814 subjects with a daily calcium intake less than 400 mg, those below the median for fractional calcium absorption (so resembling untreated coeliacs) experienced an incidence of hip fractures of about 9 per 1000 person years—2.5-fold greater than those with absorption above the median.1

The absolute life time risk of osteoporotic fractures is reasonably large in the ageing population, even if the relative risk in coeliacs is not that great. Patients will be reassured by the knowledge that BMD has improved with diet or if that individual risk has decreased. We hold that as the true risk of fracture in treated and untreated elderly coeliacs is unknown at present, judicious use of DXA measuring appropriate guidelines, to monitor calcium homeostasis and the benefits of treatment should continue.

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References
1 Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. Gastroenterology 2003;124:795–841

Collagenous colitis: constipation or diarrhoea?

As an axiom, collagenous colitis is characterised by diarrhoea, lymphocytic inflammation, and a thickened subepithelial collagen layer in the colorectal mucosa. Various case presentations in the literature have reported that frequent watery diarrhoea introduces the clinical picture of collagenous colitis and intermittent or continuous diarrhoea can remain. On the other hand, numerous cases never suffer from episodes of watery diarrhoea but suffer from chronic constipation. Can we call into question the “incontestable” definition? Bondurup et al investigated the clinical and histological effect of oral budesonide in the treatment of collagenous colitis in 20 patients and concluded that budesonide is a highly effective and well tolerated treatment. The histological inflammation grade in the sigmoid mucosa and the thickness of the collagen layer were significantly reduced. A correlation between the grade of inflamma
tion as well as collagen layer thickness and stool weight was found (Gut 2003;52:248–51).

In our recent study, we investigated 32 patients with histologically identified collagenous colitis. In contrast with the literature, 18 had chronic constipation and only 14 had the well known diarrhoea. We also treated all of them with budesonide (Budenofalk; Dr Falk Pharma) and concluded that budesonide had a clinical response: stool frequency and weight. These conflicting results suggest a role for additional factors other than the thickened collagen layer following the guidelines, to monitor calcium homeostasis and the benefits of treatment should continue.
the fact that many acute liver diseases have an immunological basis, it might have been appropriate to highlight immunology in volume I where it would fit very well with the excellent chapters on hepatic regeneration and fibrosis. Section 3 contains an informative chapter on laparoscopy but only a four page section on hepatic imaging. Imaging is subsequently covered in the individual chapters in section IV but given the major advances in interventional radiology and imaging it would have been appropriate to give each a chapter of its own. For example, there are only two brief references to positive emission tomography in the whole book.

Individual chapters are extremely well referenced although it might help to highlight the most significant references or those that provide an in depth review. One minor criticism is the quality of some of the figures. The chapters are richly illustrated but there is an irritating variation in the quality and style of the line drawings. It would have improved the overall appearance of the book if figures had been redrawn in a uniform style, and for some of the figures this would also have improved their clarity. The reluctance to use contemporary and reusuable colour images is presumably based on cost considerations. However, the recently published Comprehensive Clinical Hepatology edited by O’Grady, Lake, and Howdell (Mosby), provides how the use of modern technology can provide outstanding illustrations that enhance the readability of the book.

How do Zakim and Boyer compare with other similar volumes? The two main rivals are the Oxford Textbook of Clinical Hepatology and Schiff’s Diseases of the Liver, both of which were last updated in 1999. All three works are excellent. There are some differences in emphasis and presentation between them but all three are highly readable and cover the field comprehensively. I have greatly enjoyed having access to Zakim and Boyer over the last few weeks and would recommend the fourth edition unreservedly to anyone with an interest in liver disease, whether research scientists, specialist hepatologists, or gastroenterologists. The editors are to be congratulated on managing to improve an already outstanding reference work.

D H Adams

Genetic Disorders of the Exocrine Pancreas

This multi-author work, derived from a symposium held in April 2001, summarises our current knowledge of the genetics of exocrine pancreatic disease. As is usual with such publications, the individual chapters have been written as free standing presentations which results in a degree of repetition. The editors have grouped the chapters into sections; a consensus conference dealing with ethical issues and with guidelines for prevention, screening, and treatment is followed by sections on hereditary pancreatitis (HP), pancreatic cancer, and cystic fibrosis. Finally, there is a conference report and a monograph celebrating the work of Henry Lynch of the eponymous cancer syndromes. Celebrating the work of Henry Lynch of the screening, and treatment is followed by the work conducted

In the BSG Abstracts supplement, there was an error in abstract 179 by Li et al (Gut 2003;52 Suppl I:A44). In their results section the sentence after the table should read “1 year survival for all patients with and without pre-existing Barrett’s was 51.5% and 31% respectively, and for those undergoing potential curative resection, was 72.6% and 52.7%, respectively”. The authors apologise for the error.

In the author index of the BSG Abstracts supplement, J E Crabtree should have been listed as an author on abstract 126 by Jeremy et al (Gut 2003;52 Suppl I:A34). This was due to a technical error for which the journal apologises.
European Helicobacter Study Group (EHSG)

This meeting, on Helicobacter infections and gastroduodenal pathology, will be held on 3–6 September 2003 in Stockholm, Sweden. Further details: Professor Torkel Wadstrom, President-EHSG, Lund University, Department of Infectious Diseases & Medical Microbiology, Division of Bacteriology, Solvegatan 23, SE-223 62 Lund, Sweden. Tel: +46 46 173 241; fax: +46 46 152 564; email: Torkel.Wadstrom@mmb.lu.se; website: www.helicobacter.org

Falk Symposium

135—Immunological Diseases of Liver and Gut

This symposium will be held on 12–13 September 2003 in Prague, Czech Republic. Further details: Falk Foundation e.V., Congress Division, PO Box 6529, Leinenweberstr. 5, 79041 Freiburg/Jr, Germany. Tel: +49 761 15 140; fax: +49 761 15 14 359; email: symposia@falkfoundation.de; website: www.falkfoundation.de

European Course on Laparoscopic Endoscopy

This course will be held on 18–21 November 2003 in Brussels, Belgium. Further details: Secretary to Professor Cadière, Service de Chirurgie Digestive, Rue Haute 322, Brussels 1000, Belgium. Tel: +32 (0)2 648 07 60; fax: +32 (0)2 647 86 94; email: straeb.asmb@proximedia.be; website: www.straeb-asmb.com

The European Society of Parenteral and Enteral Nutrition (ESPEN)

ESPEN will celebrate its silver anniversary at the time of the annual congress, which is to be held on 20–23 September 2003 in Cannes, France. Further details: www.espen.org

XII Falk Liver Week

The XII Falk Liver Week, in honour of Hans Popper's 100th birthday, will be held on 15–22 October 2003 in Freiburg, Germany. Further details - see Falk Symposia above.

European Course on Laparoscopic Endoscopy

This course will be held on 18–21 November 2003 in Brussels, Belgium. Further details: Secretary to Professor Cadière, Service de Chirurgie Digestive, Rue Haute 322, Brussels 1000, Belgium. Tel: +32 (0)2 648 07 60; fax: +32 (0)2 647 86 94; email: straeb.asmb@proximedia.be; website: www.straeb-asmb.com

4th Nutrition and Health Conference

A multidisciplinary event will be held on 21–22 November 2003 in London, UK. This year's topics include cancer, obesity, exercise on prescription, menopause, ageing, motivation skills, and coronary heart disease. Further details: Tanya Carr, 16 Brownlow Court, Lyttelton Road, London N2 0EA. Tel/fax: +44 (0)208 455 2126 or 6570; website: www.nutritionandhealth.co.uk

Hong Kong-Shanghai International Liver Congress 2004

This conference will be held on 14–17 February 2004 in Hong Kong. The topic of the conference is “Liver Diseases in the Post-Genomic Era”. Further details: Ms Kristie Leung, Room 102–105 School of General Nursing, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel: +852 2818 4300/8101 2442; fax: +852 2818 4030; email: kristieleung@hepa2004.org; website: www.hepa2004.org