Severe polyneuropathy complicating active Crohn’s disease: rapid response to Infliximab

Treatment with a chimeric antitumour necrosis factor (TNF) antibody (Infliximab) has been shown to be highly efficient for patients with steroid refractory Crohn’s disease (CD). However, the mechanism of action remains largely unknown. Recently, a favourable response to Infliximab treatment was demonstrated in some diseases complicating active CD such as acute idiopathic pancreatitis. We report a case of a middle aged female with CD that developed an aggressive form of polyneuritis resistant to corticosteroids. A 55 year old White female, weighting 68 kg, presented with exacerbation of CD (Crohn activity index (CDAI) > 450) associated with an aggressive form of polyneuritis involving the right arm and leg with arthralgias, myalgias, and functional impotence. She had been suffering from refractory severe CD involving the ileum and right colon for 10 years and she was taking oral corticosteroids for two years continually with signs and symptoms of chronic corticosteroid abuse. Immunosuppressive therapy with azathioprine was rapidly stopped for gastric intolerance. Neuropathy was characterised by arthralgias, myalgias, and functional impotence of the right arm and leg. Severe muscle atrophy of the right arm was evident and demyelinating lesions of the right and left radial nerve, and spinal cord demyelinating lesions. Electromyography showed demyelinating neuropathy involving the right and left extraocular pupillae, sciatic nerve, a mixed (motor and sensory) neuropathy involving the right and left radial nerve, and an axonal neuropathy involving the right ulnar and medial nerve. Other conditions such as polycystic kidney disease and mixed cryoglobulinaemia, rheumatoid arthritis, systemic lupus erythematosus, or sarcoidosis had been excluded.

An infusion of 3 mg/kg Infliximab (Remicade; Schering-Plough S.p.A) was given at weeks 0, 2, and 4 and repeated 5 mg/kg Infliximab infusions at eight week intervals were administered. Infliximab was well tolerated and no side effects were recorded. Arthralgias, myalgias, and functional impotence of the right arm and leg progressively improved after the first Infliximab infusion. Muscle atrophy of the right hand improved dramatically two weeks later. Electromyography performed at week 22 after the start of therapy was normal. CDAI score is <150 at this time. Sign and symptoms of chronic corticosteroid therapy rapidly disappeared. In conclusion, Infliximab may be a suitable therapeutic option in patients with rare extraintestinal manifestations of CD such as severe polyneuritis not responding to conventional therapy.

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Caution with the use of cyclosporin in pregnancy

We report a case submitted for publication of a woman with fulminant ulcerative colitis in the 29th week of pregnancy. Her disease was refractory to steroids, but she refused to have cyclosporin whilst pregnant. She therefore underwent an emergency Caesarean section and was given intravenous cyclosporin post-operatively. After 48 hours of treatment she developed severe hypertension with hypertensive encephalopathy and seizures. Although cyclosporin has been considered to be safe for both mother and foetus, we would like to highlight concerns that it is associated with potentially life threatening side effects. As a result, patients must be counselled thoroughly about the potential morbidity associated with this treatment and monitored closely. We agree with Dr Alstead in that cyclosporin should be used with extreme caution in pregnancy and the postnatal period.

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References

Coeliac disease: is case finding the correct ethical and logistical approach?

I read with interest the debate pertaining to screening for coeliac disease (CD). Although one can argue that CD fulfils the tenets of any screening programme, however, we do not know the natural history of screen detected patients with CD.

Logistically when would we decide to screen—at what age and how often thereafter? Serological markers may be highly sensitive and specific but the value of these tests decrease when they are used in the general population.

Although the investigational process for population screening and case finding may be the same, there is an important ethical difference between them. If a patient seeks medical help then the physician is attempting to diagnose the underlying condition (for example: patients with CD who present with symptoms of irritable bowel syndrome). This would be classified as case finding and clearly it is the patient who has initiated the consultation and in some sense is consenting for investigation. Conversely, individuals (who are not patients) found to have CD through screening programmes, may have considered themselves as “well” and it is the physician or healthcare system that is identifying them as potentially ill.

We recently performed a primary care based cross sectional study using immunoglobulins, IgA/IgG antigliadin antibodies and endomy- sial antibodies to initially recognise CD. 1200 volunteers were recruited from January 1999 to June 2001 from 5 general practices in South Yorkshire, UK. Any participant with a positive IgA antigliadin antibody, positive endomysial antibody or only IgG antigliadin antibody in the presence of IgA deficiency was offered a small bowel biopsy to confirm the diagnosis of CD. Twelve new cases of CD were diagnosed from 1200 samples. The prevalence of CD in this primary care population sample is 1% (95% CI 0.4–1.3%). In this screening study, 9/12 diagnosed cases of CD ultimately had symptoms which could be attributed to CD (for example, anaemia or subtle gastrointestinal symptoms). We, and others have demonstrated a delay in the diagnosis of CD—surely the important change in our clinical practice (both in primary and secondary care) is to have a lower threshold for case finding.” If you look for CD you will find it.

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References
very large study conducted by an expert team in this field were that mean age at diagnosis was higher in men (p<0.01), mean FNH size smaller (p<0.001) and number of livers more often performed (p<0.001) in men (n=18) than in women (n=216). Interestingly, perhaps because of the relatively small number of men (although very large in terms of the rare occurrence of FNH in men), no cases of multiple FNH were noted in the male population.

We report here a case of multiple FNH in a 74 year old patient with a biopsy proven prostatic cancer. This patient had not received any treatment. He was referred to our unit in March 2001 for evaluation of multiple liver masses discovered on abdominal ultrasonography during the staging of his cancer. Bone scintigraphy disclosed no metastases. Liver biochemistry was normal except for a mild increase in gamma glutamyl transferase activity (Prothrombin index was 100%). Serological search for hepatitis B or hepatitis C virus infection was negative. Genetic (haemochromatosis, alpha 1 antitrypsin deficiency) and autoimmune liver diseases were carefully excluded, and alcohol consumption was below 10 g/day. Upper gastrointestinal endoscopy and colonoscopy were normal. Tumour markers of malignant primitive or secondary liver lesions were within the normal range. Liver Doppler ultrasonography disclosed multiple heterogeneous lesions with a hypoechoic pattern and without an arterial signal. Abdominal tomodensitometry before and after contrast enhancement showed multiple lesions with rapid contrast enhancement during the arterial phase. The largest lesion was located between the left liver and segment IV and measured 75 mm.

Because there was no magnetic resonance imaging (MRI) in our centre, ultrasound guided liver biopsy in both tumoral and non-tumoral areas was performed. The diagnosis of typical FNH was made in several of the lesions whereas non-tumoral liver was normal. The patient received hormonal treatment from April 2001. In October 2001, MRI confirmed a diagnosis of FNH with a central stellate area in the largest lesion. In December 2002, he was in good health with unchanged ultrasonography.

This case report is unique in that there were multiple lesions in the patient than who had not received any previous treatments or porto-caval shunt. Although from a literature search it is difficult to determine the exact number of men with multiple FNH, the number is probably very low. In this report, the discrepancy between normal bone scintigraphy and multiple liver lesions and the diagnosis of liver metastasis probable. Nevertheless, histological examination of several hepatic lesions, retrospective MRI, and outcome made the diagnosis of multiple FNH certain. This report, in common with the large series of Luciani et al, indicates that FNH diagnosis may be very difficult in men.

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Guidelines for colonscopic scoring in acromegaly are inconsistent with those for other high risk groups

We welcome the joint work of the British Society of Gastroenterology and the Associati-
colonoscopic screening recommended by Jenkins and Fairclough should be seriously questioned.

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References
1 Renehan AG, Shalot SM. Acromegaly and colorectal cancer: risk assessment should be based on population-based studies. J Clin Endocrinol Metab 2002; 87:1909
5 Dunlop MG. Guidance on large bowel screening in people with two first degree relatives with colorectal cancer or one first degree relative diagnosed with colorectal cancer under 45 years. Gut 2002; 51(suppl 3):V17–20

Authors’ reply
We thank Dr Renehan and colleagues for their comments on our data, which have also been made previously. We do not claim that our data are perfect in all respects but it seems to us, on the basis of the data we have collected in our own series and that of other groups, that patients with acromegaly should be regarded as having a significantly increased risk of colorectal neoplasia. The two contrary studies referred to by Renehan et al are his own and that of one other author who relied upon retrospective data acquired more than 50 years ago. These data and those from the population based studies preferred by Renehan suffer from flaws of their own. The morbidity associated with acromegaly has changed in the last 25 years, probably related to the increased survival associated with aggressive and effective treatment of the cardiovascular and metabolic complications of the disease. Our data and those of others show that the prevalence of colonic neoplasia in acromegaly is age dependent. Thus it is only now that patients are surviving long enough to develop this complication, and valid comparative data must therefore be acquired contemporaneously, to take account of the changing pattern of morbidity associated with increased longevity.

We are aware of at least 12 other prospective studies evaluating colonoscopic screening in acromegaly. In addition to our original report from St Bartholomew’s Hospital, 1 these include one by Renehan et al in which they reported three asymptomatic patients in whom a cancer was detected. Among such studies the optimum comparison must be simultaneous screening of asymptomatic acromegaly and colonoscopy in age-matched comparison of the data from all series using these control groups, none of which involved mixed race US populations, gives a relative risk of colon cancer in acromegaly of 13.4. We think it prudent to accept the evidence of an increased risk of colon cancer, derived from these clinical observations rather than from theoretical calculations, and to screen acromegalic patients systematically until the current hypothesis is confirmed or refuted. The rarity of acromegaly means that the increase in workload for the majority of indi-


New imaging techniques: promise or passe
I read with great interest the article by Egger and colleagues (Gut 2003; 52:18–23) evaluating laser induced fluorescence endoscopy (LIFE) and methylene blue (MB) directed biopsies for detection of dysplasia in Barrett’s oesophagus.

As the authors point out, there have been no fully published studies to date on this much talked about procedure. The authors found that LIFE and MB had limited accuracy, as did standard random biopsy. Although LIFE and MB detected a total of five cases of high grade dysplasia and 11 cases of low grade dysplasia, they concluded that these methods are “not capable of increasing the diagnostic accuracy or replacing standard four quadrant biopsies”.

How could these data lead to this conclusion? The authors discount all but one high grade and seven low grade lesions detected by LIFE or MB because they were “within the 4QB” protocol. It was assumed by the authors that these sites would have been biopsied by random techniques had it not already been sampled with AF or MB. Given that the biopsies were standard 7 mm forceps, that dysplasia can be very focally distributed, and the area included within the 4QB covers two linear centimetres, it is difficult to assume that this exact site would have been biopsied with a random technique. This assumption, if incorrect, would result in underestimation of the value of LIFE or MB.

In addition, the authors further discounted the one remaining high grade dysplasia site and four more low grade sites because they occurred in patients with known cancer who presumably would have been treated for the cancer regardless. There is little doubt that detection of low or even high grade dysplasia has little relevance if a cancer is already known. The main group of patients where LIFE, MB, and other advanced techniques should be applied are those with histologically evident tumours and cancer. Discounting LIFE and MB for this reason may further underestimate its value.

If we do not discount these cases then LIFE and MB appear to comply 4QB for the detection of dysplasia, with each technique increasing the number of detecting dysplastic sites that the other missed.

I agree that LIFE and MB remain controversial and applaud the authors for publication of their study. Given the limitations of the study however, it may be premature to proclaim these techniques incapable. More well conducted studies are clearly needed. The field of imaging technologies is also evolving rapidly and new and better techniques are constantly on the near horizon.

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Transient ischaemic colitis following an aeroplane flight
We read with interest the report of Butcher and colleagues (Gut 2002; 51:766–7) of two cases of transient ischaemic colitis following an aeroplane flight. This report represents more evidence supporting the suggestion of a possible important role of acquired and hereditary thrombophilic risk factors in the pathogenesis of ischaemic colitis.1 However, the largest study to date concerning these factors in patients with ischaemic colitis was not mentioned in the study. Moreover, the reported patients may also have other acquired or inherited thrombophilic disorders which were not evaluated. Lipoprotein (a), antithrombin III, protein C, protein S, factor V Leiden, and the G20210A prothrombin gene mutation were not studied in both patients whereas in the second case even the very important factor V Leiden mutation as well as lupus anticoagulant and homozygous levels were not evaluated. Although the aeroplane flight could be the most important risk factor in these cases, the rather incomplete thrombophilic screening does not permit us to conclude that it was “the only potential risk factor”.

It is known that deep vein thrombosis (mainly symptomless) may occur in up to 10% of long haul airline travellers.1 In contrast, the hypercoagulable states play a more significant role in ischaemic colitis, leading to the development of thrombotic occlusion of the small vessels supplying the colon. In a recent study of comprehensive thrombophilic screening in patients with an established diagnosis of ischaemic colitis, we found the prevalence of acquired and hereditary thrombophilic risk factors significantly higher compared with the prevalence of these factors in matched inflammatory and healthy controls.2 A thrombophilic tendency was demonstrated in the majority of patients and the most significant associations were with antithromophilic antibodies and with the factor V Leiden mutation. Moreover, we recently found a high frequency of neutralizing antibodies in patients with ischaemic colitis (unpublished data). Based on the recent data of the association of protein Z deficiency mainly with arterial thrombosis,3 protein Z deficiency may be involved in the development of the disease in a subgroup of patients by causing thrombosis in the small mesenteric arteries.

Transient ischaemic colitis is considered the result of localised non-occlusive ischaemia of the small arteries. In contrast, the presence of hypercoagulable states suggests a possible role of
venous obstruction. It is possible that future identification of subgroups in ischaemic colitis patients with sophisticated imaging techniques could distinguish cases with arterial or venous obstruction. In conclusion, we suggest that the mechanism of ischaemic colitis is multifactorial. Acquired and genetic factors may interact leading to disease manifestation. Arhythmia and embolic conditions, oral contraceptives, and other medications, as well long haul flights probably play a role in genetically predisposed individuals in the disease pathogenesis.

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References
2 Brandt LJ. Thrombophilia and colon ischaemia: aura popularis? Gastroenterology 2001;121:724–9

The Handbook of Clinical Trials and Other Research

Clinicians are notorious for embarking upon research without a full understanding of methodology. Perhaps in the past clinical journals were guilty of publishing papers without being sufficiently critical. No doubt this was a byproduct of well meant referring of clinicians who were themselves hamstrung methodologically, and lacking insight.

In the new world of publications, the research design has to be explicit, well laid out, and sufficiently robust to support the research reported. Many doctors have had little or no training in research methods, despite having completed an MD. This might be one reason why it is becoming increasingly difficult for even research experienced clinicians to initiate new projects. Indeed, there is a question mark as to whether research can now be done by service based clinicians or whether, because of the newer strictures and disciplines, this should be left to the professional researcher. Perhaps the answer is that clinicians ought to have access to experts who can not only guide them but see them through the entire project. Some have questioned whether clinical research is still possible, and the answer, even if only in hope, is yes, but this will require a greater familiarity with research methodology, the patience to plan thoughtfully, and with experienced colleagues.

This handbook provides definitions and contemporary examples. It provides recent references from major journals and is well illustrated. It contains material beyond explanations of research terminology and methodology including the new requirements for the Research Ethics Committees, and the EU Clinical Trials directive. Many of the chapters dealing with cytokines and Helicobacter pylori infection are brief, but these subjects are adequately covered elsewhere in numerous reviews. New and potentially useful therapeutic possibilities are examined, including the use of platelets to deliver healing growth factors, the use of polysaccharides such as heparin for gastrointestinal protection, and gene therapy with angiogenic factors.

It is not possible for any book to be complete and inclusive of all subjects in such a diverse field as mucosal repair and therapeutics, but this book does a more than reasonable job. It will be a very useful reference for research newcomers and veterans alike in the field.

E J Dial
Hepatology Principles and Practice

E Kuntz, H-D Kuntz. Berlin: Springer Verlag, colour, pp 825. ISBN 3540 42161 0

“You have a very large parcel”, Zeinab, my secretary said breathlessly as she struggled up from the post room with a copy of this enormous book. It seemed all the heavier as I lugged it around the London bus network from the wilds of East Acton on my way home and then back to work several times. Contained in a reinforced Harrod’s bag, which was the only thing I could find that was strong enough to hold it while I elbowed my way through the myriad of commuters that were forced to travel by bus in lieu of the non-existent Central line, I felt my back pain had returned with a vengeance and did not know whether to take up weight training (where the book would come in handy) or admit defeat and sue the authors for damages. However, sanity soon prevailed and I soon became engrossed in this weighty tome.

At first glance, one could say that another comprehensive book on hepatology is really not needed, given all the other titles on the market. But it turns out that this book adopts. However, I would have thought given the fact that the format of its main competitor, the Sherlock book, is not as visually inviting, the Kuntz tome would find a home in most hospital libraries, even if the local gastroenterology department is reinforced shelves by clearing a space in their local gastroenterology SpRs who would like to take up weight training on liver abscesses, bacterial, parasitic, and fungal (“mycotic”) liver disease are useful. The question of who may actually buy this book looms large. It is too big and too costly for any individual junior doctor who might be interested in this “user’s guide” approach that the book adopts. However, I would have decided to check the strength of her newly reinforced shelves by clearing a space in anticipation of her copy.

The question of who may actually buy this book is one could say that another comprehensive book on hepatology is really not needed, given all the other titles on the market. But it turns out that this book adopts. However, I would have thought given the fact that the format of its main competitor, the Sherlock book, is not as visually inviting, the Kuntz tome would find a home in most hospital libraries, even if the local gastroenterology department is reinforced shelves by clearing a space in their local gastroenterology SpRs who would like to take up weight training on liver abscesses, bacterial, parasitic, and fungal (“mycotic”) liver disease are useful. The question of who may actually buy this book looms large. It is too big and too costly for any individual junior doctor who might be interested in this “user’s guide” approach that the book adopts. However, I would have decided to check the strength of her newly reinforced shelves by clearing a space in anticipation of her copy.

S D Taylor-Robinson

NOTICES

The Association of Coloproctology of Great Britain & Ireland

This annual meeting will be held on 7-10 July 2003 in Edinburgh, UK. Further details: Conference Secretariat, The ACGBI at the Royal College of Surgeons of England, 35-43 Lincoln’s Inn Fields, London WC2A 3PE. Tel: +44 (0)20 7973 0307; fax: +44 (0)20 7430 9233; email: acgbi@acgbi.org.uk; website: www.acgbi.org.uk

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, Solvogatan 23, SE-223 62 Lund, Sweden. Tel: +46 46 173 241; fax: +46 46 152 564; email: Torkel.Wadstrom@mmib.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 6329, Leinwenberstr. 5, 79041 Freiburg, Germany. Tel: +49 761 15 140; fax: +49 761 15 14 359; email: symposia@falkfoundation.de; website: www.falkfoundation.de

The European Society of Parenteral and Enteral Nutrition (ESFEN)

This course will be held on 18–21 November 2003 in Brussels, Belgium. Further details: Secretary to Professor Cadière, Service de Chirurgie Digestive, Rue Hausser 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

European Course on Laparoscopic Endoscopy

This course will be held on 12–13 October 2003 in Freiburg, Germany. Further details - see Falk Sympoisa above.

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HK-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@1810 2442; fax: +852 2818 4050; email: kristieleung@hepa2004.org; website: www.hepa2004.org

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