Immunosuppression, IBD, and risk of lymphoma

We read with interest the two recent reports of lymphoma in patients with inflammatory bowel disease (IBD) (Farrell et al. Gut 2000;47:514–19 and Palli et al. Gastroenterology 2000;119:467–73). We believe the report from Farrell of four cases of lymphoma in a cohort of 782 patients (of whom 238 had received immunosuppression) considerably overestimates the relative risk of lymphoma in IBD patients. They calculate a relative risk of lymphoma as 31 for the whole cohort and 59 for the group treated with immunosuppressive (compared with the general population). Immunosuppressive therapy is well recognised as increasing the risk of developing non-Hodgkin’s lymphoma (NHL) in organ transplant patients.1 The risk of NHL is increased in other inflammatory conditions, such as rheumatoid arthritis2 and psoriasis, although how much is attributable to the underlying disease and how much is due to the drug is unclear.

For IBD, if the incidence of lymphoma is indeed increased, is this due to drug or disease? Two recent reviews3,4 have examined the question of immunosuppression in IBD. In both, the drug is unclear.

A number of smaller case series have been published which show an increased incidence of NHL in IBD patients. In none of these studies does the relative risk for NHL significantly exceed one, while only one study (Palli et al4) has shown an excess risk of Hodgkin’s disease (relative risk 9.3; 95% confidence interval 2.3–23.8).

Several large well designed population based studies have been performed specifically to examine the baseline risk of lymphoma in IBD. In none of these studies does the relative risk for NHL significantly exceed one, while only one study (Palli et al4) has shown an excess risk of Hodgkin’s disease (relative risk 9.3; 95% confidence interval 2.3–23.8).

A number of smaller case series have been published which show an increased incidence of NHL. This type of study, although interesting, should not be regarded as evidence of increased risk as case ascertainment bias is likely to exist.

Several studies have specifically addressed the question of immunosuppression in IBD. In total, only 11 cases of lymphoma were described in more than 4000 patients who had received immunotherapy, with over 17 000 patient years of follow up. Extrapolating these data to lymphoma rates in the general population may be unreliable, particularly as lymphoma rates vary widely geographically, by sex and age.

We believe that compared with the other known risks of immunosuppression, such as myelosuppression and infection, the risk of developing lymphoma (if it does exist) is likely to be of minor clinical significance and be outweighed by the potential benefit of these treatments in patients with IBD.

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References


Current guidelines fail young patients with oesophagogastric cancer

Wallace et al (Gut 2001;49:29–34) clearly describe the difficulties with AGA guidelines for endoscopy in the light of their study in identifying young oesophagogastric pathology. They concluded that better clinical prediction strategies are needed. In the UK we have found similar failings in our own guidelines for endoscopy for identification of young patients with oesophagogastric carcinoma. The national data suggesting oesophagogastric carcinoma is rare in patients under 55 years seemed at odds with the large number of patients we have seen in this age group in recent years.

We reviewed our oesophagogastric cancers over three years and found 76 patients under the age of 55 years between January 1997 and December 1999. The hospital records of these patients were examined with the general practice records where possible. A detailed review was undertaken in patients under 50 years old, looking at their presenting symptoms, stage, location, nature, and size of tumour. Timings were noted from the date of referral, date of diagnosis, and date of death. Kaplan-Meier methods were used to estimate survival.

Of the 460 patients with oesophagogastric carcinoma, 74 (16%) were found to be less than 55 years of age at diagnosis. Thirty eight patients (8.3%) were less than 50 years of age, and 19 (4.1%) were less than 45 years.

Detailed analysis of patients under 50 years revealed that 29 (76%) of 38 patients had dysphagia at the time of presentation (mean duration four months (range 1–9)). Three patients recalled food occasionally sticking after swallowing for 2, 15, and 29 years, respectively. Reflux or heartburn was recalled prior to presentation by 57%, with a mean duration of 6.8 years (1 weeks to 20 years). Seventeen patients (45%) had been prescribed acid suppression or antacid therapy prior to referral. Seventy one per cent were adenocarcinomas, 16% squamous, and 13% others, and average length was 6.8 cm (range 1–16).

Fourteen involved the oesophago gastric junction, 15 the oesophagus, and nine the stomach alone. Staging of 37 patients revealed: one T1 tumour, nine T2, 12 T3, and 15 T4 tumours. Forty per cent had metastasis at presentation and 34% were tertiary referrals.

Twenty three patients had a resection, nine of whom had adjuvant chemotherapy and two had radiotherapy. There were 11 palliative, nine chemotherapy, and two radiotherapy treatments. Nine patients were stented. Only four of 23 resections had no lymph node spread. There was no perioperative mortality but median survival was only one year (fig 1). Currently, only eight patients are alive.

The current UK government guidelines specifically state that “the chance of a dyspeptic patient under the age of 55 having gastric cancer is 0.0001%”. This cannot be true given that one unit saw 38 cases of carcinoma in the oesophagus and stomach under the age of 50 years over a three year period. Twenty three had disease involving the stomach; almost all had some prodomal dyspepsia and a high proportion had reflux disease.

Gastro-oesophageal cancer presents late; reliable indicators for the presence of disease are still to be found, although the association with reflux disease has been confirmed recently.7 The young patient with advanced disease and, as reported by Bowry and colleagues,8 quickly progress to end stage disease. Our referral bias does not explain this effect. We chose to look at patients under 50 years in detail, particularly as this is the proposed increase to the BSG guidelines. The BSG guidelines use 45 years to restrict access, suggesting endoscopy in those patients older than 45 years with new onset dyspepsia and only in younger patients with alarm symptoms.

Figure 1 Kaplan-Meier curve of survival of young oesophagogastric cancer patients in those less than 50 years of age.
symptoms. Guidelines issued by the UK Department of Health\textsuperscript{1} state that 35 years of age is the cut off for referral, with at least one high risk factor or new onset dyspepsia. Local Cancer Networks can allow 50 or 45 years as a cut off. In our unit, increasing the age to 50 years for patients with new dyspepsia will clearly disadvantage patients when the potential life saving window is made even smaller.

Reflux often precedes the development of oesophageal or gastric carcinoma. Is relief of symptoms using medical treatment enough to prevent malignant change or may it even mask a developing tumour? Access to endoscopy needs to be improved in young patients who present with intermittent dyspepsia as early diagnosis is to be made. The development of more sophisticated endoscopic modalities will also make inroads into achieving earlier diagnosis. Without prevention or early diagnosis in this group there is unlikely to be any progress made to extending the lives of these patients.

Our data do not prove that early endoscopy would actually save these patients from a certain death. What it clearly demonstrates is that, using the current guidelines, our small region allows 30 of 38 patients under 50 years in a three year period to die of oesophageal or gastric carcinoma. Nationally, this translates into a major failure to adequately diagnose and treat oesophageal or gastric cancer in young people. The guidelines of diagnosis fail. A screening method is urgently needed for this rapidly increasing cancer problem. Standard endoscopy is too cumbersome and expensive; new technologies may change our whole approach.

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References

Acute appendicitis in Japanese soldiers in Burma: support for the “fibre” theory

In the last three months of 1946 and the first quarter of 1947, the late Anand Pardhy and I were the graded surgeon and graded physician in a CCS (Casualty Clearing Station) which was active as a static hospital in the small town of Prome, not far from the town of Mandalay in Burma. In the same area was a camp of 1077 Japanese soldiers awaiting repatriation. They had their own medical officers and sick bay but cases requiring surgery and the more severely ill medical cases were admitted to the CCSs. During this period, we admitted from the Japanese camp 10 cases of acute appendicitis, or one case every 2–3 weeks. At the beginning I assisted Pardhy but became so familiar with the technique that I was allowed to do the operation, with Anand’s reports assisting.

We were intrigued by the high incidence of appendicitis in the Japanese soldiers and thought it might be because the camp was receiving mainly British rations which had a lower fibre content than the normal diet of a Japanese soldier. The fact that their own medical officers were surprised at the number of cases suggested that appendicitis was normally rare in Japanese troops.

Fortunately, this hospital area there were large concentrations of Indian, Gurkha, and Burmese troops, and a battalion of irregulars from the Chin Hills, on the border between Burma and what is now Bangladesh. The total number of these troops greatly exceeded the number of Japanese soldiers in the camp, yet we admitted no cases of appendicitis from these various nationalities.

In discussing the aetiology of appendicitis, Burkitt and Trowell pointed out that communities with a high fibre diet have a low incidence of appendicitis, while those consuming a Western style diet, low in fibre and high in refined carbohydrates, have a higher incidence.\textsuperscript{1} Confirmation of their theory is provided by the difference in the incidence of appendicitis between British and Indian troops in India during the period 1936–1947. Appendicitis was 4–6 times more common in the British than in the Indian troops.\textsuperscript{2} In the same period, the basic ration for Indian troops contained one third the amount of animal protein and three times as much fibre as refined carbohydrates (parboiled rice, atta (unrefined wheat flour), and pulses (dal and peas)) as that of British soldiers in India.\textsuperscript{3}

The effect of a change in the intake of fibre was also discussed by Burkitt and Trowell who cited a report that the incidence of appendicitis in Japanese immigrants in Hawaii, where they presumably ate an American style low fibre diet, was higher than in Japan.\textsuperscript{4} The same authors referred to reports that Singapore troops in North Africa and West African troops in Singapore had an increased incidence of appendicitis when they were given British rations.\textsuperscript{5} These reports are analogous to our experience with the Japanese prisoners of war but do not discuss whether the effect of a sudden change in diet produced an incidence higher than that in countries consuming a Western type of diet. A rate of 10 cases in six months would produce 20 cases a year in a population of 1000 men, or 200 cases per 10 000 population. The incidence of appendicitis among adults in England and Wales for the years 1931–1935 was estimated at 45 per 10 000\textsuperscript{6} while the annual discharge rate for appendicitis for 1959 was 27 per 10 000,\textsuperscript{7} suggesting a rate of approximately 35 per 10 000 for the 1940s. Other data on the incidence of appendicitis in the Japanese camp. Our values certainly suggest that a sudden change in diet, in this case a reduction in the intake of fibre, produces an exceptionally high incidence of appendicitis.

Van Oeverkerk\textsuperscript{8} gave an example of the opposite effect. In the Dutch internment camps in Indonesia during the 1939–45 war, appendicitis was practically unknown; the diet consisted of “rice in insufficient quantities, unprocessed vegetables, and practically without meat and fat”.\textsuperscript{9}

In conclusion, our experience with the Japanese camp tends to confirm Burkitt and Trowell’s theory that a low fibre diet causes a high incidence of appendicitis. However, recent evidence from South Africa has shown that urban Black Africans continue to have a very low incidence of appendicitis in spite of the fact that their dietary intake of fibre is lower than that of the urban white population. Clearly then, there may be factors other than the level of fibre intake determining the incidence of acute appendicitis.

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3 Medical Directorate, India. Field service hygiene notes, India. New Delhi: Medical Directorate, 1945; 111–114.

GRP and stimulation of acid secretion

We read with interest the article by Hildebrand\textit{et al} on the effect of gastrin releasing peptide (GRP) on acid secretion in healthy individuals (Gut 2001;49:23–8). This study shows that a GRP antagonist (BIM 26226) inhibits acid secretion with no effect on plasma gastrin. The authors concluded that GRP stimulated acid secretion by a non-gastrin mechanism. Their results are in agreement with previous studies from our laboratory which indicate that GRP in the rat stimulates acid secretion by a mechanism other than by gastrin release.\textsuperscript{10} We also found that GRP releases somatostatin and inhibits histamine release from the oxyntic mucosa, an effect which viewed in context should counteract acid secretory stimulation.

These studies and others demonstrate the complexity of neuropetide mechanisms in the regulation of gastric acid secretion. In our opinion, great care should be shown when interpreting the results from experiments using neuropeptides in the study of gastric physiology and pharmacology.

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References

Authors’ reply
Our conclusion that gastrin releasing peptide (GRP) is not a physiological regulator of gastric secretion in humans stands against an
impressive body of evidence collected in the past 30 years in different animal species. Even in humans, several lines of evidence would support a role for GRP as a regulator of the G cell: infusion of exogenous GRP stimulates gastrin release in humans but GRP also releases gastrin from isolated human gastric cells in vitro.14 In several laboratory animals, GRP antagonists or GRP antibodies inhibit the release of gastrin to a variety of stimuli.15-17 Our results obtained in healthy male subjects could therefore be due to species differences with respect to the physiological role of GRP as a gastrin secretagogue. As pointed out by Walldum and Sandvik, some studies in rats have also shown that GRP can stimulate acid secretion independent of gastrin release. Along the same lines, gastrin concentrations are normal in mice lacking the GRP receptor.4 As gastrin secretion is regulated by various factors, including nutrients, G cell responses to GRP reflect the balance of direct stimulatory and indirect inhibitory factors. We hope that our data will generate new interest in studying the role of this interesting peptide in regulating gastrointestinal functions.

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References

BOOK REVIEWS

Textbook of Gastrointestinal Radiology, 2nd edn, vols 1 and 2

With Margulis and Burhenne’s Alimentary Tract Radiology currently out of print, the Textbook of Gastrointestinal Radiology is the only large all encompassing reference text for gastrointestinal radiologists and interested gastroenterologists. This is the second edition and its predecessor was never far from my hand, especially when a particularly difficult or obscure differential diagnosis was required. While reviewing a book can sometimes be a necessary chore, this is a delight, not least because it is an essential purchase for any aspiring gastrointestinal radiologist. This large two volume set attempts to cover the whole gamut of gastrointestinal radiology, both luminal and solid organ, in 131 chapters. The editors state their aim “to provide complete, up to date lectures, backed up by a wealth of knowledge in gastrointestinal radiology in a practical and usable way.” While large books such as this can sometimes be criticised as cumbersome, the editor’s ambitions demand a format capable of presenting the necessary breadth and depth required of a reference text, and I would argue that the book is indeed practical and usable; I certainly found the predecessor so. The plethora of chapters is sensibly divided into those dealing with hollow and solid viscera, each preceded by sections dealing with general techniques and the principles of interpretation. There are also sections on paediatric disease and common clinical problems. The respective organ sections are generally exhaustive; for example, separate chapters are entirely devoted to postoperative appearances. I have only one criticism, albeit major. The editors claim to have assembled “an outstanding group of internationally recognised authors”. While this is probably true, they are certainly not international! Although not overtly stated, this is essentially a North American text; a paltry three of the 124 authors hail from outside this continent. I cannot help feeling this prevents the text from being truly definitive. Gastrointestinal radiology is a well defined subspecialty and the movers and shakers are by no means exclusively North American. I suspect the editor’s parochial approach is partly responsible for some glaring errors of omission. For example, anal endosonography, a clinically important and well disseminated technique, is rarely practised by North American radiologists and not even mentioned in passing. Indeed, the relative dearth of ultrasound in general probably reflects transatlantic practice. I hope other omissions, for example colonic stenting and the use of magnetic resonance imaging to assess and classify perineal fistulae, merely reflect the time taken to get a large book like this into the shops rather than spectrum bias. The absence of virtual colonoscopy is almost certainly due to publication lag; it is mentioned in the preface but absent in the book! However, there is little to criticise when staying into more conventional territory and here the North American authorship brings undoubted benefits for a reference text; it would be difficult to find more extensive references to computed tomography and principles of learning material elsewhere. From personal experience, most chapters dealing with mainstream topics can be used as well referenced starting points for indepth analysis of the particular feature described. So, with the caveat mentioned, the second edition of this book remains as invaluable as the first and is certainly a must-buy for any gastrointestinal radiologist who needs a reference text to hand in his or her office, or for more leisurely inspection at home.

R Jones

Recent Advances in Gastrointestinal Endoscopy
Edited by M S Bhutani, R K Tandon. Jaypee Brothers, pp 678. ISBN 81 7179 810 1

This is an extremely comprehensive and well illustrated reference book for experienced endoscopists wishing to extend their area of
This book celebrates the progress in imaging over the last two decades so that gross pathology is now fairly well shown by accurate and non-invasive or minimally invasive imaging methods. Microscopic histological changes are incompletely shown by imaging techniques but there has also been significant progress in characterising various processes, diseases, and tumours by imaging without biopsy.

The first section entitled “progress in imaging” considers computed tomography (CT), MRI, and developments in ultrasound. Modern CT and MR techniques are explained with suitable illustrations. Most impressive are the three-dimensional images constructed from CT and MR data.

The chapter on ultrasound introduces all of the new ideas of tissue harmonic imaging (printing error on page 33, tissue harmonica imaging!), tissue characterisation, and ultrasound contrast agents. Unfortunately, some of the images in this short chapter are disappointing and the concepts described are not completely clear.

The next section concerns anatomy and gross changes in the liver with illustrations of pathology and imaging examples. These chapters are descriptive down to the level of electron microscopy with a lot of useful diagrams and imaging illustrations. There is a further short chapter describing the relationship and pathology of the diaphragm with the liver.

Longer sections then deal with diffuse hepatic diseases with chapters on acute and chronic viral hepatitis and other causes of chronic hepatitis. There is a chapter on pathology, physical signs, and imaging in cirrhosis and further chapters on fatty liver, alcoholic liver disease, iron overload, and other diffuse changes, including metabolic disease and drug-induced liver disease.

The next section deals with vascular disease including portal hypertension, non-cirrhotic portal hypertension, portal vein thrombosis, and Budd-Chiari syndrome. Included in this section is a chapter on haemodynamics. The sometimes complex relationship between the various hepatic circulatory systems are illustrated by CT, arterial portography, and CT hepatic angiography, and also by balloon occlusion of hepatic arteries and veins. Many observational studies of this type have been published in the radiological literature, usually from Japanese centres. This type of work is useful for the understanding of odd lesions or pseudo lesions demonstrated in more conventional CT or MR examinations but they are by no means routine procedures in UK practice.

The chapter on portal hypertension and non-cirrhotic portal hypertension has many fascinating illustrations with a large number of “invasive” studies, including transhepatic portal vein catheterisation and transumbilical portal vein catheterisation. As diagnostic procedures, these would be regarded as somewhat invasive in current UK and European practice when much of this information is obtainable by CT, ultrasound, or MR. We see similar images during procedures such as TIPS but not usually for diagnosis alone.

Naturally, there is considerable discussion of hepatocellular carcinoma, a major problem in Japan and possibly an increasing problem in the western world.

All types of focal liver lesions are described with considerable emphasis on the haemodynamics contributing to contrast enhancement at CT, MRI, and ultrasound. Pathology and imaging of potential premalignant cirrhotic nodules are also reviewed. Later chapters cover other liver disorders including trauma, parasites, and liver transplants followed by extensive discussion of biliary diseases.

This is not an ordinary textbook but a collection of explanations of the pathophysiology illustrated by imaging. This leads to emphasis on CT, hepatic angiography, and arterial portography. In the UK and USA, current emphasis is more on the use of multislice multiphase CT with intravenous contrast and MRI with various, more specific, contrast agents.

Some of the images included are remarkably over the top. For example, a cystic arteriogram is shown in a case of gall bladder carcinoma. Overall, I enjoyed the book, particularly for the imaging minutiae. However, mixed up with this is an attempt to cover all types of liver and biliary disease as well as imaging and pathology. The treatment and management of many conditions are also discussed in a limited way. This gives an overall broad but uneven coverage. Although entirely satisfactory in themselves, I am not certain that it was necessary to include chapters on trauma and liver transplantation with the other material.

This is not a book for every gastroenterologist but will be of more interest to those specialising in liver diseases, particularly if they wish to delve into the complexities of imaging.

S P Oliff

Hepatobiliary Diseases: Pathophysiology and Imaging

Edited by K Okuda, D G Mitchell, Y Yao, et al.

Professor Okuda sets out the aim of this book which is to describe advances in various imaging modalities to facilitate the use of different techniques and contributions that have not come from the understanding of hepatobiliary diseases and pathophysiology. The book is edited by three Japanese professors of medicine and radiology, and one American professor of radiology with a wealth of experience in magnetic resonance imaging (MRI) specialist. The contributing authors are Asian and American with the majority from Japan. The authors include physicians, gastroenterologists, pathologists, endoscopists, and radiologists.
Recent Developments in Gastric MALT Lymphoma
This is a one day meeting organised jointly by the European Gastrointestinal Lymphoma Study Group and British Society of Gastroenterology, Gastro-duodenal Section. The meeting will be held on 20 December 2002 in London, UK. Further information and registration details: Dr A Dogan, Department of Histopathology, Royal Free and University College, Medical School, Rockefeller Building, University Street, London WC1E 6JJ, UK. Tel: +44 (0)20 7679 6015; fax: +44 (0)20 7387 3764; email: a.dogan@ucl.ac.uk; website: www.ucl.ac.uk/histopathology/egils

Postgraduate Gastroenterology
This course will be held on 15–18 September 2002 in Oxford, UK. The course has been designed for consultants and registrars, including those who do not specialise in gastroenterology. Topics will include: Barrett's Oesophagus; The Case for Endoscopic Surveillance Debate; Liver Disease; Bacteria and the Gut; IBD Therapeutics, Gastrointestinal Bleeding, Endoscopic Training. Further information: Professor Derek P Jewell, University of Oxford, Nuffield Department of Medicine, Gastroenterology Unit, Gibson Laboratories, 2nd Floor, Radcliffe Infirmary, Block 21, Woodstock Road, Oxford OX2 6HE, UK. Tel: +44 (0)1865 224829; fax: +44 (0)1865 790792; email: derek.jewell@ndm.ox.ac.uk; website: www.medicine.ox.ac.uk/gastro

British Association for the Study of the Liver
The 2002 BASL meeting will be held on 11–12 September in Newcastle, UK. Further information: Mrs Jackie Carter, Centre for Liver Research, University of Newcastle, Floor 4, William Leech Building, Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK. Tel: +44 (0)191 222 5640; fax: +44 (0)191 222 0723; email: j.a.carter@ncl.ac.uk

3rd World Chinese Congress of Digestology
This congress will take place on 23–25 September 2002 in Beijing, China. Further information: Lian-Sheng Ma, President of WCCD, PO Box 2345 Beijing 100230, China. Fax: +86 6589 1893; email: wcjd@public.bta.net.cn

EPGS Second Update on Coloproctology
The European Postgraduate Gastro-Surgical School presents this course on 10–11 October 2002 in Amsterdam, the Netherlands. Further information: visit the website www.epgs.nl or email epgs@amc.uva.nl; Tel: +31 20366 3926/4366.

Xth European Course on Therapeutic Digestive Endoscopy and Radiology
This course will take place on 24–25 October 2002 in Rome, Italy. Further information: SC Studio Congressi, Via Francesco Ferrari 40, 00191 Roma, Italy. Tel: +39 06 3290150; fax: +39 06 36306897; email: sc.congressi@stn.it; website: www.scstudiocongressi.it

Advances in the Inflammatory Bowel Diseases
This conference will take place on 6–7 December 2002 in New York, USA. Further information: Heather Drew, Imedex, 70 Technology Drive, Alpharetta, GA 30005-3969, USA. Tel: +1 770 751 7332; fax: +1 770 751 7334; email: h.drew@imedex.com; website: www.imedex.com

15th European Intensive Course (SMIER) Digestive Endoscopy
This course will take place on 16–17 December 2002 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 58.