Correspondence

Chronic hepatitis C in long term survivors of haematological malignancy treated at a single centre

In their review of 42 long term survivors of haematological malignancy Neilson *et al*[1] found two patients with hepatitis C virus (HCV) infection. Of the remaining eight patients with raised aspartate aminotransferase (AST) activity only two were explained by either hepatitis B virus infection or chronic graft versus host disease (GvHD), leaving six patients with unexplained liver dysfunction.

We are interested in the cause of continuing abnormal liver function in these patients in the light of our own experience of following long term survivors of haematological malignancy.

A review of our patients revealed that 21 were in complete remission more than three years after treatment. Two of these patients were HCV positive. They were diagnosed in 1986 and 1990 and received 41 and 28 units of blood, respectively. Five patients had raised AST activities, including both HCV positive patients. All five patients had serum ferritin concentrations (normal range 20–300 ng/ml) above the normal limit (median 863 ng/ml; range 395–4860 ng/ml). Three patients had hepatic siderosis confirmed on liver biopsy.

Murphy *et al*[2] reviewed survivors of allogeneic and autologous bone marrow transplant alive one year after transplantation and found that 38 (43%) of 88 had raised transferase activities not explained by either viral hepatitis or GvHD; 77% had a raised serum ferritin concentration consistent with iron overload and in 15/17 patients liver function improved after venesection.

Following treatment for haematological malignancy, transfusional iron overload is an important cause of increased transferase activity and should be considered when viral hepatitis and GvHD have been excluded. The long term outcome of untreated hepatic iron overload in this group of patients is uncertain but return of normal liver function after venesection suggests that this treatment may be beneficial. Maintenance of serum ferritin concentrations below 2000 ng/l has been shown to prevent complications in patients with iron overload.[3] The role of venesection in patients with evidence of hepatic iron overload and normal liver function remains unclear.

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1 Neilson JR, Harrison P, Skidmore SJ, King HA, Collingham KE, Milligan DW. Chronic hepatitis C in long term survivors of haematological malignancy treated at a single centre. *J Clin Pathol* 1996;**49**:230–2.
2 Murphy JA, Cook G, Mowat A, George K, Cameron S, McKenzie J, *et al*. Liver dysfunction in long term survivors of BMT due to hepatitis C virus (HCV) and transfusional iron overload: results of venesection therapy and liver biopsies. *Br J Haematol* 1995;**89**:5.
3 Gabutti V, Piga A. Results of long-term iron-chelating therapy. *Acta Haematol* 1996;**95**:26–36.

Drs Neilson and Harrison comment:

'We read Dr Butler's letter concerning the aetiology of the deranged liver function in our patients with great interest. We agree that iron overload may well be the cause of abnormal liver function in at least some of our patients and we have investigated this further. We have looked at both serum ferritin concentrations and non-transferrin bound iron in 38 of our patients, including the six with no obvious cause for liver dysfunction. Our initial results have been published in abstract form[1] and the full paper is published in this issue (see p853). We feel that it is worth emphasising that serum ferritin alone may not be a reliable indicator that iron overload is the cause of liver dysfunction. Hepatic damage itself leads to raised serum ferritin concentrations and like Murphy *et al*[2] we found that many patients without apparent liver dysfunction had very high serum ferritin concentrations. We agree that further study is required and we are currently involved in the MRC AML X iron overload study. This study aims to assess the effect of iron overload on liver function in surviving patients who were treated in the AML X trial. Several parameters of iron status, including serum ferritin and non-transferrin bound iron, will be assessed. Additional studies looking at putative markers for the haemochromatosis gene will be performed. We feel that this is an important area of research and would encourage others to respond favourably to requests for information and samples for the iron overload study.

1 Harrison P, Neilson JR, Marwah SS, Maddon L, Bareford D, Milligan DW. Iron overload, non-transferrin bound iron and liver dysfunction in long term survivors of haematological malignancy [abstract]. *Br J Haematol* 1996;**93**:25.
2 Murphy JA, Cook G, Mowat A, George K, Cameron S, McKenzie J, *et al*. Liver dysfunction in long term survivors of BMT due to hepatitis C virus (HCV) and transfusional iron overload: results of venesection therapy and liver biopsies. *Br J Haematol* 1995;**89**:5.

Bayesian Belief Network in histopathology

I read with interest the recent article by Montironi *et al* on the Bayesian Belief Network.[1] It is an important work because it gives general pathologists an overview of how subjective histological features in a grading system can be analysed mathematically. It is particularly impressive that a very precise probability matrix (normalised belief) can be reached at the conclusion of the mathematical analysis.

In spite of its apparent objectivity and precision, the Bayesian Belief Network depends very much on the conditional probability matrix (CPM) and the relative likelihood vector; the former is predetermined by experts and the latter by the observer. In the paper by Montironi *et al* the CPM constructed was based on the authors' experience. It is conceivable that different experts may have different CPMs and therefore different experts may arrive at totally different normalised beliefs even though they may agree on the same relative likelihood vector. With international consensus meetings, it may be feasible to standardise the CPM. However, it may be better still if the CPM is capable of renewing itself based on additional information from new cases.

Another source of interobserver inconsistency is the establishment of the relative likelihood vector, which carries with it an inherent element of subjectivity. The idea of using video images stored on computer to minimise this inherent subjectivity is a very valid and thoughtful suggestion. It is theoretically possible to have a perfect match if the number of video images is sufficiently large.

As shown by boxes 1 and 2, Montironi *et al* suggested that the final belief probability matrix was determined by *multiplying* the three internal lambdas (from tubular formation, mitosis and nuclear pleomorphism). In order to justify multiplication as the best mathematical manipulation, it has to be assumed that the three parameters are *independent* variables. Recent studies,[2 3] however, have shown that nuclear grade alone correlates with histological grade, suggesting that such an assumption may not be entirely correct. Therefore, I wonder whether it would be more reliable and accurate if the three internal lambdas are *added* together to get the final belief probability matrix. One may also take into consideration the relative importance of each parameter by first multiplying the individual internal lambdas by a scalar, followed by addition of the subsequent scaled internal lambdas. For example, if it is considered that tubular formation, mitosis and nuclear pleomorphism have a relative importance of 1:2:3 in the assessment of overall histological grade, the internal lambda for mitosis is multiplied by 2 and that for nuclear pleomorphism by 3 first and then added to the internal lambda for tubular formation to give the final belief probability matrix.

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1 Montironi R, Whimster WF, Collan Y, Hamilton PW, Thompson D, Bartels PH. How to develop and use a Bayesian Belief Network. *J Clin Pathol* 1996;**49**:194–201.
2 Hunt CM, Ellis EO, Elston CW, Locker A, Pearson D, Blamey RW. Cytological grading of breast carcinoma – a feasible proposition? *Cytopathology* 1990;**1**:287–95.
3 Cajulis RS, Hessel RG, Hwang S, Haines K, Frias-Hidvegi D, O'Gorman M. Simplified nuclear grading of fine-needle aspirates of breast carcinoma: concordance with corresponding histologic nuclear grading and flow cytometric data. *Diagn Cytopathol* 1994;**11**:124–30.

Standardisation of histopathology reports

I read with interest the paper concerning histopathology reports on primary cutaneous malignant melanoma.[1] It is surprising that even six years ago in approximately one in eight cases of malignant melanoma there was no comment on either tumour thickness or on completeness of excision of the tumour in the histopathology report. This is a good argument in favour of standardisation of reports particularly with respect to certain malignant tumours.

In the past pathologists have been reluctant to use standardised reports according to a predetermined protocol. However, the need for reports of this type is rapidly becoming more urgent.

Firstly, and most importantly, failure to mention important prognostic factors in a report on a particular type of tumour could be construed as negligent in a court of law. This is especially so in light of the fact that a standard textbook now contains prototype standardised reports for most important malignant tumours.[2] Secondly, pathologists should provide as much information in their

reports as possible to allow accurate staging of tumours by clinicians. Thirdly, the need for this sort of information is growing as tumour cancer registries rightly become more demanding in terms of the information they require.

The task is eased because many word processor programs permit the insertion of a protocol for a standardised report, which means that only the specific details of an individual case need to be entered into the report. All that remains is to persuade pathologists that reports are not literary art forms but scientific descriptions which can with advantage be standardised and quantified.

The information which is required is being published widely in journals[3 4] and texts.[2]

It is arguable whether protocols should be prepared by individuals or departments or by national or international professional bodies. There is much to be said for a uniform approach, so as to permit research on a wide scale and to aid the task of cancer registries.

Measurements made on a microscope slide are not commonly given (save for thickness of malignant melanoma) but to give a quantitative measurement of the distance to the surgical resection margin in cases of breast and skin cancer is useful and relatively simple, at least in the UK and Australia where calibrated mechanical stages are in general use.

To return to the article,[1] it represents an audit of a situation which prevailed six years ago. To move into the more modern world it is going to be essential to have regular internal and external forms of audit on procedures and on the accuracy and timeliness of reports as well as on the information contained therein. In this paper only two prognostic features of malignant melanoma out of the many which have been described have been audited.

As pathologists it would seem we all have a way to go. Roll on continuous professional education.

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1 Miller JM, Slater DN. Do histopathology reports of primary cutaneous melanoma contain enough essential information? *J Clin Pathol* 1996;**49**:202–4.
2 Rosai J. *Ackerman's surgical pathology.* 8th edn, Vol 2. St Louis: Mosby, 1996:2525–64.
3 Association of Directors of Anatomical and Surgical Pathology. Recommendations for the reporting of breast carcinoma. *Am J Clin Pathol* 1995;**104**:614–19.
4 Association of Directors of Anatomical and Surgical Pathology. Recommendations for the reporting of resected large intestinal carcinoma. *Hum Pathol* 1996;**27**:5–8.

Book reviews

Ackerman's Surgical Pathology. Vol I and II. 8th edn. Juan Rosai, ed. (Pp 2400; 2136 illustrations, 450 in colour; £229.00.) Times Mirror International Publishers Ltd. 1995. ISBN 0801670047.

The new eighth edition of *Ackerman's Surgical Pathology* weighs in at a hefty 18 lb 5½ oz compared with the mere 14 lb 1½ oz of the now seven year old predecessor. The extra weight has not gone into flab. Much of the text has been expanded and there are many additional high quality illustrations, mainly in colour. The familiar strengths of the still (amazingly) largely single author work include a unity of style and a lucid text with a wealth of relevant clinical and epidemiological information. Sections on normal anatomy and histology have been greatly expanded and there is much more information on immunohistochemistry, cytogenetics and molecular pathology. This must now be the first place to turn to for concise information on the immunohistochemistry of tumours in everyday practice. There is much helpful detail on prognostic factors in tumours. It is difficult and perhaps churlish to find any fault with the new edition. There are some occasional quirks of balance: only one short paragraph on glandular neoplasia in-situ of the endocervix with many lesser entities treated in much more detail, but the work largely succeeds in being both concise and comprehensive. It is an American book and the American nomenclature is used in—for example, germ cell tumours of the testis, though here and elsewhere other classifications are outlined. Although the layout of the two volumes is very similar to that of the previous edition and some of the text is unchanged, this is a substantially better book and a must for all Pathology Departments. It is a false economy to stick to the old edition. My review copy lies solidly on my study desk at home. I consult it so often that I am loathe to move it from there.

G M KONDRATOWICZ

Malignant Effusions. Bedrossian CWM. (Pp 275; £156.00.) Igaku-Shoin Medical Publishers. 1994. ISBN 0-89640-196-0.

Do not be misled by the title of this excellent cytopathology text/atlas. The first 100 pages cover general aspects, clinicopathological correlations and non-malignant causes of effusions with a detailed account of the many guises of mesothelial cells in reactive processes and problems in interpretation. Inflammatory processes and infective diseases presenting with effusions are also discussed and these early chapters are just as interesting and informative as the remaining two thirds of the book, which focuses on malignant effusions. Differentiating mesothelial hyperplasia from carcinoma is one of the great challenges in the cytology of malignant effusions. This problem is addressed in a style that is extremely lucid and includes the judicial use of immunocytochemistry and other ancillary techniques which may be helpful in clinching the diagnosis. Malignant mesothelioma, the differential diagnosis of small, blue, round cell tumours and metastatic non-epithelial malignancies are detailed. In fact, any tumour that is likely to lead to an effusion gets a mention. The illustrations throughout the book are of a high standard and are in colour with black and white reproductions confined to electron microscopy. Each chapter is lavishly illustrated and individual cell details are crisp and easily identifiable. This book is a treasure trove of information, not only for beginners, but also for experienced cytopathologists. Read it and improve your skill in diagnosing malignant effusions.

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Bioradicals Detected by ESR Spectroscopy. Ohya-Nishiguchi H, Packer L, eds. (Pp 352; DM 178.) Birkhauser Verlag AG. 1995. ISBN 3-7643-5077-6.

This book is a collection of papers from a conference on the application of electron spin resonance (ESR) spectroscopy to the detection of bioradicals (active oxygen radicals and transition metal ions), which was held in Japan in 1994. Following the introduction, there is a useful overview of the chemistry of oxygen radicals and three chapters which outline the physics and technological basis of ESR. There follows a section which describes the potential of ESR imaging and later chapters consider its application to the imaging of the rat brain. The technique of spin trapping the capture of radicals by stable molecules for future analysis is discussed at length. Two chapters outline the application of ESR to the study of bioradical metabolites in vivo and two are devoted to the application of probing active site structures of metalloproteins. The penultimate section considers antioxidants and foods, one chapter being devoted to vitamin E and its interactions in biological systems, while another describes research on antioxidant vitamin activities in micelles and liposomes. The theme of in vivo measurements is returned to in the concluding chapters, this section including an interesting review of the application of the technology to the investigation of drug delivery. The book is not primarily concerned with the biomedical effects of free radicals. It describes the technology of ESR in great detail and its application to the measurement of bioradicals. As such, it will be of interest to those who wish to learn more about the capabilities of this technique.

M F LAKER

The Estimation of the Time Since Death in the Early Postmortem Period. Claus Henssge, Bernard Knight, Thomas Krompecher, Burkhard Madea, Leonard Nokes. General editor: Bernard Knight. (Pp 262; £65.00.) Edward Arnold. 1995. ISBN 0 340 573 198.

Popular novels have perpetuated the myth to the non-forensic fraternity that time of death estimation is an exact science. It would certainly make our job a lot easier if it was! Unfortunately, this is far from the case, as some of us find from time to time to our embarrassment. One well-known pathologist was so disillusioned with the inaccuracy of time of death estimation, that when asked his opinion, he enquired as to the time when the deceased was last seen alive and when the body was discovered and took the midpoint between the two! Despite all the short comings of time of death estimation, it may well be an important issue in a criminal investigation. It is therefore incumbent on the pathologist to give some reasoned guidance, based on scientific principles and in the light of his/her experience. Bernard Knight's book is therefore long overdue. Many papers have been published on the subject, testimony to the difficulty encountered in solving the problem, but it is the first time in the English language literature that the collective knowledge on the subject has been brought together in one text. The contributors are all experts in different aspects of this area and have pooled their research findings and wide experience to assist the pathologist. It is both a scholarly, and at the same time, a practical approach to a difficult subject. The various