Herpes hepatitis in pregnancy

The case of pregnancy associated herpes hepatitis described by Fink *et al*¹ has many similarities with a case we presented to the Medical Society for the Study of Venereal Diseases in Zurich 1993, as well as with other documented cases. However, a literature search has shown that there were 17 reported cases and not eight as stated by the authors. These cases remain rare and the clinical features are initially those of a non-specific viral illness, but it must be borne in mind that herpes simplex is a treatable cause of hepatitis in pregnancy. Including our case, five patients have been treated with acyclovir. All of them survived. This compares with a mortality of 37% for all cases and 60% for untreated cases. It must also be noted that not all patients present with florid mucocutaneous lesions and the diagnosis must be considered in their absence. Four of the previous reported 17 cases had no mucocutaneous lesions, while in some, lesions may be scanty and initially overlooked. Even when absent, however, multiple sites are culture positive, and we recommend that oropharyngeal and genital swabs for herpes simplex virus (HSV) should be performed in all cases of hepatitis in pregnancy. Blood cultures may be positive and any biopsy material should also be cultured.

Fink *et al* suggest that dissemination is not necessarily the result of recent primary infection, but a review of the other documented cases indicates that this is more likely. None of the patients had a clear history of recurrent symptomatic herpes, and in those cases in which antibody responses are documented they are suggestive of primary infection. We know of no cases in which dissemination has been documented in the context of recurrence. This case is also notable as being the earliest stage of gestation in which dissemination has occurred. Other cases have occurred after the 25th week of pregnancy with a mean gestation of 31 weeks.

In summary, disseminated HSV in pregnancy seems to occur in the context of primary infection, usually in the third trimester, but now documented as early as 24 weeks. All cases have been associated with hepatitis; clinical findings may be non-specific and cutaneous lesions absent. Therefore, a high index of suspicion is needed if antiviral treatment is to reduce the high mortality.

I FAIRLEY
J WILSON
Department of Genitourinary Medicine,
The General Infirmary at Leeds,
Great George Street,
Leeds LS1 3EX

1 Fink CG, Read SJ, Hopkin J, Peto T, Gould S, Kurtz JB. Acute herpes hepatitis in pregnancy. *J Clin Pathol* 1993;46:968-71.

Drs Fink and Read comment:

We were most interested to read the letter by Fairley and Wilson reporting other accounts of herpes simplex hepatitis in pregnancy. Unfortunately, we do not have these references to review.

We agree that the condition is rare. It is not the first diagnosis that springs to mind for a pregnant patient who presents with signs of a flu-like illness and subsequent evidence of pneumonia. During pregnancy, liver function may be changed for a variety of reasons some of which are physiological

and as in our case, the hepatitis may be fulminant, occurring after a diagnosis of community acquired pneumonia.

Oropharyngeal and genital swabs at the acute stages of the pneumonitis and hepatitis may have isolated HSV from these sites, but as shedding of HSV is associated with pneumonia of bacterial origin² and may be seen intermittently in normal pregnancy,³ the diagnostic value for these isolations would be limited.

The correspondents suggest that "blood cultures may be positive". In our patient, in retrospect, the finding of herpes antigen staining in maternal monocytes in one placenta, suggests that we may have been able to culture the virus from a buffy coat preparation. The demonstration of viral antigens using immunoassays or by culture would be a better marker of active virus replication than the polymerase chain reaction (PCR), which may have very limited diagnostic value in this instance because it will show HSV DNA in buffy coat preparations in other patient groups without disseminated herpetic disease.⁴

Fairley and Wilson suggest taking biopsy material for culture. But what tissue would be an appropriate or justified biopsy in a pregnant patient with fulminant hepatitis and severely impaired clotting factors?⁴ We regret that in our case¹ the ascitic fluid taken during the hepatitis, which was found to contain monocytes, was not made available for viral culture, although this was a relatively late sample taken after the pregnancy was ended. HSV isolated from this particular material would have been a very strong indicator for an earlier diagnosis and would have been evidence to support starting antiviral treatment.

We are aware of reports of the successful use of acyclovir for the treatment of herpes hepatitis in pregnancy, but it should be remembered that acyclovir is not presently licenced for use in pregnancy. Concerns about its use are not so great for those in the late second or third trimesters, and in disseminated disease intravenous acyclovir would be a justifiable choice. Our difficulty¹ was that we had no indicator of a diagnosis to be able to start early antiviral treatment which may have preserved the pregnancy.

There may be some misunderstanding by Fairley and Wilson of our use of the term "primary" infection for herpes simplex. Evidence of specific antibody findings in consort studies and surveys in pregnancy^{5,6} suggest that an individual may have been exposed to the virus but that there is an absence of clinical evidence. Mucocutaneous herpetic disease may be seen later on as a first clinical episode, but is not, therefore, a primary infection. For this reason we urge a cautious approach rather than implying that all these cases of hepatitis are necessarily primary infection. This matter may be resolved when more data and good quality differential (HSV 1 and 2) antibody studies are available, but we agree that HSV associated hepatitis has not been recorded in those with a definite history of recurrent herpetic disease except in the immunocompromised.

We support the view of Fairley and Wilson that a higher index of suspicion of disseminated herpes infection in pregnant patients presenting with a pyrexia of unknown origin and a pneumonic and hepatic picture may permit earlier and thus effective antiviral treatment.

T cell lymphoid aggregates in bone marrow in idiopathic hypereosinophilic syndrome

In a recent issue of the *New England Journal of Medicine*, there is a report by Cogan *et al* reporting the presence of clonal proliferation of type II helper T cells in a patient with the hypereosinophilic syndrome.¹ This is clearly an extremely important and exciting observation. It fully supports the hypothesis put forward by Dr Metz and confirms my own comments relating to the requirement to subdivide T cells on a cytokine basis.

DN SLATER
Department of Histopathology,
Rotherham District General Hospital,
Moorgate Road,
Rotherham S60 2UD

1 Cogan E, Schandené L, Crusiaux A, Cochaux P, Velu T, Goldman M. Brief report: clonal proliferation of type 2 helper T cells in a man with hypereosinophilic syndrome. *New Engl J Med* 1994;330:535-8.

Seasonal variation in numbers of necropsies with pulmonary embolism

I read with some interest the paper by Green and Edwards,¹ although I am unable to agree with their conclusion. Having said this, however, I applaud the authors' aim of using one of the rich data sets that are hidden in laboratory records.

The problem here is that the result was not obtained by a formal, global test for seasonality, but instead was apparently found after repeated significance testing of the proportions of necropsies with pulmonary embolism in each month or season. As should be well known by now, under such circumstances the p values obtained must be interpreted with caution—for example, by a Bonferroni type of adjustment—to avoid the risk of wrongly rejecting the null hypothesis.²

Although the authors do hint in the introduction that increased morbidity due to cold weather might be a causal factor, they did not make use of this in their analysis, yet if the data had been tested on the basis of this prior hypothesis these would have provided a much more powerful and, if significant, convincing test.

Given that the original analysis can be criticised, what should have been done? One possibility is to use a significance test specifically designed to detect seasonality when the location of the peak is unspecified, on the lines of one described by Edwards.³ In its original form Edwards' test is unsuitable because it was designed for counts, so that it is applicable to the total number of necropsies per month rather than the proportion with pulmonary embolism. Using a modified version of Edwards' test suitable for binomial proportions gives a χ^2 value of 5.75 (df = 2), $p = 0.055$ —that is, it just fails to reach the 5% level of significance. On the other hand, if we apply Edwards' original test to the total number of necropsies we obtain a χ^2 value of 40.34 (df = 2), $p = 0.0000$, which is very strong evidence of seasonality. The fitted peak for total numbers of necropsies is around February which would be consistent with a cold weather effect.

Variation in the proportion of necropsies with pulmonary embolism is more likely to

be the result of a variation in the denominator than in the numerator. In fact this should not be a great surprise, because the confidence limits for each of the proportions overlap considerably.

One possible alternative is log-linear modelling of the proportions using a package such as GLIM. This has the advantage of great flexibility in the choice of model that is tested. The resulting evidence for seasonality is even less convincing: a general sine and cosine model gives a χ^2 value of 4.476 (df = 2), $p = 0.1067$; a model testing for variation between the four seasons gives a χ^2 value of 0.19954 (df = 3), $p = 0.9777$; and lastly, testing autumn + winter against the rest of the year gives a χ^2 value of 3.32 (df = 1), $p = 0.0694$. Another possibility, if there were enough data for each month of the whole 10 year period, might be a formal time series analysis that could be directly related to temperature fluctuations. Unlike the application of Edwards' test or its ad hoc modification (which can both be performed with a pocket calculator), both of the latter approaches would require access to a suitable computer package or collaboration with someone who is able to do this work.

To me, this illustrates why we should be trying to integrate statistical teaching and thinking with pathology practice. While the best way to get a feel for statistical analysis is to have a go, only appropriate training will help the novice avoid many potential pitfalls. On the other hand, while statistics does have a mathematical basis, as an eminent statistician has noted,⁴ it is a science deeply rooted in real life. In the present context this means that it is the pathologist who ultimately ensures that the question posed makes medical sense.

PAUL SILCOCKS
Department of Public Health Medicine,
Medical School,
University of Sheffield,
Beech Hill Road,
Sheffield S10 2RX

- Green J, Edwards C. Seasonal variation in the necropsy incidence of massive pulmonary embolism. *J Clin Pathol* 1994;47:58-60.
- Jones DR, Rushton L. Simultaneous inference in epidemiological studies. *Int J Epidemiol* 1982;11:276-82.
- Edwards JH. The recognition and estimation of cyclic trends. *Ann Human Gen* 1961;25:83-7.
- Box G. Scientific statistics. *Royal Statistical Society News* 1993;21:1-2.

Book reviews

If you wish to order, or require further information regarding the titles reviewed here, please write or telephone the BMJ Bookshop, PO Box 295, London WC1H 9TE. Tel: 071 383 6244. Fax: 071 383 6662. Books are supplied post free in the UK and for British Forces Posted Overseas addresses. Overseas customers should add 15% for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (MasterCard, VISA, or American Express) stating card number, expiry date, and your full name. (The price and availability are occasionally subject to revision by the Publishers.)

Systemic Pathology. 3rd ed Vol 11. **Liver, Biliary Tract and Exocrine Pancreas.** Ed DGD Wight. (Pp 736; 53 illustrations; £100.) Churchill Livingstone. 1993. ISBN 0-443-03098-7.

This concise, attractive volume is the eleventh in Symmers' wellknown series on systemic pathology and one of the best to date. As a textbook on the subject, it stands between biopsy interpretation/atlas type guides and encyclopaedic treatises, of both of which there are now quite a number; it conveniently fills the gap.

There are 14 chapters, 10 on the liver, gall bladder and biliary tract, and two on the exocrine pancreas. The title headings reflect broad groups of problems or diseases which are interrelated in some way, such as fat, alcohol, and iron or developmental and paediatric liver disease. The search for specific topics is aided by a useful index. The standard of writing is generally unfussy and clear; tables, diagrams, and illustrations—all in crisp black and white—are excellent and references are numerous up to 1990, but few thereafter. However, no major advance in concept or diagnostic utility has been overlooked. It would be invidious to rank the individual chapters in order of merit because they are all good, but Chapter 1 on development, anatomy, physiology, and patterns of injury, Chapter 5 on developmental and paediatric liver disease, and Chapter 6 on drugs and toxins are particularly helpful; Chapters 13 and 14 on the exocrine pancreas are outstanding. These are perhaps the topics where information in existing textbooks is either overabundant or sketchy, hence the usefulness of these particular chapters.

There is little to quibble about: ring granulomas are no longer considered to be specific for Q-fever, for example. It is also interesting to compare the combined length of Chapter 2 on acute and Chapter 4 on chronic hepatitis (39 pages) with that of Chapter 12 on liver transplantation (54 pages). This may be considered to be slightly out of balance, but it also reflects changes in the way in which and extent to which microscopic examination of the liver helps to solve problems in today's practice. All in all, this is a thoroughly good book; it is easy to use and it should answer the needs of all general histopathologists and their trainees in this difficult area.

PP ANTHONY

Torch Screening Reassessed. The Laboratory Investigation of Congenital, Perinatal and Neonatal infection. PHLS (Pp 122; paperback £7.95. 1993. ISBN 0-901144-35-5.

This is the second, revised edition of the book first published in 1990 which deals with congenital, perinatal, and neonatal infections. This version, produced by a PHLS working party, incorporates new recommendations, epidemiological information, and published data which have become available in the last few years and provides a comprehensive review of the epidemiology, symptoms, risk factors, laboratory diagnosis, and methods of prevention of congenital, perinatal, and neonatal infections.

There are sections on *Toxoplasma gondii*, rubella, cytomegalovirus, *Treponema pallidum*, HIV and parvovirus B19 congenital

infections. The perinatal and neonatal infection chapter includes sections on herpes simplex virus, varicella zoster virus, enteroviruses, hepatitis B virus, HTLV-1, cytomegalovirus, *Neisseria gonorrhoeae*, Group B streptococci, *Escherichia coli*, *Listeria monocytogenes*, and *Chlamydia trachomatis*.

The book emphasises the outmoded nature of the acronym "TORCH" and recommends that clinicians should request tests for specific infections based on epidemiological and symptomatic considerations. To facilitate this, the book contains a very useful series of flow charts, dealing with the investigation of babies with low birth weight, purpura, jaundice, microcephaly, and neonatal seizures, which highlight, among other things, which viruses, parasites, and bacteria should be sought in certain situations. The book also contains a section on methods of prenatal diagnosis.

This edition is much improved compared with the earlier version. It is clearly and concisely written, well produced, and has clear, useful figures and 170 references. It is an essential reference work which will appeal to microbiologists, gynaecologists, paediatricians, and epidemiologists.

TG WREGHITT

The Central Nervous System in AIDS. Neurology, Radiology, Pathology, Ophthalmology. Ed J Artigas, G Grosse, F Niedobitek. (Pp 237; hardback DM282.00.) Springer. 1993. ISBN 3-540-55839-X.

The major part of this book presents the results of the post mortem examinations of the central nervous system in the 180 patients with AIDS who died in the Auguste-Victoria Krankenhaus, Berlin, during the period 1986-1991. These findings are set in the context of the clinical and radiological changes found in the central nervous system in AIDS and draw on experience from other centres. There are five chapters. The first chapter sets the clinical background to the subject and is followed by a chapter which discusses the use of computed tomography and magnetic resonance imaging in demonstrating the various pathological lesions found in AIDS. The third chapter, written by the editors, constitutes over 50% of the main text. In it they describe the examination methods, discuss the pathogenesis of the disease, and present the pathology with frequent reference to the work of other centres. Where appropriate, results are given in simple tabular form. The final two chapters are written by authors based in France and North America and give a useful and brief account of the clinical and pathological changes found in the eye in AIDS. The book is extensively illustrated with clear, large scale black and white photographs. It will make a valuable addition to the library of any department offering a diagnostic service in AIDS and of the neuropathologist. To the clinician it is a salutary reminder of the benefit of achieving a 46% necropsy rate.

JE MCLAUGHLIN

Ophthalmic Pathology. PV Iyer, R Rowland. (Pp 212; 427 colour illustrations; £50.) Churchill Livingstone. 1993. ISBN 0-443-04240-3.

This is an annotated colour atlas, as opposed to a textbook, and is designed to

Correspondence

Pain, blood loss, and death from leaking abdominal aortic aneurysms

Anthony *et al* postulate that factors other than the volume of blood loss may play an important role in the pathogenesis of the circulatory collapse which accompanies a ruptured aortic aneurysm.¹ This may well be so; but I would make the following points about their paper:

- 1 The leakage of blood into the retroperitoneal space is accompanied by a marked acute inflammatory reaction. The mediators of this reaction have widespread systemic effects.
- 2 The shock which accompanies leaking aneurysms is associated with marked pulmonary congestion, and often by early "shock lung", both of which will potentiate the effect of any loss of circulating blood volume.
- 3 The control group presumably included many sudden deaths due to heart disease. The fact that there was no difference between the hearts in the study group and the control group may well only be a reflection of the fact that there is a lot of severe heart disease about!

C G B SIMPSON
Consultant Histopathologist,
Ysbyty Cyffredinol Bronglais,
Bronglais General Hospital,
Aberystwyth, Dyfed SY23 1ER

- 1 Anthony PP, Clarke T, Sarsfield P. Pain, blood loss, and death from leaking abdominal aortic aneurysms. *J Clin Pathol* 1994; 47:272-3.

Professor Anthony comments:

The points made by Dr Simpson are interesting but no documented evidence is offered from the literature to support them. Our study did not reveal a substantial inflammatory component in response to the presence of blood in the retroperitoneal space, pulmonary congestion was acute, and morphologically severe heart disease was not present in all cases: 15 of 25 had coronary artery stenosis of more than 80%. Death, however, was sudden and occurred within minutes to hours of the onset of symptoms. None of the patients survived beyond admission to the Accident and Emergency Department. These circumstances do not indicate a complicated sequence of events building up over a period of time, nor is it true that it is just a case of there being "a lot of severe heart disease about". Patients who survive "ruptured" or "non-ruptured" abdominal aortic aneurysms after surgical repair do not have a reduced life expectancy when compared with the general population.

Book review

Heterogeneity of Cancer Cells. Ed M D'Incalci, A Mantovani, S Garattini. Sero Symposia Publications from Raven Press Vol 95. (Pp 154; \$113.50.) Raven Press 1993. ISBN 0-88167-907-0.

This short monograph, published in the Sero Symposia series, reports the proceedings of an International Symposium on Heterogeneity of Cancer Cells held in June 1992 in Milan. A relatively large proportion of the authors are from Italy. As the title implies, the topics concern cell biological and immunological laboratory studies, many in relation to pharmacology, although the final contribution discusses heterogeneity of tumours as a clinical management problem. There are presentations on cell adhesion mechanisms, tumour vasculature and stroma, drug resistance, tumour associated leucocytes, antigen expression, tumour progression in melanoma, growth factor receptors in metastasis, and oncogenes, plus a short index. The articles are all fairly short and vary, as usual, from short reviews to reports of single experiments, but each has a comprehensive bibliography, up to 1992 in some cases. Trivially, but unusually, the formatting of references varies between papers. The book is otherwise well produced, and has appeared reasonably soon after the meeting, but it is rather expensive. It should be of interest to workers in experimental tumour pathology and related fields.

C FISHER

Notices

The Section of Pathology Glycation, Glycosylation and Disease

Tuesday 4 October 1994

Programme

Glycated proteins and diabetes *Dr E Lester, North Middlesex Hospital, London.*

The carbohydrate-deficient glycoprotein syndromes: new inborn errors. Clinical and laboratory aspects *Dr G Keir, Department of Biochemistry, Institute of Neurology, London*

Carbohydrate-deficient transferrin as a marker of alcohol misuse *Dr S B Rosalki and Dr A Y Foo, London*

Carbohydrate and protein interaction in inflammation and host defence *Dr Ten Feizi, Cancer Research Campaign, London*

Glycosylation and tumour markers *G A Turner, Department of Clinical Biochemistry, University of Newcastle upon Tyne*

Aberrant glycosylation in cancer: potential for immunotherapy *Dr Joy Burchill, Imperial Cancer Research Fund, London*

For further information contact: Miss Claire Cheesman, The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Tel: 071 290 2900. Fax: 071 290 2989.

A Residential Course in Histopathology

22-27 January 1995

Oak Hotel, Brighton, UK

This intensive residential course is part of a three year cycle aimed at providing comprehensive preparation for the MRCPPath examination in histopathology, but is equally suitable for consultants wishing to keep informed of recent developments. The course is suitable for 25 cognate points for CME. The programme includes microscopy sessions, discussions, and formal presentations. Registrants will receive a box of 100 stained sections to take away. A mock MRCPPath examination is included to give feedback on individual progress.

Speakers include Dr M Boyle (Cytopathology); Professor H Fox (Gynaecological pathology); Dr C Fletcher (Soft tissue pathology); Dr A Hanby (Molecular techniques in diagnosis); Dr N Kirkham (Dermatopathology); Dr C Parkinson (Prostatic pathology); Dr G Stamp (Pancreatic pathology); Professor W Whimster (Pulmonary pathology and morphometry); Dr A Wotherspoon (Lymphoma pathology).

The course fee of £490 includes accommodation and the slide box.

Details from Dr N Kirkham, P.O. Box 334, Histopathology Department, Royal Sussex County Hospital, Brighton BN2 5BG. Tel: 0273 664501. Fax: 0273 600182.

Dermatopathology Update UMDS St Thomas's Campus, London

Friday 27 January 1995

For further details and programme please contact:

Dr P H McKee, Department of Histopathology, St Thomas's Hospital, London SE1 7EH. Tel: 071 929 9292 (ext: 2039). Fax: 071 401 3661.

Correction

Fairley I, Wilson J. Herpes hepatitis in pregnancy (letter). *J Clin Pathol* 1994;47:478. The references for the comment by Drs Fink and Read on the above letter were not included with the original manuscript on arrival at this office. The full reference list appears below.

- 1 Fink CG, Read SJ, Hopkin J, Peto T, Gould S, Kurtz JB. Acute herpes hepatitis in pregnancy. *J Clin Pathol* 1993;46:968-71.
- 2 McFarlane JHT. Pneumonia. *Medicine International* 1991;90:3732-9.
- 3 Prober CG, Arvin AM. Genital herpes and the pregnant woman. In: *Current Clinical Topics in Infectious Diseases*. Saunders, 1989.
- 4 Read SJ. HSV sequences in buffy coat preparations found by PCR in a group of patients with post viral syndrome. 1994. (Unpublished observations.)
- 5 Mertz GJ, Schmidt O, Jourden JL, Guinan ME, Remington ML, Fahnlander A, *et al*. Frequency of acquisition of first-episode genital infection with HSV from symptomatic and asymptomatic source contacts. *Sex Transm Dis* 1985;12:33-9.
- 6 Whitley RJ, Corey L, Arvin A, Lakeman FD, Sumaya CV, Wright PF, *et al*. Changing presentation of herpes simplex virus infection in neonates. *J Infect Dis* 1988;158:109-16.