

Letters

Misconceptions of the pathology of intracranial arterial aneurysms

Correction of errors and misleading data is an educational precept, and Weller's misconception of cerebral (berry) aneurysm pathology¹ is a case in point. His illustration of their frequency distribution depicts basilar aneurysms arising from the crotch but other aneurysms arising at lateral angles of forks or junctions. Though this was perhaps inadvertent, it is grossly misleading: such localisation is rare. Furthermore he neglects the internal carotid bifurcation and incorrectly infers that posterior cerebral artery aneurysms are more common.

Weller's concept of cerebral aneurysm aetiology ignores a substantial body of research on early human aneurysms² and experimental production of similar changes and berry aneurysms by haemodynamic means.³⁻⁴ His study⁵ involved random sections of several resin embedded forks which do not provide the necessary three dimensional structure. The localisation of intimal proliferation at branching sites is incorrect.¹ An oval pad at the extremities of flow dividers is depicted when, in neonates, intimal proliferation covers the entire flow divider, with separate pads just inside the daughter branches proximally where flow separation would be expected.² Similar intimal proliferation occurs over the flow dividers of extracranial arteries⁶ and step serial cross sections do not show encroachment on the lumen, which actually expands laterally by as much as 30%.⁶ Due to poor methodology he underestimates the incidence of raphés (60% of subjects^{1,2}). Based on serial sections on several hundred human cerebral forks, I assert that medial raphés, rather than defects to indicate their true function, are universal in humans and other animals studied.^{2,3} Serial sections are essential for successful detection of raphés and no localised luminal indentation or rounding of the carina would have been invoked with perfusion fixation.

The assumption that pads cause loss of elasticity is false as elastic tissue changes precede intimal thickening^{2,6} and early aneurysmal changes occur more often to the side of the apex and apical pad.^{2,3} Early aneurysmal changes can be produced haemodynamically at experimental forks and in arteries feeding arteriovenous fistulae.^{3,6} They commence as transverse tears of the internal elastic lamina with progressive tearing or fragmentation of medial elastic laminae and loss of smooth muscle until eventually only endothelium and an attenuated adventitia remain.^{3,6} Such changes result in ectasia or more localised dilatation, and intimal proliferation may be superimposed.^{3,6} That cerebral aneurysms consist only of endothelium and fibrous tissue is false: intimal proliferation and atherosclerosis characteristically develop in cerebral aneurysms.² Thrombus forms over mural tears occurring predominantly at the fundus.

Increased pulse pressure is probably the most significant factor, as in arteriovenous fistulae, aortic valve incompetence, hypertension, and collateral circulation which are often associated with aneurysms.^{3,4} Since aneurysms indicate mural weakness, hyper-

tension when present, or any matrix abnormality associated with diminished tensile strength, potentiates aneurysm development¹: neither is an essential prerequisite.

No scientific evidence exists that smoking or true hypercholesterolaemia are causal in aneurysm formation. Epidemiological statistical correlations do not indicate causality. Weller's literature review¹ is superficial and his statements are inconsistent with considerable pathological and experimental evidence.^{2,3,6} As a result his submission must be considered as speculative, even mythic.

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- 1 Weller RO. Subarachnoid hemorrhage and myths about saccular aneurysms. *J Clin Pathol* 1995;48:1078-1081.
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The author replies

I am pleased that Dr Stehbens has responded to my leader in the *Journal of Clinical Pathology* in 1995¹ and that he has added his very considerable experience during the last 45 years of the examination of cerebral saccular aneurysms. Dr Stehbens criticises, and I am sure quite rightly, a number of detailed points in my leader, but I am disappointed that he does not bring his experience to bear upon the main questions posed in my article.

In my leader, I opened a discussion regarding the origin and formation of saccular aneurysms and explored the views commonly expressed in pathology textbooks that they are congenital and that hypertension is a major contributing factor. In his large number of articles, Dr Stehbens seems to agree that the age incidence and the pathology does not support the concept that saccular aneurysms are congenital.

Apart from less than 10% of saccular aneurysms associated with such conditions as polycystic kidneys, systemic lupus erythematosus, and arteriovenous malformations,² saccular aneurysms do tend to be unpredictable and sporadic. The major question, therefore, is which factors in individuals with saccular aneurysms lead to their formation. Hypertension has often been quoted as a factor in the formation of aneurysms. Dr Stehbens supports this proposal in a survey of patients with saccular cerebral aneurysms of non-mycotic origin published in 1962 in which the diagnosis of pre-existing hypertension was predominantly based upon whether hypertrophy of the left ventricle was said to be present by the pathologist.³ This study suggested that 48.8% of patients with saccular aneurysms had evidence of pre-existing hypertension, compared with only 38.7% of the control group. Subsequent clinical studies suggest that hypertension is no more prevalent among patients with saccular aneurysms than in those with no saccular aneurysms.⁴ With the control of hypertension among western European and

American populations, it would have been expected that the incidence of saccular aneurysms would be reduced but I can find no evidence that this is the case. Furthermore, recent articles on the incidence and prevalence of intracranial aneurysms make no mention of hypertension as a risk factor.²

We are left, therefore, with a problem regarding the formation of saccular aneurysms. Experimental studies using a combination of procedures that damage vessel walls and increase blood pressure do show that these factors can be involved in the formation of aneurysms. However, these factors do not apply in the large majority of patients with saccular aneurysms. In my leader,¹ I suggest that the formation of intimal cushions and pads at vessel bifurcations may play a part in the formation of saccular aneurysms. In support of this concept, Futami *et al*⁵ show in an experimental rat model that cerebral aneurysms arise at the portion of the artery just medial to intimal pads. The authors discuss the possible roles of intimal pads in the formation of cerebral aneurysms in man and in an accompanying commentary, Nicholas Dorsch⁶ expresses the view that Futami's paper lends credence to the pads being the primary cause of aneurysms. Further work on this exciting concept will obviously be of great interest.

The debate will continue but we must all retain open minds.

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- 1 Weller RO. Subarachnoid haemorrhage and myths about saccular aneurysms. *J Clin Pathol* 1995;48:1078-81.
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Tissue banks in NHS histopathology laboratories and the Consensus Statement

Since the publication of our paper,¹ which outlined the ethical, legal, and logistic aspects of supplying surplus surgically removed samples to commercial biomedical research organisations, a working party of the Royal College of Pathologists and the Institute of Biomedical Science has produced, jointly, a booklet entitled "Consensus Statement of Recommended Policies for Uses of Human Tissue in Research Education and Quality Control".² The Statement, originally compiled by the American College of Pathologists, is now endorsed by 20 American and British pathology societies. The booklet includes "Notes reflecting UK law and practice" and we recommend it as essential reading for pathologists, biomedical scientists, and pathology managers, whether they are contemplating human tissue banking or not. Commercial organisations using human tissue should also be aware of the contents.

The Statement includes a useful and practical definition of genetic information. The potential use of genetic information was an

area that concerned our local research ethics committee (LREC). Our proposal was not helped when we attended an LREC meeting along with a commercial collaborator, shortly after Dolly the Sheep had first been shown to the world. The LREC allow for extraction of RNA and DNA but not for cellular immortalisation or cloning. In order to monitor this, our legal contract requires the commercial organisation to provide research protocols before we supply tissue to them.

We have heard expressed the fear that one day a genetic research finding might have far reaching clinical and ethical consequences for an individual donor patient. The Statement provides useful guidance on this and recommends treating genetic discoveries in the same way as ordinary research findings, although the "Notes reflecting UK law and practice" point out some of the potential ethical risks of DNA databanks to society as a whole.

A section on confidentiality emphasises the importance of system safeguards in preventing the leak of patient data. According to the working definitions in this section, the samples we provide to commercial companies are, strictly speaking, "linked" rather than anonymised. However, in our tissue bank, "linkage" can only be made by the medical intermediary and it is difficult to conceive a situation where we would agree to do this. In order to do so we would need the consent of the patient. In practical terms, therefore, the tissue we provide to commercial firms is "anonymised".

The final section on consent further reinforces our views.¹ We would argue that a general agreement to donate tissue as part of a signed consent-to-treatment form does not constitute proper informed consent which, if done properly, places an additional burden of explanation on the surgeon, whose role in adhering to the latest GMC guidelines³ is difficult and time consuming enough. Furthermore, the "Notes reflecting UK law and practice" mention a European Directive, due to be implemented by 2000, which implies that informed consent will be required if ever a patent application is filed—the dream of many a commercial research company.

At Peterborough, we now employ two research nurses to obtain consent and counsel patients before operation. The nurses have redesigned the consent forms, produced a patient information pack, and are able to spend time with patients answering questions. This experience was presented to the British Association of Tissue Banks (BATB) in March 1999 and we hope to publish the results in due course.

There have also been important developments in the "whole body donation project".¹ What began as an informal arrangement with the North East Thames National Blood Service Tissue Services (NBSTS) is now covered by a formal written agreement. Donors who have expressed a wish to give more tissues than are currently routinely banked by NBSTS, and others identified as being unsuitable for the transplant programme by the transplant coordinators, are referred to the Peterborough Tissue Bank for postmortem tissue collection. Compared to surplus surgical material in hospital, the consent procedures undertaken by the transplant coordinators are more complicated. This is largely because of the issues that need to be covered when tissue is to be transplanted. Donors, where possible, and relatives under-

stand the cost recovery, commercial nature of the Peterborough Tissue Bank.

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- 1 Gray N, Womack C, Jack SJ. Supplying commercial biomedical companies from a human tissue bank in an NHS hospital—a view from personal experience. *J Clin Pathol* 1999;52:254–6.
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Increasing rates of ciprofloxacin resistant campylobacter

We read with interest the recent correspondence concerning ciprofloxacin resistance in campylobacter species.¹ Campylobacter enteritis is a self limiting disease in most individuals, and should not require antimicrobial treatment. If treated, the commonly used antibiotics are fluoroquinolones, or erythromycin, particularly for children. We reviewed the rates of resistance to ciprofloxacin and erythromycin in campylobacters isolated in our laboratory from 1995 to 1998 (table).

Rates of antibiotic resistance in *Campylobacter* species isolated 1995–8

Year	Total No of isolates	No (%) of ciprofloxacin resistant isolates*	No (%) of ciprofloxacin resistant cases with recent foreign travel†	No (%) of erythromycin resistant isolates†
1995	351	37 (10.5)	20 (54.1)	3 (0.9)
1996	344	37 (10.8)	16 (43.2)	6 (1.7)
1997	416	68 (16.3)	31 (45.6)	4 (1.0)
1998	495	89 (18.0)	43 (48.3)	5 (1.0)

* $\chi^2 = 14.4$, 3 degrees of freedom, $p < 0.01$.

†Trend not significant.

There was significantly increasing resistance to ciprofloxacin over the four year period. Ciprofloxacin resistance in this area is now higher than recently reported rates from Northumberland (6.7%) and the Laboratory of Enteric Pathogens (12%).¹ This suggests wide variation in resistance within the United Kingdom.

Considerably higher levels of ciprofloxacin resistance have been found in other countries, such as Spain (45%) and Thailand (84%).^{2,3} However, we found that only around half of resistant strains were acquired abroad, with no significant increase in the proportion over the four years, suggesting that resistance is now well established within this area. If this is true for the United Kingdom as a whole, the data add further weight to the calls for more controlled quinolone usage both in veterinary and human medicine.⁴

As resistance to ciprofloxacin rises, erythromycin becomes a more important therapeutic option. Our data show that we have not found erythromycin resistance to be a significant problem for several years.

Knowing that local rates of quinolone resistance are rising may help influence prescribing habits. It would seem reasonable to restrict quinolone treatment to patients

with severe illness or risk factors for poor outcome,⁵ to limit further promotion of resistance to these valuable antimicrobial agents.

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- 1 Galloway A, Dickinson G, Harrison M. Ciprofloxacin resistant campylobacter [letter]. *J Clin Pathol* 1998;51:487.
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Book reviews

Molecular Biology of the Lung, Vol 1: Emphysema and Infection; Vol 2: Asthma and Cancer. Edited by D Raeburn and M Gienbycz. (DM 528.00.) Birkhauser, 1998. ISBN 3 7643 5969 2.

These two volumes of this series represent a timely addition to an expanding field. The style, content, structure, and illustrations in both volumes are excellent. The information contained in them is accessible enough for the non-specialist while being detailed enough to be of interest to those working in the field.

The first volume deals with emphysema and infections. There is an interesting chapter on the use of transgenic mice which sets the scene nicely for the ensuing chapters. Emphysema is well covered, with several areas being highlighted including $\alpha 1$ antitrypsin deficiency, recombinant SLPI elastase inhibitors, proteases, and connective tissue genes. The chapters on infection, particularly those dealing with cystic fibrosis, are excellent.

In volume 2, leading lights in the field take us through the genetics of asthma including transcription factors, cytokine gene clusters, β adrenoceptors, and control of eosinophil migration. The section on cancer, while smaller, gives an excellent insight into gene expression in lung cancer and potential targets for genetic therapy. These volumes are essential reading for cell biologists with an interest in respiratory disease. They will provide a useful reference source for clinical scientists with an interest in other fields.

A J KNOX

In-Situ Hybridization—Principles and Practice, 2nd ed. Edited by J M Polak and J O'D McGee. (£39.95.) Oxford Medical Publications, 1999. ISBN 0 19 854880 X.

The first edition of this book sits on the bookshelf in our laboratory. It dates from 1989, almost a geological age ago in molecular biological terms. The new second edition

remains a "nuts and bolts" book that provides fundamental information on the practical aspects of in situ hybridisation techniques.

The format of the previous edition is retained in this book. Individual chapters deal with different hybridisation technologies. Each starts with a section on basic principles and proceeds to cover practical points including probe manufacture, the conditions needed for using the technique concerned, and the standards required. The chapters end with specific illustrative examples, a reference list, and an appendix that contains precise laboratory protocols for the in situ method(s) discussed. The latter are highly detailed and include sources for many of the reagents required.

The book begins with a chapter on the general principles of in situ hybridisation and follows this with three chapters on design, preparation, and use of different probe types. These cover DNA and RNA probes, together with strategies for non-radioisotopic hybridisation. Quantitative in situ hybridisation methods are covered in the next two chapters. Following this there is a completely new section on detecting genetic changes in cancer using interphase cytogenetics and comparative genomic hybridisation. The colour plate accompanying this chapter is a spectacular illustration of the power of these techniques. Other areas covered include detecting nucleic acids in clinical material, combining in situ hybridisation and immunocytochemistry and supersensitive methods of in situ detection.

The book is reasonably priced, up to date, and well referenced. The chapter structure leads to some minor overlap of content but this does not detract from the book's value as

a practical guide to in situ hybridisation technology. It is not a book for casual reading and is not aimed at pathologists or clinicians who simply want an outline of the latest techniques. However, workers wishing to establish in situ methods in their laboratory will find this an excellent starting point and a useful resource to have on their shelf.

A RAMSAY

CD-ROM review

The Johns Hopkins Atlas of Surgical Pathology. Edited by J I Epstein, N Agarwar-Antal, D Danner, and K M Ruska. (£153.63.) Harcourt Brace, 1999. ISBN: 0 443 07933 1.

As the authors admit, this CD-ROM is not really a source of detailed information and in-depth knowledge: "other texts are more encyclopedic." But what a nice toy to feed into your PC! In an easily accessible way, it presents the key features of over 1500 entities, covering the entire field of surgical pathology by means of short descriptions of specific entities, illustrated by small sets of micrographs which appear as clickable thumbnails. Thus it provides an enjoyable means of surveying the key facts about specific entities you may not be so familiar with, or to refresh and update your knowl-

edge. Also, it is a very nice self teaching tool for registrars preparing to sit a surgical pathology exam.

The feature I liked best is the self assessment part, where the same sets of clickable thumbnails, which provide the key features of the histology, are presented together with a summary of the clinical information, and the "answer" can subsequently be disclosed. Many entities can be recognised even from the thumbnail sized pictures; the not-so-gratifying mistakes one is bound to make when shooting from the hip at very high speed provide a lesson in modesty, and of course data tend to stick in your mind much better when you started out by making a mistake!

The program covers all of surgical pathology, but the level of detail is limited. If you search for a rare entity, chances are that it won't be included. In that respect, the contents do not really necessitate the rather elaborate searching and bookmarking options which are included. In a way, the CD-ROM is like a modest but nice little bookshop: if you walk around without any specific wish, you come across many interesting things. If you go in with one specific request that is out of the ordinary, there is a real chance are that you will be disappointed.

There is a disturbing flaw, which I need to mention: the quality of quite a number of micrographs is less than optimal. Even entities which are not very rare are sometimes presented with downright poor pictures. But before you lose interest, I should hasten to add that practically always, the key features are clearly visible.

W J MOOI

Notices

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References

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 - 2 Washington JA. Conventional approaches to blood culture. In: Washington JA, ed. *The detection of septicemia*. West Palm Beach, Florida: CRP Press, 1978:41-87.
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- 1 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *BMJ* 1991;302:338-41.
 - 2 International Committee of Medical Journal Editors. Protection of patients' rights to privacy. *BMJ* 1995;311:1272.

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