Vitamin K and metabolic bone disease

The report by Vermeer and colleagues that vitamin K may be important in the causation of metabolic bone disease is interesting, but there is an alternative hypothesis that could account for some of the apparently vitamin K-mediated bone effects. Vitamin B-6 is an essential cofactor for the enzyme ornithine decarboxylase which is the rate limiting enzyme in the formation of putrescine which regulates osteoblast glucose-6-phosphate dehydrogenase activity and thus osteoblast NADPH concentrations. NADPH is essential for the vitamin K cycle in which the epoxide form of vitamin K is converted back to the naphthoquinone form which is required for γ-carboxylation of osteocalcin. It is therefore possible that vitamin B-6 status could modulate the effects of vitamin K on bone metabolism.

Although the chain of events described above may seem excessively complicated there is evidence that vitamin B-6 deficiency in rats reduces bone healing and that vitamin B-6, as well as by high performance liquid chromatography, is lower in patients who spontaneously (traumatically) fracture their hips than in patients whose hip fracture is at the hands of an orthopaedic surgeon as an elective procedure. Further research into the interaction of these two vitamins may be indicated.

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3 Mamony PS, Bohlen P, McCann PP, et al. Alpha methyl ornithine, a potent competitive inhibitor of ornithine decarboxylase blocks prolifera-
4 Reynolds T, Marshall P, Brain A. Simple internal standards in the extraction and determination of 15O-labeled
5 Humphreys P, Wong A, Vogelstein B, et al. Anti-
synthetic peptide antibody reacting at the fusion junction of deletion-mutant epidermal growth factor receptor in human glioblastoma. Proc Natl Acad Sci USA 1990;87:5207–11.

In response to the recent editorial by Addison, I would like to outline two potentially important theories on the aeti-
ology of SIDS which, if true, may act in concert. First, long QT interval. Schwartz et al performed electrocardiography on 33 034 newborns at three to four days of age and subsequently found that of the 34 deaths in this group, 24 were due to SIDS. Twelve infants who died of SIDS, but none who died from other causes, had prolonged QT intervals [p 0.01]. Long QT interval is known to be a marker of cardiac electrical instability and is therefore a predisposition to fatal cardiac arrhythmia. It is also known that the QT interval is increased from the second until the fourth month of life, returning to previous values by the sixth month. This is also the period of peak incidence of SIDS. Therefore, it is hypothesised that a sudden increase in sympathetic activity may be the trigger which leads to fatal arrhythmia in these cases.

Second, neonatal Helicobacter pylori infection. As reviewed by Pattison et al, epidemiological aspects of SIDS and H pylori infection are similar; both are more common in males, pose significant problems, and a large proportion of SIDS deaths are thought to be due to SIDS and H pylori infection are associated with growth retardation and familial clustering; and H pylori infection has been documented in infants aged three to six months. In an H pylori infected neonate, vomiting or gastro-oesophageal reflux of gastric juice containing H pylori urease, combined with microaspiration may result in deposition of large amounts of urease in the alveolae, resulting in alvea destruction and ammonia supplied to the systemic circulation, with possible respiratory arrest due to ammonia toxicity. In addition, gastric inflammation due to H pylori infection results in synthesis of the cytokine interleukin-1 (IL-1), leading to fever, activation of the immune system, and increased deep sleep which, combined with a relatively minor additional infection, overwrapping, or prone sleep position, may lead to hyperthermia. These two theories are consistent with each other, in that IL-1 is known to activate the sympathetic nervous system in humans. Therefore, in neonates with cardiac electrical instability resulting from long QT interval

We read the paper by Berthau and colleagues with interest. We have made similar observations in our laboratory while investigating the expression of the androgen receptors (AR) and epidermal growth factor receptors (EGFR) in sections from formalin fixed, paraffin embedded archival prostate specimens. Studies on the heterogeneity of androgen receptor expression in prostate cancer have focused exclusively on epithelial cells, while reports on the EGFR content of similar tissues have been conflicting results.1 We aimed to determine the differential expression of androgen receptors in the stromal and epithelial compartments of prostate cancer glands, and also to scrutinise these neoplasms for the presence of a variant-type EGFR (EGFRVIII). As part of the initial tests to ascertain the validity of our results, we sought to exclude time related antigen degra-
dation by investigating the effect of storage (at room temperature) on the intensity of staining in serial paraffin sections. During these tests we used five different antibodies which recognised antigens in the nucleus (anti-ERGFR clone 31G7, Cambridge Bioscience; anti-prostatic specific antigen [PSA], Europro; and anti-prostatic acid phosphatase (PAP), Sigma). Three of these antibodies required pretreatment of the sections (microwave, anti-AR, and anti-EGFR; or protease, anti-EGFR) for antigen retrieval, while the other two (anti-PSA and anti-PAP) did not.

In the androgen receptor studies, we found that the intensity of nuclear staining seen in serial sections from androgen receptor posi-
tive prostate cancer specimens was not reduced (or even reduced) in sections stored after 10 days storage, and was completely lost after three weeks. On the other hand, the intensity of the immunoreac-
tions to the anti-ERGFR and anti-PSA were constant for three months but were reduced thereafter, though some staining was still vis-
ible in sections that were a year old. However, the intensity of both anti-ERGFR and anti-PAP staining remained virtually unchanged in sections that were stored for a year.

From these results we also concluded that there is a variable degree of antigen degrada-
tion in stored paraffin sections, and that this loss is proportionate to the length of storage. The rapidity of decline in the intensity of staining is also dependent on the antigen, and seems to be highest in nuclear steroid recep-
tors. Similarly, we found that the loss of immuno-
reactivity was not limited to antigens that require pretreatment for the exposure of the relevant epitopes. We would therefore agree with the authors that previous conflicting results from immunohistochemical stud-
ies on archival tissues could be caused in part by differences in the age of stored sections used. We also supported their suggestion that the use of unstained paraffin sections that have been in long term storage should be avoided, and that immunohistochemical sys-
tems should be checked for age induced anti-
gen degradation before carrying out both diagnostic and research studies, to ensure better standardisation of results. We have fol-
lowed these protocols in our studies on archival material that have been done after these observations were made.

We would like to thank Ms A Lyceyt, C Whiteley, and F Wright for their assistance with this project.

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3 Maddy S, Chisolm G, Busuttil A, et al. Epider-
5 Humphrey P, Wong A, Vogelstein B, et al. Anti-
synthetic peptide antibody reacting at the fusion junction of deletion-mutant epidermal growth factor receptor in human glioblastoma. Proc Natl Acad Sci USA 1990;87:5207–11.
6 Olapade-Olapoja E, MacKay E, Sandhu D, et al. Mechanisms for hormone resistance in prosta-

Letters

Sudden infant death syndrome, long QT interval, and Helicobacter pylori

In response to the recent editorial by Addison, I would like to outline two potentially important theories on the aeti-
ology of SIDS which, if true, may act in concert. First, long QT interval. Schwartz et al performed electrocardiography on 33 034 newborns at three to four days of age and subsequently found that of the 34 deaths in this group, 24 were due to SIDS. Twelve infants who died of SIDS, but none who died from other causes, had prolonged QT intervals [p 0.01]. Long QT interval is known to be a marker of cardiac electrical instability and is therefore a predisposition to fatal cardiac arrhythmia. It is also known that the QT interval is increased from the second until the fourth month of life, returning to previous values by the sixth month. This is also the period of peak incidence of SIDS. Therefore, it is hypothesised that a sudden increase in sympathetic activity may be the trigger which leads to fatal arrhythmia in these cases.

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and who become infected with H pylori. IL-1 mediated activation of the sympathetic nervous system may provide the trigger for fatal arrhythmias leading to SIDS.}

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Epithelial-myoepithelial carcinoma?

In the July edition of this journal, McCluggage et al describe a myoepithelial carcinoma arising in a pleomorphic adenoma. The report is interesting but raises the question as to whether the original tumour was in fact an epithelial-myoepithelial carcinoma, with the subsequent recurrences representing overgrowth of the malignant myoepithelial component. In their description of the original tumour, McCluggage et al describe the epithelial element as being set in a hyalinised stroma with other areas showing myoepithelial cells in a myxoid stroma. It is not clear from the illustration, but could the former be the sclerotic pattern of epithelial-myoepithelial carcinoma as described by Simpson et al? The encapsulated nature of the first tumour would not be against this diagnosis as this is an accepted feature of epithelial-myoepithelial carcinoma. The subsequent recurrences could then be interpreted as overgrowth of the myoepithelial element, again a well recognised feature of epithelial-myoepithelial carcinoma; this would be supported by the presence of ducts and tubules in the first recurrence. Although I would not dispute that malignant transformation occurs within pleomorphic adenomas the slighty atypical appearance of the original tumour in this case should perhaps raise the possibility of an epithelial-myoepithelial carcinoma.

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Authors’ response
We thank Dr Jones for his letter concerning our recent case report of myoepithelial carcinoma arising in a pleomorphic adenoma. We are confident that the original diagnosis of a pleomorphic adenoma (albeit with some atypical features) was correct and that this neoplasm does not represent an epithelial-myoepithelial carcinoma. Epithelial-myoepithelial carcinoma is characterised by tubules with a double layer of outer epithelial and outer myoepithelial cells. The ducts and tubules in the original tumour and in the first recurrence in the case we describe had a single cell lining. These cells were morphologically and immunohistochemically (AE1/AE3, EMA, and CEA positive; S-100 protein, α smooth muscle actin, and vimentin negative) characteristic of epithelial cells. We agree that from the illustration (fig 1A) it is not entirely clear whether the tubules have a single or double cell layer but we consider that the impression of more than one cell layer is due to plane of section artefact.

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Is the practice of haematology evidence based?

For the record, serum ferritin is measured in juglure. Storage iron deficiency may be assessed indirectly by this index when iron metabolism is in equilibrium. For functional iron deficiency the percentage of hypochromic cells is the most direct yardstick, irrespective of the serum ferritin level.

Haematology used to be a laboratory based discipline. Because no result or interpretation could be better than the method by which it was produced it was the haematologist’s job to worry about the details so that the clinician could interpret each result with confidence. The increasing emphasis on clinical haematology has meant that some things have had to be left behind and the chief of these is the increasing involvement in the laboratory. Indeed, it is likely that nowadays the most informed opinion on the diagnosis and treatment of iron deficiency may be found within renal units.

Yes, I cavil at the details.

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Authors’ response
We thank Dr Cavill for his letter, which we read with a wry grin. The data used for serum ferritin were reproduced as they appeared in the text we referred to in our paper. We agree we should have pointed out the inaccuracy of the units used in the original source material but somehow, in our enthusiasm to make our point, we slipped. Sorry!

Dr Cavill’s slightly tongue-in-check letter does not, however, mask his disappointment at the shrinking laboratory role of many haematologists. We share that disappointment. We agree that on appointment most haematologists undertake both a clinical and a laboratory role. It is one of the consequences of, for example, the reduction in junior doctors’ hours that haematologists now have to spend more of their time to clinical activities at the expense of the laboratory work. The 1997 haematology report from the Clinical Benchmarking Company4 showed that the majority of haematologists spent 45% of their time in activities related to laboratory work. For those laboratories who par-
major innovations over material already available and is only a first step on the way to making the right call. ANGELA WOOD

Book reviews


This book is meant to offer a complete and comprehensive review of the neoplastic cell and tumour diagnosis. It differs from other publications by being shorter and simpler. Unfortunately, however, the book suffers from various shortcomings that make it poorly suited to its goal. First and most importantly, the author has chosen to "ignore references to specific entities." As a result, numerous structures are extensively described without even the slightest reference to their possible diagnostic meaning. To name a few examples: what is the use of reading detailed descriptions of Birbeck granules and Weibel-Palade bodies, to look at no less than 22 illustrations of nuclear characteristics, or to read that mitochondrial cristae can be lamellar, tubular, or vesicular without any further information or discussion?

Second, the quality of the illustrations is extremely poor, even taking account of the fact that they are from routine clinical material. As a result, many features are hard to distinguish or are not distinguishable at all. Examples are the mast cell granules which do not display any trace of the "typical scrolls and fingerprints" mentioned in the text, and the collagen fibrils in which the "characteristic banding" is virtually invisible.

Third, there are numerous small and large omissions and mistakes of various kinds. Thus, structures like anchoring fibres, desmosomes, hemidesmosomes, and so on are depicted as irrelevant and careless way and therefore have lost all diagnostic meaning. Also, the importance of measuring structures is stressed, but the author himself frequently fails to mention, for example, the periodicity of the striations found in melanosomes or that of the banding of fibrin. In other instances, the author apparently forgot to apply his own methods to measure structures: according to the magnifications given, the "long spacing" collagens depicted in two micrographs have periodicities of about 30 and 65 nm, respectively!

In conclusion, this booklet cannot be recommended as a primer in the field of diagnostic electron microscopy, not even (or especially not?) for beginners. K P DINGEMANS


This is the second edition of the volume that Dr Mostofi published in 1981. That book was widely recognised as one of the most comprehensive and useful accounts of renal tumour pathology available, becoming the reference book for many pathologists. The new book corrects some of the previous deficiencies in the classification of benign and malignant tumours. This book is illustrated throughout in colour. The new figures are well chosen and make their points clearly and well. The text has been brought up to date. It is organised into sections that deal with each of the major tumour groups and tumour-like lesions of the renal parenchyma and pelvis. Several new entities unrecognised in 1981 have been discussed, including metanephric adenoma, chromophobe carcinoma, and renal medullary carcinoma. Renal adenomas have been presented in more detail. More extensive discussion of nephroblastic lesions is given, including mesoblastic nephroma and cystic nephroma. Two new entities are included: clear cell sarcoma and rhadoblast tumour. A list of miscellaneous tumours is also added. Various new tumour-like lesions have been included. The definitions and explanatory notes are very clear and easy to understand by pathologists not familiar with the English language.

The second part of the book includes 145 colour photomicrographs that cover most of the morphological spectrum of the lesions described in the first part. These are of good quality and useful for a quick reference and consultation in routine work. I have had this book by my microscope for several weeks and can confirm its value in day to day practice. Anyone who works in renal tumour pathology will want to get a copy without delay. In addition to this, I have used this book as a teaching tool for renal pathology for the undergraduate medical students. They have found it very useful because of the clarity of the definitions and explanations and, above all, for the wealth of images. R MONTIRONI

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For further details and application form, contact Dr N Kirkham, Histopathology, Royal Sussex County Hospital, Brighton BN2 5BE; tel 01273 664501; fax 01273 481012; email: nigelk@pavilion.co.uk

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