LETTERS TO THE EDITOR

Are calculated globulin measurements useful in screening for paraproteinaemia?

Measurement of total protein¹ and the provision of calculated globulin value in biochemical profiles have been regarded as a useful screen for paraproteinaemia. There is no published evidence, however, that this supposition has undergone critical analysis, although the use of cellulose acetate electrophoresis as a screen for paraproteinaemia has been discussed.²

The results of 561 successive liver function tests performed between June and August 1987 were reviewed. Total protein and albumin measurements were made on a Cobas Bio centrifugal analyser using Biuret and bromocresol green methods, respectively. Protein electrophoresis was performed on cellulose acetate paper using barbitone buffer at pH 8.6 and stained with Ponceau S. Assessment of separation of individual bands was visual: a numerical value for globulin concentration was obtained by subtracting albumin from total protein concentration. Reference ranges were as follows: total protein 60-80 g/l; albumin 32-48; globulin 20-38 g/l.

The results of protein electrophoresis were then used to assess the usefulness of globulin concentration in identifying unconfirmed paraproteinaemias not suspected on haematological or clinical grounds.

Thirty four (6.2%) paraprotein bands were seen in 561 consecutive specimens. These specimens were classified according to whether clinical suspicion of a condition associated with paraproteinaemia, such as myeloma, was stated on the request form. On these grounds, 22 of the specimens were excluded from further study.

Twenty high globulins were found in the remaining 539 specimens. In only three of these (from three patients) was a paraprotein band subsequently found to reflect myeloma. Paraproteinaemia was seen in seven specimens (from seven patients) on protein electrophoresis that would not have been suspected on the basis of total protein and albumin measurements: six of these patients were subsequently found to have monoclonal paraproteinaemia, with myeloma confirmed on bone marrow examination. The effectiveness of calculated globulin measurement in detecting paraproteinaemia is shown in the table.³

Predictive value of calculated globulin measurement

True positives	High globulins and paraproteinaemia	3
False positives	High globulins without paraproteinaemia	17
False negatives	Normal globulins and paraproteinaemia	7
True negatives	Normal globulins with paraproteinaemia	512

Sensitivity = $TP/TP + FN \times 100 = 30.0\%$

Sensitivity = $TN/FP + TN \times 100 = 96.7\%$

Predictive value of a positive test = $TP/TP + FP \times 100 = 15.0\%$

Predictive value of a negative test = $TN/TN + FN \times 100 = 98.6\%$

Although globulin measurement is specific and likely to be negative as an arbiter of paraproteinaemia in normal patients, it not only failed to identify patients with paraproteinaemia satisfactorily, but also misclassified those whose increases in globulin concentration were all due to a polyclonal increase in immunoglobulins, typically associated with infection or chronic disease.

Protein electrophoresis remains mandatory as the first investigation in patients with suspected myeloma, irrespective of the globulin concentration or absolute values of total protein and albumin: in this series most paraproteinaemias would have been missed but for protein electrophoresis.

The use of protein electrophoresis itself as a screening test remains debatable due to doubts as to its cost effectiveness and influence on clinical management.²

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- 1 Riches PG, Hobbs JR. Laboratory investigation of paraproteinaemia. *J Clin Pathol* 1988; 41:776-85.
- 2 Gutteridge JE, Challand RWJ, Firth GB. Laboratory screening for paraproteinaemias—is it clinically justified? *Ann Clin Biochem* 1988;25(suppl):148s-50s.
- 3 Galen RS. Selection of appropriate laboratory tests. In: Young DS, Hicks J, Nipper H, et al, eds. *Clinician and Chemist*. Washington, DC: American Association of Clinical Chemistry, 1979:69-105.

T cell non-Hodgkin's lymphoma with uveitis, pancreatitis, digital gangrene and multiple chromosomal abnormalities

A 62 year old male smoker and regular drinker presented with lower abdominal pain and vomiting of sudden onset. Purpura were noted over the lower trunk. There was diffuse

abdominal tenderness and reduction in bowel sounds but no swollen organs or adenopathy. The only investigative abnormalities found were two pancreatic cysts (1 cm in diameter) visualised on ultrasound scan, a neutrophil leucocytosis, and a plasma amylase activity in excess of 4500 U/l. Acute pancreatitis was diagnosed, and he was discharged after two weeks of symptomatic treatment. Three weeks later he reported symptoms of acute bilateral anterior uveitis which responded to local treatment with corticosteroids. The cysts were undetectable by ultrasound scan. The leucocytosis and raised amylase activity were resolving.

After remaining symptom free for three months he was readmitted with weight loss, abdominal pain, vomiting and dehydration. The terminal phalanx of the left fifth toe was necrotic. Hepatosplenomegaly and para-aortic adenopathy were confirmed on scanning. Anaemia (Hb 8.5 g/dl), a neutrophil leucocytosis of 49×10^9 and plasma amylase activity of 2950 U/l were found. He improved with supportive measures alone; the amylase activity returned to normal, but leucocytosis persisted and became lymphocyte predominant.

Two weeks later the abdominal pain recurred, now with an overlying macular rash, gangrene of six digits, and further uveitis. Peripheral blood surface marker tests showed only CD5 to be expressed normally; CD3, CD4, and CD8 were expressed very weakly. CD1, CD2, and nuclear TdT were absent as were B cell and monocyte markers. Histological examination of an axillary lymph node biopsy specimen showed replacement of the node by a malignant lymphoma, composed of medium sized cells with scanty cytoplasm and irregular nuclei containing one or two nucleoli. There was associated proliferation of high endothelial venules and scattered collections of epithelioid histiocytes. The lymphoma cells were strongly positive with MT1, weakly positive with MT2 and UCHL1, and negative with MB1, MB2, L26 and MAC387. Peripheral T cell lymphoma of the intermediate monomorphic type was diagnosed (Professor PG Isaacson).

Karyotype from phytohaemagglutinin stimulated peripheral blood sample. The chromosomes involved in the complex translocations are indicated (arrows). The loss of chromosome 4 in this karyotype is a random loss.

by pathologists for pathologists", and volume 1 compares favourably with the *Recent Advances in Pathology* series. The articles cover aspects of gynaecological, urological, and nephrological pathology.

Much of this volume describes cancers with low malignant potential, and the term "borderline" in ovarian tumours is used not only for serous and mucinous tumours, but also endometrioid, clear cell, Brenner and mixed Mullerian tumours. The diagnosis of persistent and proliferative gestational trophoblastic disease is clearly described.

There are chapters on early prostatic malignancy, and the lack of editorial censorship is shown by one author warning of the risks of treating incidental prostatic carcinoma, while the subsequent chapter advocates radical prostatectomy for similar lesions. The book also describes papillary prostatic urethral lesions and malignant testicular stromal tumours, and there are chapters on the multiple causes of crescentic glomerulonephritis and fibrillary glomerulonephritis.

This is a very valuable collection of articles, and reasonably priced. If subsequent volumes are of a similar standard *Progress in Reproductive and Urinary Tract Pathology* will be a very welcome series of publications.

KM GRIGOR

Cyclosporin. Mode of Action and Clinical Application. Ed AW Thomson. (Pp 372; £50.) Kluwer Academic Publishers. 1990. ISBN 0 7462-0124-9.

It is trite to note that the use of cyclosporin has greatly enlarged the clinical possibilities of transplantation, and it is a truism to state that trying to understand the mechanism of its actions has pained immunologists by showing up a huge area of their ignorance. The understanding of molecular and cellular signal transduction and effector activation are being applied to cyclosporin and its new rival FK506, but there is still much to learn—and much to be learnt from studies of the pharmacology of cyclosporin.

Dr Thomson, whose own work has combined functional and morphological investigations in this field, has edited an attractive and useful synoptic account of our general understanding up to early 1989. There are 15 chapters by active scientists and clinicians from Australia, Britain, France, Switzerland and the USA. They review in varying detail the effects of cyclosporin A on mechanisms of cellular and humoral immune response initiation and amplification (20% of the book), and its therapeutic potential or proven value in human diseases of the bone marrow, eye, diabetes, skin and autoimmune disorders (40%). The remaining third covers pharmacokinetics, drug metabolism—harmful effects in clinical practice and pathological changes in experimental models.

Each chapter contains a tidy statement of current knowledge, plentiful illustrations, and a good supply of references. Most can only report phenomena, as our understanding is deficient, but others do discuss likely mechanisms involving binding to a specific cytoplasmic protein and downstream consequences on interleukin 2-mediated cell activation and proliferation.

To the basic scientist the book offers a useful but inevitably slightly dated review. For the applied researcher and clinician it provides valuable guidance on the possibilities and problems of treatment. For a compound with such a narrow therapeutic range it is disappointing that almost no author

describes the detail of any dosing regimen used—the drug is just administered! Apart from that lapse, Dr Thomson has provided a book of great use to immunologists and pathologists.

AD DAYAN

Management of Orbital and Ocular Adnexal Tumours and Inflammations. Ed JA Mauriello, JC Flanagan. (Pp 285; Hardcover DM 280.00.) Springer. 1990. ISBN 3 540 51155 5.

This is a profoundly disappointing book, which is a great pity because it contains some very good things. These include excellent photomicrographs, clinical illustrations, and gross pathological photographs, many of rare entities, culled from AFIP alumni and from Dr Flanagan's extensive practice. There are also a large number of well organised tables throughout the book. These good points only serve to highlight the deficiencies and chaos of the text. Although designed to be dipped into, rather than read as a whole, the organisation of the text constantly flits from one topic to another and frequently places a whole team of horses before the cart. I asked two "busy ophthalmologists", at whom the book is aimed, to look at it; both found the format and indexing irritating and elusive. From the pathologist's standpoint it is unsatisfactory to have paragraph headings of conditions that are not synonymous and to describe only the first, an example being: angiolymphoid hyperplasia (Kimura's disease, eosinophilic granuloma, eosinophilic folliculosis) when only Kimura's disease is described. Pick out the plums and you will enjoy it. Read it all and you risk indigestion.

ACE MCCARTNEY

Pharmacology—Drug Actions and Reactions. Ruth R Levine. (Pp 576; soft cover £24.95) Churchill Livingstone. 1990. ISBN 0-316-52217-1

This book is a useful introduction to the concepts of pharmacology and toxicology. Many medical graduates will have covered most of the ideas presented in their undergraduate years. The clinical scientist or MLSO rotating through his or her department's drug analysis section for the first time, however, will find it invaluable. Indeed, the hardest part of writing this review has been prising the book loose from the toxicology section, where it has rapidly become a fixture on the bookshelf alongside Clark, Goodman, and Gilman, the *British National Formulary*, and the *Data Sheet Compendium*. Strongly recommended: a definite "best buy".

ARW FORREST

Lung Pathology

London, 10–12 June 1991

A comprehensive course of lectures, hands-on microscopy sessions, and a slide seminar will be held at the Brompton Hospital. The programme will include J Wigglesworth on perinatal disease, M Dunnill on defence mechanisms and fibrosis, A Gibbs on pneumoconiosis, C Wagenvoort on hypertension and a variety of internal speakers on airway disease, infections, interstitial disease, angiitis and tumours.

Fee £150 (or US\$290).

Applications to Professor B Corrin, Histopathology, Brompton Hospital, London SW3 6NP.

Centre for Health Planning and Management

Diploma in Management (Diagnostic Services)

Applications are invited for places on this part-time diploma, beginning in October 1991. It is aimed at heads of department and potential heads in Pathology.

The Diploma in Management covers applied management principles, health policy, management of human resources and operations management. It aims to provide the candidate with a sound backing in both scientific and behavioural aspects of management, and the curriculum relates to the NHS of the 1990s and beyond. Potential applicants wishing to discuss the programme further should contact either Professor Roger Dyson or Dr Calum Paton on 0782 621111 (ext 3646).

Further details and full application materials are available from: Tanya Matthews, Centre for Health Planning and Management, Suite 2.1, Science Park, University of Keele, Staffordshire, ST5 5SP

Corrections

An error appeared in the bottom line of the first column of the table in the letter, "Are calculated globulin measurements useful in screening for paraproteinaemia?" (*J Clin Pathol* 1990;43:694). The correct line should have read:

Specificity = $\frac{TN}{FP + TN} \times 100 = 96.7\%$.

Two authors names were omitted from a letter to the Editor, "Breast carcinoma cellularity and its relation to oestrogen receptor content." (*J Clin Pathol* 1989;42:1166–8). The names of P Coy of the Victoria Cancer Clinic, The Cancer Control Agency of British Columbia, and C Fletcher of the Special Development Laboratory, Greater Victoria Hospital Society, should have been included.

NOTICES

ACP Locum Bureau

The Association of Clinical Pathologists runs a locum bureau for consultant pathologists.

Applicants with the MRCPATH who would like to do locums and anyone requiring a locum should contact The General Secretary, School of Biological Sciences, Falmer, Brighton, BN1 9QC. Tel and Fax: 0273 678435.