LETTERS TO THE EDITOR

Are calculated globulin measurements useful in screening for paraproteinaemia?

Measurement of total protein 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 assumption has undergone critical analysis, although the use of cellulose acetate electrophoresis as a screen for paraproteinaemia has been discussed.1

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 20–30 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 measurements

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<th>True positives</th>
<th>False positives</th>
<th>False negatives</th>
<th>True negatives</th>
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<td>High globulins and</td>
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<td>17</td>
<td>7</td>
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<td>paraproteinaemia</td>
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<td>High globulins</td>
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<td>without paraprotein</td>
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<td>paraproteinaemia</td>
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<td>Normal globulins</td>
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<td>and paraproteinaemia</td>
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<td>Sensitivity = TP/TP + FN \times 100 = 30%</td>
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<td>Specificity = TN/FP + FN \times 100 = 96%</td>
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<td>Predictive value of a positive test = TP/TP + FP \times 100 = 15%</td>
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<td>Predictive value of a negative test = TN/TN + FN \times 100 = 98%</td>
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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 concentration, typically associated with infection or chronic disease.

Paraprotein 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

LN SANDLER

DM ALDERSON

Departments of Chemical Pathology and Haematology,

Trafford General Hospital,

Moorside Road,

Droylsden, Manchester M31 3SL


Cells of similar morphology were identified in a gastric biopsy specimen and in the narrow and peripheral blood.

Chromosome analysis of phytomyagacin-glutamin stimulated peripheral blood lymphocytes was carried out as mitoses were not observed in unstimulated cultures. Of 28 G-banded cells, one showed a 46,XX, normal male karyotype and 14 cells showed a complex karyotype of 43,Y,t(X;14) (q26; q11), -12, -13, -20, t(3;7;9) (p21; q11; q12), t(11;19)(q13;p13). 1, + mar 1, + mar 2. + mar 3. The translocations t(3;7;9) and t(11;19) appeared to be not completely reciprocal as the derivative chromosome 7 (der(7)) and der (11) were missing, or involved in the formation of the marker chromosomes. Marker I involved the q arm of the deleted chromosome 6 and marker 2 involved der (9) of the t(3;7;9). Marker 3 may have represented der (14) from the t(X;14). The remaining three cells also showed the above karyotype with del (17)(p11) (figure).

His clinical condition continued to deteriorate. He died three days after starting combination chemotherapy. At necropsy multiple thick walled abscesses were found along the pancreatic border (probably derived from pseudocysts) and in the small bowel mesentery and retroperitoneum. Lymphomatous deposits were present in the liver but not in the spleen or marrow (effect of chemotherapy?).

A computer search of the literature has shown that although pancreatic carcinomas has been reported with a variety of solid tumours, such as carcinoma of the stomach, lung, and tonsil,1 it has rarely been found with lymphoma.2 Francis and Glazer reported direct pancreatic disease with Burkitt's lymphoma, but in other cases of tumour associated pancreatitis obstruction to the pancreatic duct was postulated.3 The second patient reported by Anderson et al.2 had pseudocyst formation as reported here. The digital gangrene and uveitis remain unexplained; vasculitis was not found at necropsy.

The most common chromosome abnormality in non-Hodgkin's lymphoma is t (14;18), found in association with follicular lymphoma of follicular centre cell origin. This patient showed a translocation involving chromosome band 14q11. Croce et al. postulated that all rearrangements affecting 14q11 in T-lineage malignancies involve the T cell receptor (TCR) chain locus, which is present within this chromosomal band. The del (6) described in our patient has previously been reported in non-Hodgkin's lymphoma.

We can find no cytogenetic details in earlier reports. The combination of clinical features with the cytogenetic findings and T cell origin of this lymphoma seems to be unique.

P. MANSON
Department of Histopathology, Dudley Road Hospital, Dudley Road, Birmingham B18 7QH.

P. ADAMS PET 1SAACS
Department of Medicine, Victoria Hospital, Blackpool.

N. FLANAGAN
Department of Pathology, Victoria Hospital, Blackpool.

J. HARRISON
Department of Cell Biology, Paterson Institute for Cancer Research, Manchester.


Intraepithelial stage of signet-ring cell carcinoma of the stomach

Histological observations on minute gastric carcinomas have indicated that "differentiated" (intestinal) type carcinomas seem to originate in metaplastic intestinal epithelium and that "undifferentiated" (diffuse) type carcinomas containing signet-ring cells (SRC) seem to originate in non-metaplastic gastric mucosa.1 Dysplastic and in situ changes in intestinal metaplasia associated with differentiated (intestinal) type carcinoma are well known. It is generally believed that SRC gastric carcinoma arises de novo at the glandular level2 and forms a layered structure in the lamina propria.3

According to the multistep theory of neo-plasia, it is equally possible to have a sequential evolution of the SRC gastric carcinoma from an intermediate intra-epithelial stage. On the other hand, it has already been documented that SRC gastric carcinoma may have spread through tissue strictly adhering to pre-existing basement membrane.4 Recently, Ghan-dur-Mnaymneh et al defined the criteria for dysplasia of non-metaplastic gastric epithelium and proposed that it may have a possible association with diffuse type gastric carcinoma.5 The main feature of this dysplasia is the replacement of the differentiated cells lining the glands by undifferentiated cells with a varying degree of atypia, but in the absence of architectural glandular derangement.

We document an additional case of intraepithelial carcinoma associated with multifocal, minute, poorly differentiated adenocarcinoma with an SRC component, in a selected stomach specimen of a 60 year old man. The intraepithelial carcinoma cells ended abruptly at the junction with the adjacent periodic acid Schiff positive foetal cells (figure). Fusion or severe distortion, or both, of the neighbouring tubules were not detected.

The component cells of the intraepithelial carcinoma were uniformly of a columnar shape with a thin brush border (figure). They showed enlarged, ovoid, vesicular, moderately pseud stratified nuclei with prominent nucleoli (figure). The cytoplasm was generally not stained with periodic acid Schiff, alcin blue, or high iron diamine. Very occasionally these intraepithelial carcinoma cells exhibited small vacuoles, which appeared "optically empty" or contained a variable amount of neutral mucins, sialomucins, and sulphomucins. Atypical mitoses were frequently found. A histological continuity between intraepithelial carcinoma and poorly differentiated adenocarcinoma glands was observed in some cases (figure).

Both the poorly differentiated adenocarcinoma cells and isolated SRC showed a granular positivity for sialomucins as well as large cytoplasmic vacuoles, which appeared "optically empty" (figure).

In our case the presence of intraepithelial carcinoma may reflect the proliferative activity of a distinct population of atypical cells which are not fully transformed into malignant cells, being between adenoma and invasive cancer in nature. In fact, besides possessing the ability to migrate along the foveolar wall, the intraepithelial carcinoma cells show peculiar morphohistochemical features such as their columnar shape, brush border, and rare mucin granules. By contrast, invasive adenocarcinoma cells are capable of forming gland-like structures (poorly differentiated adenocarcinoma) or which show a complete loss of the gland-forming ability (isolated SRC). Moreover, abundant mucous production seems to be a feature seen predominantly in invasive adenocarcinoma and only in a few cells of the intraepithelial carcinoma.

In conclusion, our data indicate the possibility of an intraepithelial stage with peculiar morphohistochemical features during the progression of SRC gastric carcinoma.

RA CARUSO
Department of Human Pathology, Viale Tigo 6, 98168 Messina, Italy.

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


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 gained immunologists by sharing in 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 synthetic 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 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 instructive 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


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 folliculitis) 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


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 MSK rotating through his or her department's drug administration 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 definitive "best buy".

ARW FORREST

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, Palmer, Brighton, BN1 9QG. Tel and Fax: 0273 678435.

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 Dunill on defence mechanisms and fibrosis, A Gibbs on pneumonia, C Wagenoort on hypertension and a variety of internal speakers on airway disease, infections, interstitial disease, angitis 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 back-ground in both scientific and business/financial 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 = TN FP + TN × 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.