Correspondence

ACP Broadsheet No 145—Investigation of patients with autoimmune haemolytic anaemia and provision of blood for transfusion

It is unfortunate that this ACP Broadsheet,¹ published with the full authority of the Association of Clinical Pathologists, neither reflects best practice, nor provides hospital blood banks with a workable protocol for investigating a patient with suspected autoimmune haemolytic anaemia. It is merely an account of the various techniques available for investigating a positive direct antiglobulin test (DAT), irrespective of the medical history, which would lead a clinician to suspect a warm or cold autoimmune haemolytic anaemia, and whether active haemolysis is present or not. There is no discussion about the clinical value of each test, or how the series of investigations described should be prioritised. Neither is guidance provided regarding which tests should be undertaken by hospital laboratories and at what point samples should be sent to a reference laboratory. The Broadsheet is based on the procedures used at one particular Blood Transfusion Centre and reflects local practices and individual prejudices.

Worryingly, there are numerous errors and misconceptions. For instance, the paper refers to genotyping, where it should state phenotyping; polyspecific AHG reagents need only contain anti-IgG and anti-C3, as defined by both UK and ISBT guidelines and the presence of other specificities, such as anti-IgM, is not mandatory. The abbreviation "LISS" only refers to the Moore and Mollison formula for low ionic strength solution which is not the reagent recommended for use with the Diamed gel direct antiglobulin test cards. The recommended solution for the gel test is a low ionic diluent supplied by the manufacturers, which is not LISS; the two cannot be used interchangeably. Some of the described serological techniques are obsolete and in general do not follow those recommended in current BCSH guidelines for hospital blood banks, etc, etc.

This complicated series of expensive tests, supposedly devised to investigate patients with autoimmune haemolytic anaemia, seems to be totally divorced from the reality of the internal market and meaningful patient care. For instance, there is no clinical value in performing red cell eluates, except where the patient has recently been transfused. On the other hand, the importance of excluding underlying red cell alloantibodies, which may be masked by autoantibodies, in the case of patients who are likely to need blood transfusion is not stressed. Furthermore, clinicians should be made aware that the allogeneic stimulus of blood transfusions sometimes exacerbates the autoimmune process and may also lead to the development of alloantibodies. For this reason, blood transfusion should be given only when there is a very strong indication.

Unfortunately an opportunity to provide much needed clear guidance to hospital laboratories for the investigation of a commonly encountered problem has been lost.

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- 1 Sokol RJ, Booker DJ, Stamps R. ACP Broadsheet 145: Investigation of patients with autoimmune haemolytic anaemia and provision of blood for transfusion. *J Clin Pathol* 1995;48: 602-10.

Drs Sokol, Booker and Stamps comment:

We read with interest the comments made by Dr de Silva and colleagues on our Broadsheet, but as it is based on over 30 years experience of autoimmune haemolytic anaemia we stand by our views. It is helpful to have the thoughts of experienced colleagues as we can all learn from each other. The purpose of the Broadsheet was to make hospital blood banks aware of the range of investigations currently available and to help them overcome commonly encountered serological problems; it was never our intention to dictate to them which tests to carry out; the algorithm clearly shows which tests are considered more appropriate for specialist centres.

We are fully aware of the various transfusion serology guidelines and regard them as valuable indicators of minimum standards. The term "broad spectrum" was chosen so that we could recommend a screening reagent for direct antiglobulin testing which contained an anti-IgA component (anti-IgM was not mentioned in this context). In the *Guidelines for the Blood Transfusion Service* (HMSO, 1994), "LISS" refers to a low ionic strength solution defined by pH, conductivity and osmolality; there is no mention of a particular formula; also, the abbreviation "LISS" is printed on the label of the Diamed diluent bottle. We would agree that the term phenotyping would probably have been more appropriate, and that whilst some techniques may be used infrequently, none can be considered obsolete.

In our experience, clinicians are fully aware of the potential antigenic stimulus of blood and only transfuse when necessary; the idea that patients with autoimmune haemolytic anaemia should be given blood only in the last resort is a myth. The importance of detecting alloantibodies in the presence of autoantibodies and the methods for doing so are well covered in 10 paragraphs in the Broadsheet.

Our major disagreement with the views of Dr de Silva and colleagues is in the value of red cell eluates. We feel that studies on eluates are extremely important in order to provide meaningful clinical information; as clearly stated in the Broadsheet, it is wrong to assume that a positive direct antiglobulin test is solely due to autoantibodies or a delayed transfusion reaction. We need to be able to recognise the many patients who have an autoimmune haemolytic component within a very complex clinical situation, as well as investigating those suffering from frank idiopathic autoimmune haemolytic anaemia.

With regard to the internal market of which we are all acutely aware nowadays, the procedures described in the Broadsheet are extremely cost-effective, as well as keeping open the path of intellectual and scientific progress which results in a better service to patients.

Macroscopic examination of prostatic specimens

The recent ACP Broadsheet by Harnden and Parkinson¹ is timely and welcome. It does, however, contain a small contradiction which I think should be corrected.

The authors rightly stress the importance of staging prostatic cancer and the evidence that, in TURP specimens, the area fraction of tumour or the proportion of chips which contain tumour provides valuable prognostic information. Later, however, they give the advice, carried over from the days before the importance of tumour volume was recognised, that "... any white or yellow fragments (which may prove to be tumour) are included in the cassettes". This contravenes the basic requirement for a quantitative technique such as assessing tumour volume—that is, that sampling must be at random. Furthermore, the extent to which the quantitation is degraded will be unknown, as the pathologist cannot know how accurately malignant chips have been identified. This problem may be reduced by the large volumes of tissue which the authors recommend should be processed, but this advice is unlikely to be followed to the letter in most hard-pressed district general hospital laboratories.

We should be clear about what we are trying to achieve. The ideal is to process a large sample, taken at random. We will then detect small tumours, and we will know what proportion of the sample they occupy. We will, however, expend a lot of time and money.

An alternative, which is in widespread use where finances are constrained and workloads are high, is to take a smaller sample but attempt to include any "suspicious" fragments. This risks missing low volume tumours which are not macroscopically obvious, and it should be recognised that it completely invalidates any assessment of tumour bulk.

My own preference attempts to get the best of both worlds. I first take at random a sample which is as large as I think reasonable given the patient's age, clinical suspicion, etc. If there remain any fragments which look suspicious, I then put these into a cassette which is identified separately, and which I know cannot be used for assessment of tumour volume. Do the authors think this an acceptable variation?

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- 1 Harnden P, Parkinson MC. ACP Broadsheet No. 146. Macroscopic examination of prostatic specimens. *J Clin Pathol* 1995;48:693-700.

Drs Harnden and Parkinson comment:

We thank Dr Furness for his thoughtful criticism of the recent Broadsheet and do not dispute his assertions concerning the mathematical theory of volume measurement. We look forward to seeing the details of the random sampling method, the results and the costings of the approach he suggests.

In the Broadsheet, when referring to those cases where only a proportion of the specimen would be processed, the term "sampling" was intentionally used in contrast to "random sampling", although we should perhaps have stressed this in our discussions.

The mathematical model to apply to the sampling of prostatic chips is complex because we are dealing with a specimen which itself is a sample already influenced by the variability of the clinical situation and the constraints of the operative procedure. We are aware that to randomise the selection of chips in the laboratory, we would need to introduce a validated mathematical technique, such as a grid labelled with random

numbers. The consistent application of such a method would be of course time-consuming. Furthermore, the published work that we have quoted either makes no attempt to randomise, or mentions it in passing with no detail given as to the methodology. In particular, the papers that specifically address the question of tumour extent in TURP specimens in relation to survival are based on archival material with no mention of the sampling technique other than the number of blocks available. Therefore, we have no way of knowing whether macroscopically "abnormal" chips were specifically included or not, and our advice to include such fragments was an attempt to be thorough. Whilst none of the studies are perfect in terms of design (as is often the case when dealing with clinical material in an imperfect and cost confined world), they do provide methods for obtaining useful information. In other words, they "work".

The details of sampling prostatic fragments for carcinomas are always a discussion point—not least in an attempt to reduce cost and tedium. However, one must not lose sight of the fact that the major decision that we take is not with respect to sampling techniques but as to whether and when to sample. Thus, whilst giving definite advice on processing the entire specimen from men aged 60 years or less, we advocate some form of sampling for TURP specimens from men over 60 years old. We hope that this Broadsheet will increase awareness of protocols with respect to prostate pathology, particularly as regards the false negative rate in the diagnosis of carcinoma, and facilitate discussions with clinicians in order to adopt the protocol that is best suited to local circumstances. The greater public concern with cancer diagnosis and treatment will inevitably lead to more questions being asked and decisions challenged, and we therefore feel that it is imperative that pathologists and clinicians have clearly defined, defensible and mutually acceptable protocols. Our reasons for discarding numerous grams of prostatic tissue from TURP specimens whilst meticulously examining levels of fine biopsy cores from the same organ may at some time have to be made clear to "the man on the Clapham omnibus" who is usually blissfully unaware that histopathology departments are under unremitting pressure with increasing workloads requiring more and more complex levels of interpretation in the face of resources which are at best static but more often are decreasing.

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Cytopathology of the Central Nervous System. SH Bigner, WW Johnston. **ASCP Theory and Practice of Cytopathology 3.** (Pp 206; \$184.00.) American Society of Clinical Pathologists. 1994. ISBN 0-89189-362-8.

For departments in which central nervous system (CNS) cytology forms only a small part of the workload, the subject is full of potential pitfalls, and an authoritative book that addresses the diagnostic problems likely to be encountered is long overdue. When it is written by authors with the experience of Bigner and Johnston, it is especially welcome.

After a brief opening chapter, the authors cover neuroanatomy, normal cells and contaminants, infective and non-neoplastic conditions in successive chapters. The sections on haematological malignancies and metastatic carcinoma are detailed and useful. The chapter on primary neoplasms is most helpful for tumours such as medulloblastomas, germ cell tumours and choroid plexus papillomas, where examination of the cerebrospinal fluid often yields a diagnosis.

The illustrations on the whole are of an extremely high standard, both cytological preparations and the excellent gross specimens. The low power histology sections would possibly have been more informative with some arrows, as the anatomical structures referred to in captions may not always be familiar. The variable quality of the staining of the Romanowski preparations accompanying the leukaemia section means that the distinction between different types of blast is not always clear.

My only real criticisms relate to the last three chapters. The chapter on stereotactic biopsy, while containing useful tables for differential diagnosis of CNS tumours, is not likely to be of real use to either cytologists or neuropathologists. The chapter on immunocytochemistry gives considerably more theoretical detail than necessary for readers of this book (although the latter part is of practical use), and the same criticism could be levelled at the last chapter on molecular genetics. Finally, there is no attempt to cover intraoperative smear diagnosis of CNS tumours. Apart from those minor reservations, this is an excellent, well thought out and informative book, providing both essential background information and practical diagnostic help for those at whom it is directed.

J GEDDES

Molecular Methods for Virus Detection. Eds DL Wiedbrauk, DH Farkas. (Pp 386; £46.00.) Academic Press Inc. 1995. ISBN 0-12-748920-7.

This small, rather poorly bound book will provide a useful reference source for researchers in microbiology and histopathology who are interested in developing rapid tests for the detection of organisms which cannot be readily cultivated. The principles behind the methods for the detection and amplification of nucleic acid and techniques for recognising the end products—for example, chemiluminescence, are described in detail. A particular strength of many of the chapters is the emphasis which has been placed on identifying problems that can arise when

introducing and performing the tests and discussion of relative advantages and disadvantages. There is also the welcome inclusion of an entire chapter related to the topical issue of quality assurance. Each chapter includes detailed protocols, often illustrated by line drawings, but many diagnostic laboratories would probably prefer more specific examples. This issue is addressed by providing extensive bibliographies, some of which are surprisingly up to date, 1994. The majority of the authors work in the private sector and, therefore, it is not surprising that some of the chapters direct the users to commercial assays and the protocols read like the instructions to a kit. Anyone who is interested in the principle behind many of the commercial assays which are currently being introduced or developed—for example, multiplex PCR and chemiluminescent DNA probe tests, will find it a valuable source of information. The clearly presented protocols should enable many research and development departments to develop in house assays.

D CUBITT

Biopsy Interpretation of the Lung (Biopsy Interpretation Series). Y Shimamoto, RR Miller. (Pp 416; \$107.50.) Raven Press. 1994. ISBN 9-7817-0168-6.

This is another contribution to the successful Biopsy Interpretation Series which covers the subject in a well structured way. Most pathologists are exposed to pulmonary pathology through transbronchial rather than open lung biopsy specimens. This book will certainly help both the general and specialist histopathologist obtain as much information as possible from the tissue sent.

The subject of lung pathology divides conveniently into non-neoplastic and neoplastic disease, and this book uses this very practical approach to cover the subject. In view of the nature of problems encountered in biopsy specimens, particularly those of transbronchial type, non-neoplastic disease is covered under the heading "infiltrative" disease.

The book has a very pragmatic approach to the subject. There is a short chapter on the diseases of small airways, particularly bronchiolitis. A description of how this process relates to chronic bronchitis and chronic obstructive airways disease would have been useful. It is not clear, however, how the subject of bronchiolitis relates to—for example, organising pneumonia.

I like the classification of acute infiltrative diseases into those involving immunocompromised and immunocompetent hosts. This is a very useful and problem orientated way of dealing with the subject. Chronic infiltrative disease is covered using the American classification, but the transition is easily made between the two systems.

The section on tumour pathology includes a chapter on cytology, which is useful in view of the increased use of this technique.

This book is a compact and up to date account of lung pathology which will be of great use to surgical pathologists, and I particularly recommend it as a reporting room bench book.

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