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Correspondence

Comparison of electron microscopy and immunocytochemistry in tumour diagnosis

Dar *et al*, in a careful retrospective review, compared the relative usefulness of electron microscopy and immunocytochemistry in tumour diagnosis.[1] The authors' material did not include small round cell tumours of children and young adults, in which electron microscopy is very useful in diagnosis and in the recognition of "new" entities.[2 3] In our experience, electron microscopy may also be helpful in diagnosing primary or metastatic large cell undifferentiated tumours, as well as in other "fine print" situations.

I believe that the relative merits of electron microscopy and immunocytochemistry in tumour diagnosis are very difficult to assess, even retrospectively. They achieve similar results in most cases, albeit by very different means (identifying ultrastructural features characteristic of a normal cell or specific tumour cell type on the one hand, and typical antigenic expression on the other). Either technique, if used alone, may be non-diagnostic in a given case,[4] although the combined ultrastructural findings and immunostaining pattern are frequently complementary and precise enough to make the diagnosis. In practice, most pathologists have no problem in deciding whether to use immunocytochemical "markers" or electron microscopy: they have no access to an electron microscope; and they have little experience in interpreting ultrastructural features. Furthermore, immunostaining is perceived as convenient, less time consuming, and less expensive.

Restricting the use of electron microscopy in tumour diagnosis (as opposed to its use in medical biopsies, identification of unusual infectious agents, evaluation of cilia, etc.) deprives both pathologists and pathologists-in-training of an important means of improving their diagnostic ability and understanding of basic morphology. Electron microscopy not only clarifies the light microscopy appearance, but also clearly illustrates—in black and white—what is staining brown in light microscopy sections.

Finally, I support the authors' statement that electron microscopy must be done judiciously, but it should also be done promptly, and not solely as a last resort on suboptimal material, when the submitting pathologist has been overwhelmed by "immunoconfusion".

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1 Dar AUH, Hird PM, Wagner BE, Underwood JCE. Relative usefulness of electron microscopy in tumour diagnosis: 10 years of retrospective analysis. *J Clin Pathol* 1992; 45:693–6.
2 Haas JE, Palmer NF, Weinberg AG, Beckwith AG. Ultrastructure of malignant rhabdoid tumor of the kidney. A distinctive renal tumor of children. *Hum Pathol* 1981;12: 646–57.
3 Gerald WL, Miller HK, Battifora H, *et al*. Intra-abdominal desmoplastic small round-cell tumor. *Am J Surg Pathol* 1991;15: 499-513.
4 Gaffney EF, McCormick C, Sweeney EC. Nondiagnostic electron microscopy. *Proc Roy Microsc Soc* 1989;24 **(Suppl)**:4–5.

Professor Underwood et al comment:
We welcome Dr Gaffney's support for the judicious use of electron microscopy in tumour diagnosis and for his advocacy of its utility. The purpose of our paper was not to encourage restricted use of electron microscopy, but to enable a more rational decision if meagre tissue samples or laboratory resources force a choice to be made between electron microscopy or immunostaining in an individual case.

A viscometric method of measuring plasma fibrinogen concentration

We have also studied the correlation of plasma fibrinogen concentration against the difference in viscosity between plasma and serum. We can confirm the work of Ernst *et al*[1]; we obtained a similar correlation coefficient of $r = 0{\cdot}824$ ($p = <0{\cdot}001$) using samples with values that were not excessively raised. The relation, however, does not hold true for samples with raised serum viscosity as seen in myeloma or macroglobulinaemia[2]; when these were included in our correlation we obtained $r = 0{\cdot}117$ ($p = NS$).

The relation of fibrinogen to serum viscosity is not simple linear arithmetic as suggested by Ernst *et al*. It is exponential. Using logarithmic transformation we obtained a correlation of $r = 0{\cdot}927$ ($p = <0{\cdot}001$). This included normal and abnormal samples with high fibrinogen as well as myeloma and macroglobulinaemia.

As a simple quick calculation the method of Ernst *et al* can be used in normal subjects but the limitations of this method in abnormal conditions must be borne in mind.

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1 Ernst E, Resch KL, Saredeth T, Maier A, Matrai A. A viscometric method of measuring plasma fibrinogen concentrations. *J Clin Pathol* 1992;45;534–5.
2 Peterson WE. The viscometric determination of blood fibrinogen. *J Lab Clin Med* 1953; 42;641–5.

Professor Ernst comments:
Recalculating our data we still find the linear approach superior ($r = 0{\cdot}87$). The situation is different using the raw data of the Clauss method (seconds) instead of the derived mg/dl. The fact that here we have a quadratic correlation leads to a higher value of r in the logarithmic approach ($r = 0{\cdot}85$) compared to the linear one ($r = 0{\cdot}79$). So it should be clarified whether Lane and I'Anson calculated their correlation coefficient applying mg/ml to both methods.

We did not include haematological diseases (myeloma, macroglobulinemia, etc.), where interactions between fibrinogen and pathological proteins are not unlikely to have a major role. There might indeed be some other diseases, where the viscometric method fails and future studies will have to address this.

Lane and I'Anson did not mention the number of cases their results are based on. If the number is small, the constellation they report could be influenced by hazard. We keep on collecting data and will hopefully be able to present a recalculation of our formula based on several hundred additional cases in a while.

It would be very interesting to establish contact with Lane and I'Anson and discuss the remaining open question in more detail.

Bone marrow trephine biopsy in lymphoproliferative disease

Schmid and Isaacson present their experience of the pattern of marrow disease for various types of non-Hodgkin's lymphoma.[1] In their experience malignant lymphoma centroblastic/centrocytic (ML cb/cc) most commonly gives rise to a nodular pattern of marrow disease while malignant lymphoma centrocytic (ML cc) most frequently manifests in the marrow in a paratrabecular distribution. This is at variance with our observations, particularly with regard to the paratrabecular distribution and has led us to examine the published finding. The latter is surprisingly inconsistent and a comparison of the various studies is, of course, confounded by the multiplicity of classifications which have been applied to malignant lymphoma.

An early study,[2] using the Rappaport classification, states that both diffuse, well differentiated, and nodular poorly differentiated lymphomas tend to show a focal pattern and that in many of the patients in whom the pattern is focal, there seemed to be a distinct paratrabecular distribution. A subsequent paper from the same department[3] studied nodular lymphoma specifically and, where the degree of marrow disease was limited, found the distribution to be usually paratrabecular; this became less easily recognised as the extent of marrow disease increased. A third paper from this group[4] used the Lukes-Collins classification. Of 87 cases of malignant lymphoma, follicle centre cell, small cleaved, 31 (64%) showed a focal paratrabecular pattern. The paper also states that 76 of these 87 cases (87%) showed a follicular pattern in the affected lymph nodes. The study by Conlan[5] uses the Working Formulation and therefore cannot be interpreted in detail, but a paratrabecular pattern was seen in a range of lymphoma types of low and intermediate grade, both B and T cell. Bartl *et al*[6] have published a very large series in which bone marrow biopsy specimens from 3229 patients with lymphoproliferative disorders were studied; a paratrabecular pattern was uncommon (2% of affected trephines) but correlated strongly with MLcc, while a nodular pattern was more common (9% of affected trephines) and was seen with ML cb/cc and immunocytoma. However, a subsequent paper by Bartl *et al*[7] is illustrated with two cases of ML cb/cc showing paratrabecular disease.

We have therefore studied the pattern of marrow disease in trephines from our archival material, and have reviewed the lymph nodes from these cases to verify the lymphoma typing. Forty six trephines from cases of ML cb/cc and ML cc were examined without knowledge of the lymph node morphology and an attempt was made to