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Difficulties in the diagnosis of acquired immune deficiency syndrome

Diagnosis of the acquired immune deficiency syndrome (AIDS) requires reliable evidence that an opportunistic infection or immunodeficiency related tumour is present with an acquired impairment of T cell function, usually first indicated by lymphopenia. Following the report by Dr Burt and others[1] we would like to present our experience with a similar patient who fulfilled the diagnostic criteria of AIDS.[2] In this patient the presence of opportunistic disease, although suspected, was not reliably identified during life despite extensive microbiological, radiological, and histological evaluation. In addition, lymphopenia and T cell lymphopenia never developed, although a considerable reduction in the proportion of T helper cells and increase in T suppressor cells, with a consequent reduction in the T helper to T suppressor cell ratio, was present, together with skin test anergy.

A 45 year old promiscuous male homosexual, presented with a one month history of malaise, anorexia, loss of weight, a dry cough, and night sweats. Medical history and clinical examination were unremarkable. Abnormal investigations included an erythrocyte sedimentation rate of 135, hypergammaglobulinaemia, a reversed T helper to T suppressor ratio, a decreased percentage of T helper cells, an increased percentage of T suppressor cells, and bilateral pulmonary infiltrates. Absolute numbers of lymphocytes and T lymphocytes remained normal throughout his illness and extensive investigation failed to reveal any evidence of infection or malignancy. Over a five month period. no appreciable IgG antibody titres were found to several antigens, including cytomegalovirus, herpes simplex, *Toxoplasma gondii,* and *Pneumocystis carinii.* Histological examination of liver and bone marrow were normal and, although a transbronchial biopsy raised the suspicion of pneumocystis pneumonia, organisms were not shown.

Co-trimoxazole was given without noticeable benefit and was discontinued because of the development of a maculopapular rash. Empirical antituberculosis treatment was then started with rifampicin, isoniazid, and ethambutol; this resulted in some improvement, which was sustained over the next three months.

His symptoms and lung infiltration then returned, and despite further courses of co-trimoxazole and antifungal therapy he died. Again, investigations had not provided any conclusive evidence of opportunistic infection. Needle specimens of lung, heart, and liver were obtained at a limited necropsy. The lung biopsy was characteristic of *P carinii.*

Until we have a diagnostic test for AIDS (such as that recently proposed[3]), emphasis is placed on characteristic but non-specific laboratory features. Lymphopenia, particularly T cell lymphopenia, is a typical finding in adult patients with AIDS[4,5]; more severe disease is associated with lower absolute lymphocyte counts and lower T helper to T suppresor ratios.[5] This patient was unusual in having normal absolute lymphocyte and T lymphocyte counts which failed to reflect his underlying immunological state, with a considerably decreased proportion of T helper cells (OKT4), increased proportion of T suppressor cells (OKT8), and a severely reduced T helper to T suppressor ratio of 0·15 (normal 1·0–3·0). This underlines the importance of determinations of T lymphocyte subsets in these patients.

The lack of any appreciable antibody titres was also unusual as high levels of IgG antibody to herpes viruses are commonly seen in homosexual males with AIDS.[6,7] Tissue destructive infections can occur, however, without producing a rise in IgG antibody[1] and without specific IgM production.[6,8] Meaningful interpretation of serological results may therefore be impossible. Where feasible, culture of the organism from a normally sterile site, tissue identification, or tests for antigen are more appropriate in the diagnosis of current infection.

Despite the initial response to antituberculosis treatment, we believe that mycobacterial infection was unlikely as repeated attempts at isolation before and after death were unsuccessful. It is possible that rifampicin displayed some in vivo activity against pneumocystis pneumonia; serologically diagnosed infection which responded to rifampicin has been described.[9] Animal experiments, however, have found rifampicin to be ineffective in the prophylaxis and treatment of *P carinii* infections,[10] while it may further suppress the immune response.[11]

As with the case described by Dr Burt and others[1] this report exemplifies some of the difficulties that may be encountered in diagnosing AIDS.

We are grateful to Dr M Serlin and Dr FJ Nye for permission to report this patient who was under their care.

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Since this letter was written we have received a report on the immunofluorescent test for antibody to HTLV III virus, which was positive. (We are grateful to Dr MS Pereira, Virus Reference Laboratory, Central Public Health Laboratory, Colindale, London, for this result.)

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Alcohol induced liver disease

Dr Fleming's and Professor McGee's excellent review of alcohol induced liver disease[1] contained the following sentence: "The hepatocyte may be massively swollen, often being three times normal size." This could mean that the cell volume is three times normal, the cross sectional area is three times normal (therefore cell volume roughly five times normal), or the cell diameter is three times normal (therefore cell volume roughly 27 times normal). In this instance the photographs imply that the cell diameter is three times normal, but this inaccurate usage of the undefined term size is widespread throughout medical published work and may lead to serious misunderstandings.

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Professor McGee replies as follows:

Dr Simpson makes a very cogent point in that the term size is open to misinterpretation when applied to a histological feature in a tissue section. When we stated that "The hepatocyte may be massively swollen, often being three times normal size" we did, in fact, mean that the maximum dimension of the two dimensional image of a hepatocyte was three times normal. We did not imply that size referred to diameter. Only circles have diameters; swollen hepatocytes are not circles and cannot be defined accurately by any standard geometric shape.

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Value of factor VIII related antigen as a means of demonstrating extramedullary megakaryopoiesis

We were interested to read the brief report by Dr Crocker and Dr Smith on the value of factor VIII related antigen (VIIIRAg) as a marker for the immunohistological demonstration of megakaryocytes.[1] Since the original immunological localisation of VIIIRAg in platelets[2] this antigen has been used as a marker for these and for megakaryocytes,[3] but a word of warning is needed. Most commercial antisera of the type recommended by Dr Crocker and Dr Smith are prepared for relatively insensitive immunoprecipitation assays of VII-IRAg (von Willebrand factor antigen) and are not necessarily sufficiently specific or purposely absorbed for the much more sensitive immunohistological methods.[4] Thus antisera may be contaminated with weak antibodies to fibronectin or other antigens and much more rigorous testing is needed to ensure monospecific antisera for immunohistological work.[4 5] Use of monoclonal antibodies to VIIIRAg or antisera to specific platelet antigens such as β thromboglobulin could circumvent these problems. Blocking controls using commercial "factor VIII" are not answers to this problem since even high potency therapeutic concentrates are crude mixtures of factor VIII complex (factor VIII coagulant and von Willebrand factor) with fibronectin, fibrinogen, and other proteins which, in fact, are their main constituents. In addition the difference between "factor VIII related antigen" and "factor VIII" is an important semantic problem which should be recognised by histologists.[6]

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Book Reviews

Aluminium Analysis In Biological Fluids. Ed MR Wills and J Savory. (Pp 132; $25.00.) University of Virginia Press, USA. 1983.

These are the proceedings of a conference held at the University of Virginia in June 1983. To some, aluminium analysis might seem to be a rather esoteric topic for a meeting and the proceedings likely to be of little interest to pathologists. But even though the clinical importance of aluminium has been recognised for barely ten years the measurement of aluminium in water supplies, biological fluids, and tissues has become an important procedure in many clinical laboratories. Thus the clinical and toxicological importance of aluminium is now well established and should be of general interest to all pathologists.

Aluminium is the third most abundant element in the earth's crust and it is widely distributed in nature. In the healthy adult, the body-burden of aluminium is less than 300 mg. However, in patients with chronic renal failure there is unequivocal evidence of a general increase in the body burden of aluminium. In such patients aluminium is strongly implicated in the aetiology of encephalopathy, microcytic anaemia, and osteomalacia. It may be implicated also in the pathogenesis of Alzheimer's disease and some other neurological disorders, although here the evidence is less certain.

In their foreword to the conference proceedings the editors state that their purpose was to review the "state of the art" in analytical methods for the assay of aluminium in biological material. In this reviewer's opinion they have succeeded admirably in the task. The volume contains 14 papers on various aspects of analysis from acknowledged experts in the field. The variety of techniques reviewed includes electrothermal (flameless) atomic absorption spectrophotometry, neutron activation analysis, scanning electron mic-