The Cambridge dilemma

A marked depletion of the CD8 T cell subset in the peripheral blood of patients with arteritis temporalis and polymyalgia rheumatica (AT/PMR) has now been reported from several centres and has been found in 80-90% of patients with active, untreated disease. How is it, then, that the group from Addenbrooke’s Hospital in Cambridge in a report on this subject in the November 1993 issue of the *Annals* concluded “that the case that CD8+ cells are lowered in patients with PMR/AT is not proven”?

We would like to comment on the paper in the light of our and other recent results. In the period 1984–91 we performed temporal artery biopsy and simultaneous determination of the CD8 T cell subset in 411 patients. All patients were admitted to hospital, between 08:00 and 09:00 (before the subject undertook any exercise), blood specimens were drawn and separated within 30–60 minutes with the Ficoll-Hypaque method, followed by immediate incubation with monoclonal antibodies. We have previously described our inclusion criteria, the use of age and sex matched controls and our method, which includes most of the analytical and biological variables important in evaluating T cell subsets such as storage, exercise, age, diurnal variations, and treatment with prednisone. As shown in the figure, the depletion of percentage (and number, not shown) of CD8 cells was restricted to the 148 patients with active, untreated AT/PMR, with the exception of some patients with other vasculitides. CD8 T cell depletion is thus not a common feature of other rheumatic or medical diseases. It may also be used for screening purposes (table).

Other concerns of the Cambridge group have been about the density gradient separation method, in particular, use of Ficoll-Hypaque separation of blood cells, which they believe may decrease the CD8 T cell subset selectively. This is obviously not the case, as we found normal values of CD8 T cells in controls and in a large group of patients with a variety of other medical and rheumatological diseases. When freshly obtained blood is used, as we did, exactly the same values for CD3, CD4, and CD8 are obtained with and without such separation, method and the whole blood lysis methods.

Another question posed by the Cambridge group was whether selective depletion of CD8 T cells may be caused by some intrinsic factor, specific to patients with AT/PMR, which affects the migration of lymphocytes on a density gradient used to separate the mononuclear cells from other blood cells. However, significant depletion of CD8 T cells has now been demonstrated by whole blood lysis methods also and, although intriguing, this viewpoint seems to be untenable.

Finally, the Cambridge group found a significant depletion of numbers of CD8 T cells in 13 patients with “severe” AT/PMR (a rate of 30–61% which, incidentally, has a 95% confidence interval of 17–1 to 58–9%) and concluded that the CD8 T cell depletion was caused by an overall lymphopenia in these patients. As the term “severe” AT/PMR has not been characterised by the authors or been described in the literature, we cannot respond specifically to this finding. Signs of an overall lymphopenia in patients with active, untreated AT/PMR have not been reported previously, and we have re-examined our results with reference to this point. We found a median number of lymphocytes—counted on an automated haematological counter—of 1.7 × 10^9/L (CI 95% 1.6 to 1.8), which is comparable to the figures for controls (CI 95% 1.3 to 3.5) and to published data (healthy persons, age 18–70 years: 25–75 percentiles 1.6 to 2.4 × 10^9/L). We have found no difference between patients with AT and PMR.

On this basis we still maintain that the percentage and number of CD8 T cells has proved to be a valuable diagnostic test which, in time, may be incorporated in the diagnostic armamentarium used for this disease.

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**References**


Matters arising


Another of our results from the Ficoll-Hypaque separation in normal individuals has shown that 13-3% of lymphocytes are lost from the interface to the bottom of the tube, and that this fraction contains an increased proportion of CD8 cells.1 Direct comparison has shown that the percentage of CD8 cells measured after Ficoll-Hypaque separation may be significantly reduced compared with that after use of a whole blood technique, and this effect is more pronounced if samples are aged before processing.1 It is also worth noting that the percentage of CD8 cells in control subjects in the studies cited by Eling and colleagues differs considerably, depending on the laboratory techniques used. After Ficoll-Hypaque separation, the median or mean values of CD8 cells in control subjects were 21%, 24-30%, 26-66%, 22.1% and 24% in the figure in the accompanying paper.2 By comparison, the percentage of CD8 cells in control groups with lysed whole blood techniques were used were 34-2 and 28%, and median values of 35% and 33% have been reported in larger population studies using these techniques. Several factors may contribute to these differences; however, the consistent difference is the preparative technique used.

At present no data are available comparing the effects of different preparative techniques when lymphocyte subsets are enumerated in pathological conditions. However, it is possible that differences in activation, survival, or senescence parameters may affect lymphocyte migration on a gradient. These and other biological variables would be expected to differ between control and study groups, and indeed increased numbers of activated CD8 cells in patients with active PMR/GCA have been documented.6 Differences in CD8 cells recovered from the plasma-Ficoll interface and the bottom of the tube have not been exagerated may affect lymphocyte migration on a gradient. These and other biological variables would be expected to differ between control and study groups, and indeed increased numbers of activated CD8 cells in patients with active PMR/GCA have been documented.6

Through the gradient, the CCR 2 is often well through the control studies and, therefore, is not required by CCR 2. A similar CCR 2 is less well-studied in patients with active PMR/GCA. Studies have shown that increased CCR 2 expression is associated with disease activity and disease progression.7, 8

We read with interest the article by Sanchez-Roman and colleagues describing a high prevalence of clinical and biological autoimmune manifestations in 50 workers after occupational exposure to silica.9

In 1990 at the 3rd International Anti-Monoclonal Antibodies and Cell-Mediated Cytopathology (ANCA) Workshop, we first described three silicotic patients with renal involvement, in a group of 28 ANCA positive patients. By contrast, no ANCA were found in seven silicotic patients with renal involvement.10

The three patients differed from those previously reported with silicoprotein nephropathy, usually of the rapidly progressive glomerulonephritis (RPGN) type.11 All three were slate workers and had a proven pulmonary silicosis. They did not fulfill the criteria for RPGN, either clinically (two had stable chronic renal failure) or histologically (no diffuse extracapillary proliferation). All had ANCAs with an antigenic specificity for MPO, which are more frequent in RPGN.2

Patient 1 (table) had focal and segmental hyalination with stable renal function over eight years. MPO-ANCA were present at the same time.
