Predicting who will progress to AIDS

At least four laboratory predictors available

The profound immune suppression that underlies AIDS was originally thought to develop soon after infection. Prospective studies of homosexual men infected with the human immunodeficiency virus (HIV) are, however, showing that the rate of progression from infection to AIDS is slow. At the recent fourth international conference on AIDS in Stockholm the consensus was that in homosexual men it takes an average of eight to 10 years to progress from infection to AIDS and that overall 75-90% of those infected will develop AIDS (R Edison *et al* and A Munoz *et al* fourth international conference on AIDS, Stockholm, 1988).^{1,2} [For the rest of this editorial all unpublished references in parentheses are abstracts from the programs and abstracts of the fourth international conference on AIDS, Stockholm, 1988.] Several studies of infected haemophiliacs and subjects infected by transfusion of blood products have reported similar results (C A Lee *et al*).^{3,4}

The epidemiological data suggest that AIDS should be thought of as the late stage of a long term mostly asymptomatic "HIV disease." Doctors must decide whether they want to use antiviral treatment in the long asymptomatic period, and thus interest in trying to predict which patients infected with HIV will develop AIDS is increasing. Four predictors that are being studied are the number of CD4 "helper" lymphocytes, the presence of the HIV p24 core antigen, and increased serum concentrations of β_2 microglobulin and neopterin.

CD4 lymphocyte count—In homosexual men infected with HIV peripheral blood lymphocytes bearing the CD4 phenotype decline by a mean of $60-100 \times 10^3/l$ a year from a normal value of $800-900 \times 10^3/l$. In the first few years after infection most men are asymptomatic and have counts of CD4 lymphocytes greater than $400 \times 10^3/l$: in three years about 14% of those men progress to AIDS.¹ About half of the asymptomatic men with counts of CD4 lymphocytes less than $400 \times 10^3/l$ progress to AIDS in three years; and about 90% of symptomatic men with fewer than 400×10^3 lymphocytes/l progress to AIDS (A R Moss *et al*).¹ These averages conceal, however, wide individual differences, making other predictors necessary. Counts of CD4 lymphocytes, though widely used clinically, are variable and a crude predictor of progression when taken by themselves. They are also expensive to perform and difficult to obtain in many countries.

HIV p24 core antigen—The p24 core protein of HIV is usually first detectable at infection; it appears again late in the disease.⁵ Some people, however, continue to be positive for the antigen from infection, and in them the disease progresses

rapidly (C A Lee *et al*).⁶ Between 10% and 20% of asymptomatic homosexual men infected with HIV have detectable p24 antigen on enzyme linked immunosorbent assay (ELISA) and are at high risk of progressing to AIDS. The results of tests for p24 antigen may be combined with counts of CD4 lymphocytes to improve predictions of which patients will progress to AIDS: about 45% of asymptomatic men with counts of CD4 lymphocytes above $400 \times 10^3/l$ and detectable antigen will develop AIDS in three years, whereas the figure for men with counts below this value and detectable antigen is about 80%. The rate of development of AIDS in this last group is comparable with that in men with AIDS related complex (A R Moss *et al*). The presence of the antigen also predicts AIDS in infected haemophiliacs (C A Lee *et al*).⁶ The usefulness of the test is reduced, however, by the measurement of antigen unbound by antibody on ELISA, which may give negative results long after infection—sometimes even in patients with AIDS. Additionally, the quantity of the p24 antigen is variable and is not a good predictor of progression to AIDS (D Osmond *et al*). Despite these limitations the assay is finding a clinical place.

β_2 Microglobulin—This protein, which is part of the major histocompatibility complex class I antigen, is shed into the serum of patients infected with HIV and other agents, and the serum concentrations of β_2 microglobulin may reflect lymphocyte turnover. The normal value of β_2 microglobulin in blood donors and uninfected homosexual men is 1.7 (SD 0.7) mg/l. Like the presence of p24 core antigen, serum β_2 microglobulin concentration spikes in acute infection,⁷ declines, then rises during the infection⁸ (E H Cooper *et al* and R E Anderson *et al*)—usually to values of 5.0 mg/l or more when AIDS is diagnosed (M A Jacobson *et al*).⁸ Serum β_2 microglobulin concentration predicts AIDS both independently and together with counts of CD4 lymphocytes: about a quarter of men who have counts of CD4 lymphocytes more than $400 \times 10^3/l$ and serum concentrations of β_2 microglobulin greater than 3 mg/l will progress to AIDS over three years, whereas as many as three quarters of men with lower counts of CD4 lymphocytes and equivalent concentrations of β_2 microglobulin will progress to AIDS in the same time (A R Moss *et al*).¹ In subjects infected with HIV raised concentrations of β_2 microglobulin clearly suggest progression to AIDS. Unlike the concentration of p24 core antigen that of β_2 microglobulin may be measured in any infected person. It is stable over the short run, predicts independently of p24, is clinically familiar

from monitoring allograft rejection, and declines after treatment with zidovudine (M A Jacobson *et al*). The concentration of β_2 microglobulin also has predictive value in haemophiliacs and intravenous drug users infected with HIV (E H Cooper *et al* and J I Wallace *et al*).

Neopterin concentrations in urine, and more recently serum, have also been proposed as predictors. Serum neopterin concentration is 5.4 (SD 2.3) nmol/l in uninfected people and rises steadily in people infected with HIV to 20 nmol/l or more when AIDS is diagnosed (D Fuchs *et al*).⁹ Like the presence of p24 antigen and serum concentrations of β_2 microglobulin serum neopterin predicts AIDS in homosexual men both independently and in combination with counts of CD4 lymphocytes (D Fuchs *et al* and A Kramer *et al*). As neopterin is produced from macrophages interest in it has increased as the importance of macrophages in HIV infection has emerged. Serum concentrations of β_2 microglobulin and neopterin are highly correlated (A R Moss, unpublished data), and so β_2 microglobulin may also be produced from macrophages. As yet neopterin has not been investigated in combination with other predictors in epidemiological studies, and it is not yet clinically familiar in the United States or Britain.

In San Francisco, where the art of prediction in HIV infection is evolving rapidly, counts of CD4 lymphocytes and the presence of p24 antigen are widely used to monitor patients infected with HIV, while serum β_2 microglobulin concentration is on the brink of acceptability as a predictor. It is not clear whether these or other predictors may replace CD4 counts when they are hard to obtain. Doctors will need more reports from the large epidemiological studies; the predictors

should also be explored for their usefulness in stratifying subjects for trials of treatment and as measures of outcome. Laboratory predictors have not been combined with clinical staging systems. Oncologists faced with similar problems of prediction evolved staging systems combining clinical and laboratory data for diseases such as lymphoma and breast cancer. The same process must now begin for HIV disease.

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Politics and the royal colleges

Be political but with sound data

At the beginning of this year the presidents of three of the royal colleges met with the then Secretary of State for Health and Social Security, John Moore, and complained about the deteriorating state of the National Health Service. After the meeting Mr Moore issued a joint statement admitting the need "for action . . . to increase the total resources for health care."¹ He was immediately denounced by the chief secretary of the Treasury, Mr John Major. This humiliating episode revived the debate about whether the royal colleges should intrude into politics.

The boundary between stated concern about standards of professional care and comments on political policies is ill defined. The accusation that an institution has become "too political" commonly relates to its criticising government policy. Controversy over the colleges' political activities is not new as was evident at the start of the NHS. Their charitable status stops them, however, from participating in such medicopolitical activities as negotiations on doctors' pay, a function carried out by the BMA's craft committees. But the government and doctors recognise the colleges' authority in setting standards in their specialties. So when political policies threaten these standards the colleges may well have something to say to the departments of health. One channel for representation is through the Joint Consultants Committee—set up in 1949² and comprising representatives of the colleges and the BMA's hospital and community doctors—which regularly meets with the departments'

officials. For general practitioners the General Medical Services Committee is the recognised representative channel, with the Royal College of General Practitioners advising on professional and educational standards.

The presidents of the London colleges (including the Royal College of General Practitioners) are also ex officio members of the only statutory standing committee that advises the government across the whole of medicine—the Standing Medical Advisory Committee. Both the Joint Consultants Committee and the standing committee have direct access to the chief medical officer and through him to the secretary of state, so the colleges rarely feel the need for direct access to ministers. Their members thus believe that the colleges' political activity is small.

Although instances of direct conflict with the government such as the recent visit of the three presidents to Mr Moore are rare, the colleges often engage in wider political debates. They have made public statements on several topics of political concern—for example, the Royal College of Obstetricians and Gynaecologists gave advice on the morbidity likely to follow the lowering of the gestation period for abortion, the Conference of Royal Colleges defined brain death,³ the Royal College of Psychiatrists advised on reducing alcohol problems,⁴ and the Royal College of Pathologists advocated the continuation of the Public Health Laboratory Service.⁵ The link between tobacco and lung cancer was first publicised by the Royal College of Physicians,⁶ and political recom-