The next step in AIDS treatment

The apparently well-founded discovery that AZT is not a useful drug for the treatment of people infected with HIV does not mean that it is useless in the treatment of those with AIDS.

THE drug AZT, an inhibitor of DNA synthesis, has been for several years the only treatment for those with symptoms of overt AIDS. Nobody has claimed that it can clear the infectious organism, HIV, from a person's system. Rather, it has been used as a retardant of the progression of AIDS, largely on the basis that it seems to sustain the subpopulation of T cells that appears especially vulnerable to HIV in the overt stage of the disease.

Later, beginning in the United states, AZT was also used in people infected with HIV but not yet showing symptoms of overt disease, again on the basis that administration of the drug appeared to abate the decline of vulnerable T-cell counts. But now a paper in *The Lancet* (**341**, 889; 1993) appears to some to have thrown a spanner in the works: certainly it has caused a furore of misinterpretation by newspapers and others.

The new development is a preliminary account of an Anglo-French controlled trial of the use of AZT (proprietary name Zidovudine) in the treatment of symptomless people. It is a substantial study, including more than 1,700 people infected with HIV and divided into matching placebo and treatment groups. Although the CD4 counts of the 877 people given AZT were consistently greater than those of patients receiving only placebo, the first three years of follow-up have shown that the proportions of people in the two groups progressing to overt AIDS or even to death were not significantly different at roughly 18 per cent. The conclusions are that AZT is not an effective prophylactic of AIDS in those infected with HIV and that the CD4 cell count may not be a reliable proxy for the progression to AIDS in infected people.

Of the two conclusions, the second is the more soundly based. The first, that AZT may be ineffective in postponing the development of overt AIDS, would be more persuasive if the length of the follow-up reported in this preliminary study had been greater. It is, for example, possible that those in the treated group who have succumbed are a particularly susceptible group within the whole; whether that is likely will be more easily assessed when the data so far gathered by the study have been analysed to show the fate of subgroups, for example those with different CD4 cell counts at their recruitment. The new data are, in any case, consistent with the conclusion of the Veterans' Affairs Cooperative Study, published a year ago (*New Engl. J. Med.* **326**, 437; 1992). In a comparison of the administration of AZT to infected people before and after the appearance of AIDS, early treatment was found not to affect the eventual outcome, but merely to postpone the rapid decline of CD4 cells in the blood.

The implications of these findings are not, of course, encouraging. On the face of things, the use of AZT as a prophylactic of the emergence of AIDS in infected people is ineffective; probably it will now be abandoned. But nothing is implied by the new study of the utility of AZT in the treatment of those in whom symptoms have already appeared; there is no case for abandoning that treatment, at least on the evidence now available. It is much more disconcerting that the CD4 count has been shown to be an unreliable indicator of the effectiveness of drug treatment in HIV infection. That, so far, has been the standard test. How quickly can those concerned with the search for new drugs switch to examination of lymph-node biopsy material for this assessment? Two recent articles in *Nature* by Fauci *et al.* and Haase *et al.* (**362**, 355 & 359; 1993) showed that these organs (among others) are sites at which the virus multiplies during the often long latency period in AIDS, but more will have to be known of this process before it can be the basis of a routine assay.

The reaction to these developments has been marked by a note of hysteria, at least in the British press. Variously, headlines have proclaimed a "bleak shadow over" or a "setback for" AIDS research. Those are justifiable, if only just. But another, in the *Sunday Times*, announces a page-long article under the banner "The cure that failed", goes on to boast of "How we broke the story" (in 1989) that treating AIDS patients with AZT might not be valid and then went on to complain that "doctors, en masse, have taken up [AIDS] as a crusade, at the expense of science". "Perhaps", it continues, "the worst feature of the medical and scientific professions' behaviour has been the enormous dominance of a single focus — HIV — for research, prevention and therapeutic efforts, to the exclusion of other approaches."

Three issues are raised by the nature of these reactions, one of which is the extremes to which criticism of both professions will be carried while there remains no cure for AIDS. It is an atavistic reaction, born partly of disappointment that decades of believing that infectious diseases are a danger past and partly from the underlying despair of those infected with HIV and the anger of the groups that represent them. It is also a dangerous reaction, if only because (in the United States at least) it is likely to mould programmes of AIDS research in directions that will not yield the benefits expected of them. Needless to say, those infected with HIV are unlikely to be much comforted by intemperate comment of this kind.

There is also a regulatory issue. AZT was approved in the United States in 1987 for use after symptoms of AIDS have appeared, after a controlled trial was brought prematurely to an end when it emerged that the treated group was doing better than the placebo groups. Similarly, the use of AZT in early AIDS was quickly approved after the appearance of a report on a controlled trial in April 1990 (*New Engl. J. Med.* **322**, 941; 1990). Those who now complain that these approvals were given too quickly overlook the sense of crisis which the spread of AIDS has engendered over the past decade, not to mention the eagerness of all concerned to match the pathos of those infected with HIV with anything that might be an effective medicine.

The position of the Wellcome Foundation, the chief manufacturer of AZT, is unenviable. Over the past few years, AZT has been the chief source of optimism about the company's fortunes. Just as the price of its shares rose dramatically at the outset, so it has now fallen. Yet there is no reason for anybody to believe that the company has behaved dishonourably. It is right now to insist that nothing in the Anglo-French study shows AZT to be ineffective in the late treatment of AIDS; it is to be hoped that point will be tested by a new controlled study. But the company is probably right also to say that several drugs in combination are likely to be involved in more effective drug therapy. Some of the justification for that may be the recent argument of Y.-K. Chow *et al.* *Nature* **361**, 650; 18 February 1993).

The pattern of AIDS research is also likely to be profoundly shaped by the events of the past few weeks, but more importantly by the articles by Fauci and Haase and their colleagues than by the preliminary report of the Anglo-French study. The first and obvious need is to turn the knowledge that HIV is alive and all too well, from the outset of infection, into a workable assay of the progress of disease.

The general application of such as assay will probably in itself provide a better understanding of the pathogenesis of AIDS. But the way in which the lymph nodes (like some other organs of the immune system) sequester replicating HIV particles is so unexpected that it may well point to unexpected and more effective means for the treatment of AIDS. All that, of course, would be based on what the sceptics insist on calling the 'HIV hypothesis': there is no other, and thus no choice.

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