

DRUGS FOR AIDS: HOPES, NEW CHALLENGES

BY

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The estimated number of persons with AIDS in the world increases inexorably year by year. Most cases of the underlying HIV infection are now transmitted heterosexually and the proportion of women among those infected is rising. The risk of mother-to-child (or vertical) transmission of the disease has been estimated to range from some 15% in Europe to as high as 35% in Africa (1), and the disease is already reported to exert a substantial impact on childhood mortality both in developed and developing countries (2, 3)

these demographic trends have been followed by maintaining national registers of HIV-infected children, and by anonymous testing of antenatal and neonatal blood samples (4). For as long as therapeutic intervention was without demonstrable influence on the risk of transmissions, this post facto record of events simply served to alert the world to the gravity of the disease. However, the situation has now changed dramatically with the demonstration that perinatal use of zidovudine substantially reduces the risk of the infant becoming infected (5,6). There is even hope that antiseptic applications to the birth canal might have similar effect (7).

It has suddenly become of vital importance to both mother and child for HIV infection to be identified in advance of parturition. However, there is still much to be achieved. The results of many further clinical studies conducted in different settings are needed to provide a basis for refining and simplifying perinatal zidovudine therapy. The aim must be to reduce the complexity and the cost of the intervention to the fullest extent possible without loss of efficacy in order that the benefits can be shared by the maximum number of people.

The success of this programme of clinical investigation and the speed with which it can be accomplished will be vitally dependent upon the willingness of those who have risked infection to come forward and seek medical advice as early as possible. Perceived or valid concerns that this confidential information could filter into other channels and expose them to some form of disadvantageous discrimination is an important dissuasive influence. Even in countries where official policy encourages people to seek medical advice early about the possibility of HIV infection (9) there is widespread reticence within the population to respond. Throughout London as few as 12% of the total number of pregnant women known to be HIV positive by anonymous testing are currently consenting

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to voluntary named testing, after being encouraged to do so in antenatal clinics(10). Similar reticence is a cause of concern within the USA (11)

It has been suggested that, as management of the condition is improved and as stigmata attached to HIV infection and AIDS are eroded, HIV testing may come to be accepted as "routine" alongside testing for rubella, syphilis, and hepatitis B virus (12). This is doubtless true, but there is a need for governmental involvement that will encourage and promote this process. The need derives from evidence now accumulating that improved management of the condition, whether it is incurred perinatally or latter in life, will be dependent upon confirmation of suspicion of HIV infection at the earliest possible moment in the course of the disease.

Most tellingly, two independently conducted studies reported in the same issue of The New England Journal of Medicine within the past few months indicate that to be effective in ameliorating the course of the HIV infection, zidovudine needs to be started during the primary infection (or the acute retroviral syndrome) rather than later in the asymptomatic period (13, 14). Indeed, there is now optimism that it may prove possible to suppress, or even to eradicate HIV infection by using two or three different types of antiretroviral drugs in combination at the earliest stage of infection (15).

That the evidence to support this expectation was collected at all demonstrates the dedication and commitment of the investigators involved: it took, for instance, 33 months at 27 centers in eight highly development countries to recruit 77 patients in the phase of primary HIV infection. It seems that only a small minority of persons, apprehensive that they may have contracted HIV, are prepared to come forward promptly to obtain medical advice. Yet, in a future that may not be far distant, prompt treatment may be the determinant of whether the patient's disease is eradicated, or whether it progresses to AIDS.

Suddenly, pessimism about the value of antiretroviral therapy has been dispelled. Zidovudine holds far more promise than was credited to it a year ago. Several analogous drugs are already available. More such drugs are under development. Some of them attack different stages in HIV's replication mechanism. They will need to be compared with each other; they will need to be tested in combination; optimum dosage regimens will need to be defined; and unwanted effects will need to be monitored and investigated. To achieve all of this within the time frame that urgency demands will require the collaboration of many infected patients, and these patients must be identified and encouraged to collaborate at the earliest stages of infection.

However, lessons from the past show how readily urgency can generate disruptive pressures. Clinical studies of zidovudine have been plagued in the past by cycles of over-optimism followed by disillusionment; by desperation among the patients whose lives are at stake; and by calls from politicians and the public at large to accelerate the clinical assessment of candidate drugs. Scientific discovery cannot be accelerated by proclamation. To attempt to do so risks to place science itself in disrepute. A picture has recently been portrayed in Science (16) of disillusioned and deseperated patients prepared in the

late, symptomatic stages of infection to "cheat to get into clinical trial protocols, fail to follow the trial protocols, and drop out in record numbers".

It is a tribute to scientists in the United States and Europe that, against this background, so much secure fundamental knowledge about HIV and the disease that it causes has been generated over the past decade. The opportunity may not well exist to convert this investment into secure therapeutic gains. If, at best - and it remains far from certain at this state- it should prove possible to cure HIV infection by hitting the virus early and hard with combinations of antiretroviral drugs (15), the pressure will be on achieve global eradication and to move ahead as quickly as possible before the virus evolves its own defence against attack.

This feat has never yet been accomplished with a sexually transmitted disease. In any circumstance it will be a challenge of virtually unprecedented scale and complexity. It will be impossible for as long as the disease is perceived as a stigma that merits discrimination; for as long as society is judgemental rather than compassionate in its attitude; and for as long as those afflicted feel a need to hide away in shame. Much can be accomplished by education, but little by repression. Now that the promise of real therapeutic gains are on the horizon, the failure of those affected to seek help voluntarily could prove to be the greatest impediment to success in controlling the disease.

Policy makers in developing countries will undoubtedly question searchingly the relevance of these developments to their own circumstances. Too often in the past, their populations have reaped scant benefit from tangible technical advances taken for granted elsewhere. Diagnostic tests have been developed for screening blood for transfusion against HIV and other pathogenic viruses. Advances have been made in the diagnosis and therapy of pathogenic and opportunistic infections. But tangible - often, prohibitive - expense is involved in assuring the safety of the unit of blood, or in prescribing a reserve antibiotic to a patient who fails to respond to primary therapy. In fact, a gulf is being cleaved everywhere between what is possible and what is practicable to provide in the health sector. This creates a dilemma for governments, a quandary for its legal institutions and, above all, and inextricable predicament for the medical and allied professions. forced to compromise standards through lack of resources, doctors are at risk of accusation of negligence or worse whenever their professional judgements are called into question.

Against this background, the development of a vaccine that protects against HIV infection, or of a drug that either cures the infection, or suppresses it to the extent of interrupting transmission will have to be treated as a matter of global significance. The more decisively the disease is attacked from the outset, the greater is the likelihood that it will be effectively controlled. The countries best placed to benefit will be those that have inculcated attitudes towards HIV infection in anticipation of the therapeutic benefits about to stem from the technical advances now in the making.

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