tales of the (apparently) UNINFECTED

In the last Positive Nation, we reported on a study that confirmed one of the best-kept secrets of HIV - that there are substantial numbers of people out there who show signs of contact with HIV, including alterations in their immune systems, but who do not test HIV positive (see "HIV negative - but 'infected'", page 14, PN 49/50). No one knows how much HIV these people have in their systems, whether they can infect others, or will eventually get ill. We asked the renowned HIV doctor Joseph Sonnabend to comment on this neglected corner of the epidemic.

Research on HIV has been spectacularly successful in advancing our understanding of how viruses reproduce. Most importantly, while a cure for Aids may not be a realistic possibility now; we finally have, after many horrible years, treatments that can make a significant impact on the course of the disease, even if these are far from perfect. With these successes it might seem that it would be difficult to identify areas of research that have been neglected. However, in my view, there is one unsolved problem that has been ignored, and could have been pursued since about 1985. This concerns Individuals who have been exposed to HIV, sometimes repeatedly, but who remain healthy and do not even become HIV antibody positive.

I am not referring to the so-called 'long-term non-progressors'. Perhaps about five per cent of individuals who are HIV antibody positive will not progress to Aids, or progress very slowly, and the basis for this is already being studied.

But what has been neglected is that there are people who are exposed to HIV but remain antibody negative. Based on what we knew about how retroviruses reproduce, as far back as the 1970s, it was always likely that there would be such individuals.

I will firstly outline some of the evidence that there are indeed such people, and then indicate the possible benefits that might result from understanding this phenomenon.

Around 1984, a scheme of the perceived course of HIV infection was confidently presented that stated that after a "window" period of a few months all infected persons became antibody positive, following which the CD4 T-lymphocytes commenced an inexorable decline for the next 11 years until full-blown Aids developed. There was however no factual basis to support this scenario as the inevitable outcome of HIV infection. We had no precedents of human retroviral infections on which to draw analogies, which in this case were derived from the course of more conventional viral infections, such as measles or polio.

Retroviruses are different. As part of their life cycle they insert their genetic material, (which is converted into DNA) into the DNA of the host cell. In effect, it joins our genes. It becomes part of our substance.

The next step is that the spliced-in HIV DNA is activated by various signals to start the process of making **new** viral particles. We know about a lot of these signals; they are the cellular messenger chemicals, the cytokines.

Once enough HIV proteins start appearing - as free-floating virus or expressed on the surface of cells - then antibodies are made. Antibodies are protein molecules whose job is to neutralise foreign substances, either directly or by labeling infected cells for destruction. The initial infecting virus probably does not represent enough protein to elicit an antibody response, and this only happens when large numbers of viruses start to be produced by infected cells in which HIV DNA has become activated.

The trouble is that there has never been any evidence that the first step - infection of the cell and insertion of HIV DNA into our genes – is always followed in some weeks by the second step - activation of HIV

DNA, with the release of many new viruses and the production of antibodies. Infection and seroconversion - the production of antibodies –are two different things, and there is no evidence that one leads inevitably to the other.

Seroconversion illness - the flu-like symptoms that accompany antibody production - is cited as evidence for the traditional point of view, in that it always seems to take place roughly the same number of weeks after exposure to HIV. However, despite claims that these so-called primary infection symptoms are usual, they may in fact occur rather infrequently.

Many people recall no primary infection symptoms despite testing antibody positive. It is also the exception rather than the rule that the time of exposure can be ascertained.

A more radical suggestion is that the primary illness may sometimes represent a pre-existing latent HIV infection that is suddenly activated - either by another exposure to HIV, or to a different infection altogether.

The first actual evidence supporting the possibility that infection may not always be followed by seroconversion came about 10 years ago, when it was shown that HIV negative people exposed to HIV through sex or infected needles, while having no antibodies, did have other kinds of immune responses to HIV. Their immune systems recognised HIV, and the fact that they were antibody negative was attributed to infection with defective viruses or to some capacity to rid their body of the virus. A few, of course, may have been in the 'window' period.

The possibility that they were indeed infected with HIV, but had the capacity to maintain the virus as a truly latent, inactive infection was hardly considered.

These observations, that some people who remain antibody negative have immune systems that can still recognise HIV have been witnessed several times using different techniques. This year, at the Chicago Retrovirus Conference and later, in an article published in the Journal of Infectious Diseases, the presence of dormant, unexpressed HIV DNA was shown in some of these individuals. It is quite puzzling why this important observation did not capture the imagination of those who report on developments in HIV research.

The traditional course of infection, with early seroconversion, may indeed be what happens most frequently. But since there do appear to be at least some people who do not become antibody positive and remain well, it might be useful to look at the establishment of a progressive infection as needing two events with each having its own risk factors -although these may overlap. The first is the infection of the cell with insertion of HIV DNA into our genetic material. The second is seroconversion, which follows the activation of HIV DNA. We know some of the factors that can activate viral DNA – the cytokines produced during the course of common infections.

From analogies with other latent viral infections, even this may not be enough to result in seroconversion because the immune system may destroy cells that are staring to produce HIV.

Again, since there are people who can remain infected, antibody negative and well, we have to ask what is happening in those who are less fortunate.

The fact that there are HIV antibody negative people who are infected with HIV but who seem to remain healthy is important for these reasons;

It shows us that it is possible to live with HIV in good health, possibly for a full life span.

If we understood the mechanisms involved in such a response, new therapeutic approaches might be developed.

It shows us that immunisation is possible, because many of the individuals studied were repeatedly exposed.

If we knew what underlies this immunity this could lead to new approaches to vaccine development.

It means that the epidemiology of HIV infection as we accept it may be quite wrong. What we know is the distribution of HIV seropositivity.

This may not equal the distribution of HIV infection.

We could start to clear this up in several ways, but one suggestion is to look for HIV by genome detection techniques in a large number of unselected autopsies in high incidence areas.

Athough difficult now, ascertaining the time of infection will be even more problematic.

This potentially fruitful area of research might have begun almost as soon as HIV was discovered if a rigid and really rather fanciful picture of the course of HIV infection had not been so persistently disseminated as fact rather than speculation.