# Natural Immunity and HIV

October 19, 2010 By Joseph Sonnabend, MD

A current supplement to the Journal of Infectious Diseases is devoted to natural immunity to HIV infection.

It's focus is on individuals who have been repeatedly exposed to HIV but remain seronegative. Several different genetic and immunological mechanisms have already been discovered that can account for their apparent resistance to infection. The best known may be the inherited absence of a particular cell surface molecule that HIV needs in order to infect a cell as a result of a genetic mutation (CCR5delta32).

Gene Shearer, a pioneer in the study of HIV exposed seronegative individuals published some of the earliest reports on this phenomenon. In this journal supplement he with Mario Clerici estimate that about 10 - 15 % of individuals repeatedly exposed to HIV remain uninfected.

They note that in the first years of the epidemic "little attention was given to the chance observation that mucosal [or] parenteral exposure to human immunodeficiency virus type 1 (HIV) would not consistently induce infection, and none to the possibility that such putative non-infectious exposures might induce protective immunity ".

I can't recall that there ever was an assumption that mucosal or parenteral exposure to HIV would consistently induce infection. This would have accorded HIV the probably unique ability among infectious agents to infect 100% of those exposed to it. However I certainly recall that in the earliest years after HIV was discovered it was assumed that infection would invariably lead to disease. HIV infection, it was claimed was like a Mack truck with nothing but time standing in the way of its inevitable progression to disease. This too would have made HIV infection almost unique among infectious diseases. Rabies may be the only infectious disease where 100% of infected (and unvaccinated) individuals become ill, although I believe some exceptions have been described.

The rapid acceptance of the assumption that HIV infection always leads to disease was quite remarkable at that time, as there could not yet have been sufficient observations to justify ascribing such an unusual property to HIV infection. Yet this view was so firmly held by the HIV research leadership that it was left to AIDS activists to alert them in the 1990s (1) to the fact that there were indeed individuals who appeared not to have progressive disease, or whose disease progressed very slowly.

By 1981 we had come to understand that infection and disease are not synonymous terms. But it almost seemed that this important lesson learned at least a century ago had somehow been

ignored by some of those producing a detailed picture of the course of HIV infection at a time when so little was known about it.

These words were written by Rene Dubos, a great microbiologist, in "Man Adapting" published in 1966.

*".....this approach requires that the determinants of infection be separated conceptually from the determinants of disease; its objective will be to understand and control the processes responsible for converting infection into overt disease"*

That there is a distinction between infection and disease is something I learned as a medical student in Johannesburg in the 1950s which I in turn tried to pass on when I taught medical students in New York in the late 1960s until 1977. Even in the first years of the epidemic I sent copies of Man Adapting to several individuals involved in the early response as I was discovering with surprise that some concepts that I thought were firmly established in our understanding of infectious diseases seemed all too frequently to have been forgotten

Rene Dubos, was associated with the Rockefeller University in New York for 50 years. He was a towering figure. His writings helped move us beyond the oversimplification that is the germ theory of disease.

While recognizing that the doctrine of specific etiology - as represented by the germ theory of disease was "the most powerful single force in the development of medicine", he also wrote that "there is now increasing awareness that it fails to provide a complete account of most disease problems as they naturally occur".

Rene Dubos died in 1982, one year after AIDS was first recognized. The "now" in the above quotation refers to a period before 1966, when "Man Adapting" was published. The increasing awareness of the limitations of the doctrine of specific etiology had apparently dissipated by 1981, at least in the medical response to AIDS. At that time, genetic factors, socio- economic factors, behavioral factors, the effect of concurrent infections, or anything else were not going to slow the Mack truck. By 1990, only six years after HIV had been discovered we were also told that, except for a period of 3 to 6 months after infection, called the window period, tests for HIV antibodies could not fail to detect infection.

But reality cannot be held at bay indefinitely, and to the surprise of some there did indeed appear to be individuals who were HIV infected but were able to control the infection to varying degrees, as well as those who were infected for prolonged periods but had no detectable antibodies. However when the first reports of these phenomena appeared, the authors were subjected to a torrent of outraged criticism, much of it abusive.

David Imigawa and The Window Period.

In 1989 David Imagawa, reported that in 31 of 133 HIV antibody negative individuals it was possible to detect the presence of the virus (2) for periods longer than 6 months. In 27 of these individuals, HIV continued to be detected for up to 36 months despite remaining HIV antibody negative. This publication in the New England Journal of Medicine resulted in a furious response

culminating in a letter to the New England Journal of medicine from David Imagawa and Roger Detels that almost appeared to be a retraction but certainly was not.

David Imagawa and his colleagues were subjected to hostile and baseless criticism, not only from leading researchers but also from journalists.

This is the headline of a story in the New York Times in 1991 which will give some idea of the kind of response the report received.

**THE DOCTOR'S WORLD; Researchers in Furor Over AIDS Say They Can't Reproduce Results.**

This is how the article starts:

"THE scientists who came up with one of the most shocking scientific findings about AIDS -- one that set off alarms concerning the safety of the blood supply and about the state of mind of people at risk -- now cannot reproduce their own results. But they still have not said clearly that their finding was incorrect".

It includes this statement:

"Even this confusing letter would not have appeared without constant pressure behind the scenes from officials of the National Institutes of Health who paid for the original research and who were determined to try to straighten the record".

But how secure was the record from which David Imagawa and Roger Detels had strayed?

In 1989, only 5 years after the discovery of HIV, with the relatively little experience that had then accumulated, we could only be at a stage of establishing a record. There was no firmly established record at that time when activists had yet to alert officials that long term non progressors really existed.

Whatever attributes science possesses that distinguishes it from more metaphysical pursuits surely one is a requirement to as best as we can describe phenomena as they are, rather than as we might wish to see them.

The constant behind the scenes pressure exerted on David Imagawa noted by the New York Times seems more like demands made on an apostate to recant.

David Imagawa's observations were in fact correct. Similar observations have been made by others.

Sadly he did not live to experience the vindication of his pioneering studies. He died of a heart attack shortly after the New York Times article appeared.

A fairly detailed account of the course of HIV infection had been constructed only 5 to 6 years after the discovery of HIV that had no place for prolonged seronegative infection. This account is illustrated in the very familiar diagram of the typical course of HIV infection that appeared in the 1990s.

The rapid acceptance in those early years that there even was a typical course of HIV infection is particularly odd as not **only was the disease newly recognized, we then had no precedents of human retroviral diseases (apart from HTLV-1** associated disease); the techniques used to study the disease were themselves new. The ability to identify T lymphocyte subsets with monoclonal antibodies is about as old as the HIV epidemic. So we had no idea at that time of the variation in T subset numbers in health and disease. Other new immunological and virological techniques were, and continue to be introduced.

At that time, only 5 to 6 years after the discovery of HIV there could not have been a solid enough

empirical foundation to justify the confident assertion, in the case of sexually transmitted HIV that there could not be situations where integrated HIV DNA is carried for prolonged periods without seroconversion. Unlike infections acquired by blood or blood products, the time of initial infection can rarely be known. The infecting dose of virus in the case of sexual transmission could be even orders of magnitude less than that when infection is acquired by blood transfusion.

How then to account for the persistence of recoverable virus for up to 36 months in the absence of seroconversion?

In the original New England Journal of Medicine publication David Imagawa and his colleagues raised the possibility of "silent" HIV infection, suggesting that HIV in the form of proviral DNA integrated into the genome could persist without production of HIV virions. This is a perfectly reasonable suggestion.

But in their subsequent letter, they changed their minds and ascribed their finding to the ability of the men to overcome the infection. Because of continued high risk activity virus was repeatedly detectable. In a more recent article Roger Detels expands on this explanation, noting: "The fact that we isolated HIV ONLY from those men who continued their high-risk exposure suggested that transient infection and clearance of HIV was the more likely explanation".

Of course this may be the explanation. If so, HIV sequences should have been consistent on repeated isolations, whereas if infections were transient, variations would surely have been seen between repeated isolates. This is because HIV, when it is in the form of DNA, remains unchanged. Sequence variations between different virus isolations may have been reported somewhere.

But in another report of prolonged carriage of HIV DNA in seronegative individuals, sequences remained constant (3). In the abstract of this paper the authors note: (ES refers to exposed seronegative individuals)

"*Some individuals remain inexplicably seronegative and lack evidence for human immunodeficiency virus type 1 (HIV-1) infection by conventional serologic or virologic testing despite repeated high-risk virus exposures. Here, we examined 10 exposed seronegative (ES) individuals exhibiting HIV-1-specificcytotoxicity for the presence of HIV-1. We discovered HIV-1 DNA in resting CD4(+) T cells (mean, 0.05 + /- 0.01 copies per million cells) at multiple visits spanning 69 to 130 weeks in two ES individuals at levels that were on average 10(4)-to 10(6)-fold lower than those of other HIV-1-infected populations reported. Sequences of HIV-1 envelope and gag genes remained markedly homogeneous, indicating little to undetectable virus replication. These results provide the evidence ..... suggesting that extraordinary control of infection can occur. The two HIV- infected ES individuals remained healthy and were not superinfected with other HIV-1strains despite continued high-risk sexual exposures to multiple HIV-infected partners.* ***Understanding the mechanisms that confer diminished replicative capacity of*** *HIV-1* ***in these hosts is paramount to developing strategies for protection against and control of*** *HIV-1* ***infection*****".**

At the heart of the furious response to David Imagawa's observation was the fear it might have raised about the safety of the blood supply and the peace of mind of those testing HIV negative. Roger Detels in the article linked to above makes these comments:

"We were presented with an ethical dilemma -- should we publish knowing that there was a possibility that the publication would create panic, or should we not publish to prevent the panic? "

As far as the blood supply is concerned, the most reliable data on the window period were derived from observations on transfusion related infections, and antibody tests have been hugely effective in ensuring the safety of the blood supply (even without additional tests reducing the risk to less than 1 in 1,000,000). So the New York Times article and others like it were quite unjustified in raising fears for the safety of transfused blood based on observations made on sexual transmission.

As far as the peace of mind of individuals testing negative is concerned, if there should be those who are able to maintain HIV in latency in the form of proviral DNA, that is never fully expressed,

it’s entirely possible that in some of these individuals, HIV has had an immunizing effect rather than causing productive infection.

It appears that to this day the reluctance to even consider HIV seronegative infection persists.

Returning to the supplement of the Journal of Infectious Diseases dealing with natural immunity to HIV, the possibility of stable HIV infections that remain unexpressed is not considered at all as at least one explanation for the continued absence of antibodies in some individuals exposed to HIV. It seems to be just taken for granted that these individuals are resistant to infection.

We are told:

*Approximately 15% of HIV exposed seronegative individuals repeatedly resist infection, a phenomenon that has been observed in all investigated HIV?exposed cohorts.*

But how can it be known that all of these seronegative individuals exposed to HIV have resisted infection? Some may carry HIV in the form of unexpressed proviral DNA. Even if this is not detected in cells circulating in the blood stream this does not mean a great deal as only a tiny minority of CD4 + cells circulate, and the DNA containing HIV may be in cells without the CD4 receptor.

If HIV can be carried in a stable integrated form as proviral DNA, that is not expressed at all or only partially and intermittently expressed, then this may be the basis for the apparent resistance of some ESNs. Such an individual would not be resistant to infection, but for probably a variety of reasons connected both with the virus, as well as the host, infection is aborted at the stage of integration.

We know some of the signals that can activate HIV DNA to start the process of making new viral particles. Some cytokines are potent activators of HIV and can also appear during the course of other infections. In the absence of sustained activating signals and with a small infecting dose of virus abortive but persistent infection might occur. If there is very limited viral replication this may be sufficient to induce a cell mediated immune response, ensuring that cells expressing HIV antigens are killed, as is the case with EBV infected B lymphocytes.

HIV infection, like other chronic viral infections can progress in different ways. If we had been more open to this, rather than trying to discourage work that did not conform to the early preconceptions about the course of HIV disease there may have been greater interest and funding into research that investigates the various factors that influence how the disease progresses.

This is a slightly changed and shortened version of something I posted elsewhere and contains material written last year. HIV infection in seronegative individuals.

http://www.poz.com/articles/hiv_macs_anniversary_401_16589.shtml

"Gonsalves recalls a meeting with Anthony Fauci, MD, head of the National Institute of Allergy and Infectious Diseases, in the early 1990s. He and fellow activist Mark Harrington, along with a New York City physician named Joseph Sonnabend, explained to Fauci that Sonnabend had a small group of patients with HIV who didn’t seem to have disease progression. They wanted Fauci to explore this phenomenon--and it was the MACS that took up the question.

Phair says he and other MACS researchers confirmed the existence of these nonprogressors ...."

2:

Imagawa, D.T., M.H. Lee. S.M Wolinsky. et al. Human immunod eficiency virus type 1 infection in homosexual men who remain seronegative for prolonged periods. New England Journal of

Medicine 1989 320:1458-1462.

3:

Persistence of extraordinarily low levels of genetically homogeneous human immunodeficiency virus type 1 in exposed seronegative individuals.

Journal of virology, {J-Virol}, Jun 2003, vol. 77, no. 11, p. 6108-16,

Zhu-Tuofu, Corey-Lawrence, Hwangbo-Yon, Lee-Jean-M, Learn-Gerald-H, Mullins-James-I, McElrath-M-Juliana.

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