A New Twist in the HIV/AIDS Saga

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Although the correlation between human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) is undeniable, the AIDS debate concerns a critical question: 'Is HIV both a necessary and sufficient cause of AIDS, or is it only a necessary but not a sufficient cause?' While the majority of retrovirologists represented by Robert Gallo et al. adhere to the first view, the second has been held by a small minority headed by Peter Duesberg. This second view was completely rejected and Duesberg lost his credibility. However, the critical question has been put back in the scientific news as a result of two breakthrough experiments by Canadian and British scientific groups. Hoffmann et al. (the Canadian group) found that mice injected with T-cells from another mouse strain (never exposed to HIV) generate HIV antibodies against P24 and GP120 of which they were innocent. Their explanation was that AIDs could be an autoimmune disease in which T-cells have lost the 'anti-self' interdiction. The British experiment of Stott et al. reported that two of four control macaque monkeys were protected and immunized against simian immunodeficiency virus (SIV) despite the fact that the vaccine they had been inoculated with had never seen SIV either alive or dead giving the possibility that SIV may not be the sole determinant of anti-SIV production. These new experiments and the old arguments have emphasized how little we still know about AIDS and HIV despite the huge amount of information gathered. There is still a long way to go before many questions concerning AIDS can be answered.

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In recent years, a great dispute has surfaced about the relationship of HIV and AIDS. The main debate is whether HIV is both necessary and sufficient to cause AIDS?; or is HIV only a necessary but not a sufficient cause of AIDS? These two opposing views were contradictory and
while the majority of retrovirologists represented by Blatter, Gallo and Temin adhered to the former view, a minority headed by Duesberg challenged them and stuck to the latter view. This article attempts to give a balanced review of both sides of this argument. Peter H. Duesberg, the well known virologist and a professor of molecular biology at University of California (Berkeley), USA has achieved a certain notoriety in the past 5 years because of his unorthodox theory of AIDS.\textsuperscript{1-5} He thinks that the question of a causal relationship between the lentivirus human immunodeficiency virus and AIDS is wrongly framed, and his view is based on four main points. First, HIV violates Koch’s postulate\textsuperscript{7} as HIV does not reproduce AIDS when inoculated into chimpanzees; they develop antibodies to HIV indicating their susceptibility, but they never develop AIDS even after being seroconverted for more than 5 years.\textsuperscript{8} Second, HIV synthesis is detected only in one of $10^4$–$10^6$ T-cell lymphocytes, so the virus expression is at a low level which cannot account for the loss of T-cells which is considered the hallmark of AIDS. Even if all the actively infected T-cells died, then during the 2 days it takes for a retrovirus to replicate, the body generates about 5% more than enough to compensate for the presumptive losses.\textsuperscript{9} Third, AIDS occurs despite the presence of anti-viral immunity as evidenced by anti-HIV although, in all virus infections, the presence of antiviral antibodies signals a successful rejection of the virus concerned. HIV does not follow this universal viral rule. Fourth, there is the long latent period that may extend from 2 to 20 years or more between HIV infection and AIDS. That prolonged latency is incompatible with HIV replication as while models of other lentiviruses as Visna/Maedi virus either cause rapid acute, or slow subacute infection, or asymptomatic latency so Visna/Maedi virus is either eliminated by the immune response or restricted to latency. In other animal models which can develop simian or feline AIDS, all show high infectivity and the respective disease appears shortly after infection of the monkey or the cat respectively.\textsuperscript{8} From these points and more, Duesberg put his view that states in short that HIV is a necessary but not sufficient cause of AIDS.\textsuperscript{1-4,8,9}

Duesberg's numerous opponents represented by Blattner, Gallo and Temin\textsuperscript{6} contradict this view and consider HIV to be both a necessary and sufficient cause of AIDS.\textsuperscript{6,8} They gave their views on and criticism of all his points as they discussed that accidental needlestick injuries with HIV contaminated blood have resulted in HIV seroconversion and clinical AIDS, while the fact that AIDS symptoms have not been obtained in anti-HIV-positive chimpanzees has a parallel in simian viruses which can be transmitted between tolerant and non-tolerant species (example African green monkey and Rhesus macaque).\textsuperscript{8} And though it is true that HIV infects only a small fraction of T-cells, about 15% of the macrophages and monocytes in AIDS patients are positive for viral protein P24 and the high concentration of P24 in AIDS cases indicates HIV activity, while the exact mechanism of T-CD 4\(^+\) cells depletion in AIDS cases is not yet fully explained.\textsuperscript{8} Regarding the occurrence of AIDS despite the presence of HIV antibodies, Blattner, Gallo and Temin stated that many viruses become highly pathogenic after evidence of immunity appears. For example, reactivated herpes zoster causes shingles, reactivated herpes simplex causes local lesions as well as lethal encephalitis, hepatitis B virus causes chronic active hepatitis, and Visna/Maedi virus causes degenerative central nervous system lesions after the appearance of the specific neutralizing antibodies, and all these diseases have long latent periods.\textsuperscript{8}

Duesberg’s theory, largely ignored by the mainstream scientific community, had been buried in April 1988 by the American Foundation for AIDS Research.\textsuperscript{4} Since then, Duesberg had lost his credibility and been silenced and threatened with suspension of his research funds and even his scientific job.\textsuperscript{10} That was the drama of his life.

But the AIDS saga did not stop, as very recently in September 1991 two breakthrough research experiments were reported that may give some small support to Duesberg’s long fight for his theory. These came from two high calibre scientists in Canada and the UK. Tracy Kion and Geoffry Hoffmann of British Columbia, Canada found that mice injected with T-lymphocytes, from another mouse strain, that were never exposed to HIV in any form generated HIV antibodies against two main gag and env gene-encoded proteins P24 and GP120 respectively.\textsuperscript{10-12} The question raised was how can a mouse develop antibodies against protein constituents of a virus of which it is innocent? The explanation given by these authors is that AIDS could be essentially an autoimmune disease in which T-cells have lost the normal ‘anti-self’ interdiction and so, instead, kill each other.\textsuperscript{11} Alternatively the GP120 of the env HIV coat is likely to carry a close structural similarity to Class II major histocompatibility complex (MHC) protein, or the HIV might have evolved to ‘fool the body’ into thinking that it was like the MHC antigens.\textsuperscript{12,13}

The other experiment was by Stott \textit{et al.} from The National Institute For Biological Standards,
Herts, UK. They reported their findings on the macaque monkey (Macaca fascicularis) which is usually used as a simian system to model the HIV vaccine programme researches, as the macaque monkey if infected with a simian immunodeficiency virus (SIV) develops a disease similar to AIDS in humans.

This British group immunized a group of four animals with formalin-inactivated human T-cells (C-8166 cells) that had been infected with SIV, at week 0 and week 4, and another four macaques with identical T-cells (C-8166 cells) that had not been infected with SIV. Three animals of the first group were protected against a later challenge at week 6 with SIV as expected, while two of the control group of four were also protected despite the fact that the vaccine they had been inoculated with had never seen SIV either alive or dead. This means that an immune response against foreign cells protects against infection with SIV.

In other words it seems that the presence or absence of SIV is not the sole determinant of the production of antibodies apparently diagnostic of vulnerability to infection. When the protected animals—in the previous experiments—were re-vaccinated at week 27 and re-challenged at week 29, two of the first group, and one of two of the second group were protected, while four of four unvaccinated controls became infected. And it was noticed that the uninfected cell vaccine did not produce SIV antibodies, and all the vaccinated animals gave anti-C-8166 (10-fold higher than the infected ones). This could mean that the distinctive diagnostic feature of the protection against a later challenge with SIV is the level of antibodies against T-cells from which the vaccine was derived. This experiment led to the conclusion that the antibodies directed against the host cell antigens could inhibit the release of virus from cells infected with the virus. Possibly therefore, the release of SIV was reduced by immune interaction between host cell determinants on human T-lymphocytes and antibodies stimulated in the macaques by inoculation of these human cells.

It is difficult to make a general conclusion on these matters. The correlation between HIV and AIDS is undeniable, yet the previous debates and the two new experiments have shown how slight is our current knowledge about the AIDS/HIV problem. However, since the discovery of HIV an extraordinary amount of information about AIDS/HIV has been accumulated. Indeed AIDS has been studied much more than any other disease in history. Despite all this knowledge there are still many questions to be answered. We can not support the view that says HIV is a necessary but not sufficient cause of AIDS, as by that view HIV would be an ‘idle’ virus and its role would be to trigger a chain of immunogenic processes that eventually result in the destabilization and self-destruction of the immune system. Even if the involvement of HIV in AIDS was of such a passive nature we have to call it necessary and unless other exogenous stimuli are required that are not inevitably linked with HIV infection, also sufficient for the causation of AIDS.

Irrespective of how one might assess the new findings, one might use the Latin legal question ‘In dubio pro reo’ or ‘Who is to be blamed for AIDS?’. To answer this very difficult question, we need to know more about HIV, the cell(s) it infects, and the pathogenic mechanisms before we can decide whether HIV is only a necessary, or both a necessary and a sufficient cause of AIDS. It is possible that the new findings may cause a revolution and complete reappraisal of HIV researches and the progress towards therapy and prophylaxis for AIDS.

References