The Sink and the Murder Scene: Rise and Fall of a Causal Model for AIDS Pathogenesis

Vincenzo Crupi
Department of Cognitive and Education Sciences, University of Trento (Italy)
e-mail: vincenzo.crupi@unitn.it

1. Introduction
Although a remarkable body of relevant knowledge has been collected over the years, AIDS pathogenesis has been challenging researchers for more than two decades. In what follows we will focus on an important episode in the history

© The Author 2007
Published by L&PS – Logic and Philosophy of Science
http://www.units.it/~episteme/ – ISSN: 1826-1043
of AIDS: the proposal and overcoming of an account of AIDS pathogenesis, the “sink model”, which has been widely influential and discussed. A brief exposition of the historical background and problem situation is given at first, followed by a reconstruction of the model and of its appraisal against evidence. Finally, further and more recent developments are outlined, which both shed new light on old issues and open up novel problems in research on the pathogenesis of AIDS.

2. Backstage: A brief history of AIDS research

The birth of AIDS research dates back to the beginning of the Eighties. Starting from 1980 a new mysterious pathological condition killing previously healthy persons was observed in the United States and soon recorded by the epidemiological surveillance federal agency CDC (Centers for Disease Control). First patients suffered from an unusually severe form of Kaposi’s sarcoma and from opportunistic infections, such as *Pneumocystis Carinii* pneumonia. They especially included young homosexual males from big urban areas (Los Angeles and New York City)\(^1\) and intravenous drugs users,\(^2\) but soon other populations were identified as involved in the epidemic (such as hemofiliacs and infants).\(^3\)

Susceptibility to opportunistic infections suggested a pathological lack of immunocompetence and was readily associated with lymphocytopenia observed in patients’ blood.\(^4\) This connection guided the first official definition of the newly observed clinical phenomenon as a *syndrome*, i.e., a condition which manifests itself as a collection of symptoms due to an underlying pathological condition, *immunodeficiency*, which is *acquired*, namely non-congenital.\(^5\) Early aetiological hypotheses have been directed to the causal role of an infectious agent, at first suggested on the basis of epidemiological data,\(^6\) as well as towards non-infectious pathogenic factors possibly associated with behavioral phenomena.\(^7\) The former line of thought encouraged virus hunters: viruses were major candidates for aetiology given that antibiotics were clearly unable

---

\(^1\) CDC (1981a; 1981b; 1981c); Friedman-Kien (1981); CDC (1982a; 1982b).

\(^2\) CDC (1982c).

\(^3\) CDC (1982d; 1982e; 1982f).

\(^4\) CDC (1981a); Gottlieb *et al.* (1981); Masur *et al.* (1981); Siegal *et al.* (1981).

\(^5\) CDC (1982g).

\(^6\) CDC (1982a; 1982h; 1982i); Auerbach *et al.* (1984).

\(^7\) Durack (1981); CDC (1982a; 1982b); Goedert *et al.* (1982); Marmor *et al.* (1982); McManus *et al.* (1982); Jaffe *et al.* (1983); Newell *et al.* (1984).
to control the disease and that, despite routine screening for bacteria in blood products, there was evidence of possible transfusion-associated AIDS.8

In 1983 and 1984 scientific reports by Luc Montagnier’s, Robert Gallo’s and Jay Levy’s research teams appeared announcing the isolation of a newly discovered virus in AIDS patients, then still labeled LAV (Lymphoadenopathy Associated Virus),9 HTLV-III (Human T-Lymphotrophic retroVirus type III),10 or ARV (AIDS-Related Virus).11 The virus was found to target a family of immune system cells (T-lymphocytes) whose depletion was typically observed in AIDS patients’ blood, and a decisive element of the chemical basis for this tropism was soon identified in the CD4 surface receptor.12 Moreover, some in vitro cytopathic activity was observed.13 Finally, several studies reported a strong association between infection by the virus and the clinical symptoms of AIDS.14

In a couple of years the viral approach in AIDS research was shaped in its essential lines and rapidly gained wide acceptance. In 1986 HIV (Human Immunodeficiency Virus) was established as a unifying label, partly as the widespread recognition of a causal link between the virus and the disease.15 The same year, the HIV-AIDS research programme was authoritatively established by the influential volume Confronting AIDS, a survey of knowledge and a blueprint for action published by the US National Academy of Sciences’ Institute of Medicine.16 Prepared by a panel consisting of prominent virologists, clinicians, public health experts, and social scientists, the book encapsulated the official body of knowledge about AIDS at the time as centred around three main theses. First, the committee concluded that the isolation of HIV and later research “led to its definitive identification as the cause of AIDS”.17 Secondly, Hiv is consid-

---

8 CDC (1982i); Curran et al. (1984).
9 Barré-Sinoussi et al. (1983); Montagnier et al. (1984).
10 Popovic et al. (1984); Gallo et al. (1984).
12 Dalgleish et al. (1984); Klatzmann et al. (1984).
13 Levy et al. (1984); Montagnier et al. (1984); Popovic et al. (1984).
14 Kitchen et al. (1984); Sarngadharan et al. (1984); Salahuddin et al. (1985); Ou et al. (1988); Darby et al. (1989).
15 Coffin et al. (1986).
16 USA Institute of Medicine (1986).
17 Ibid., p. 39. The statement of the causal link between HIV-infection and the development of AIDS has been meant to imply that the increase in the probability of the occurrence of the disease provided by the occurrence of the infection approximates that from 0 to 1: on one hand, HIV-infection is seen as a strictly necessary condition for AIDS, i.e., p(AIDS|not-HIV) = 0; on the other hand, it is considered as a typically sufficient condition, i.e., p(AIDS|HIV) >> 50%. This is, I think, no overstatement of the prevailing position. For HIV as necessary see, for instance, Blat-
ered a pathogenic agent *newly* introduced in human populations in the last decades and *recently* spread worldwide. In fact, one of the most powerful factors driving AIDS research at its beginnings and contributing to the elaboration of the viral approach has been the quest for an answer to the obvious question: “Why AIDS *now*?” and, although the details of the microbiological mutations and inter-specific breakthrough allegedly leading to the epidemic have been and somehow remain debated, a “new disease, new agent” principle has been explicitly invoked.\(^{18}\) Moreover, and finally, unprotected sexual intercourse and blood exchange are identified as typical ways of transmission of the infection, and hence of the disease. As a consequence, unsafe sex and shared usage of needles (common in intravenous drug consumption) are classified as major at risk behaviors for AIDS.

Meanwhile, AIDS epidemics were being registered in Europe\(^{19}\) and Africa\(^{20}\) and the AIDS case-definition was being importantly adjusted and expanded.\(^{21}\) Moreover, a different but related retrovirus, called “HIV type 2” or simply “HIV-2”, was isolated in West Africa and also found to be associated with AIDS disease.\(^{22}\)

Then, between the end of the Eighties and the beginning of the Nineties, some researchers, notably Peter Duesberg and Robert Root-Bernstein, challenged essentially all the basic tenets of HIV-AIDS research and claimed that their acceptance had been premature and not well founded.\(^{23}\) Duesberg, in particular, presented a partially renewed and extended version of early views, according to which different AIDS-related pathological conditions are produced by the exposition to non-infectious factors which severely damage the organism on chemical grounds, such as drugs consumption and malnutrition.\(^{24}\) Mainstream HIV-AIDS researchers and distinguished scientific commentators have

\(^{18}\) Gallo and Montagnier (1988); DeVita, Hellman, and Rosenberg (1997, pp. 5-6).
\(^{19}\) Thomsen *et al.* (1981); Downs *et al.* (1987).
\(^{20}\) Bayley (1984); Piot *et al.* (1984); Van de Perre *et al.* (1984); Serwadda *et al.* (1985); Quinn *et al.* (1986); Quinn *et al.* (1987).
\(^{22}\) Clavel *et al.* (1986); Clavel *et al.* (1987).
\(^{23}\) Duesberg (1987; 1988); Root-Bernstein (1993). An epistemological analysis of this background controversy on the role of HIV in AIDS has been presented in Crupi (2000).
\(^{24}\) Duesberg (1992); Duesberg and Rasnick (1998); Duesberg, Koehnlain, and Rasnick (2003).
repeatedly and vigorously rejected the criticisms\textsuperscript{25} and the alternative views\textsuperscript{26} of dissenter and have insisted on the necessity of continuous efforts to fully understand the pathogenetic processes involved in HIV infection in order to block more and more effectively its harmful consequences.\textsuperscript{27}

In what follows, I will mostly focus on one particular attempt in this direction, which represents a remarkable episode in the history of AIDS research.\textsuperscript{28}

3. The central paradox of AIDS pathogenesis

The guiding commitments of HIV-AIDS research constitute an original convergence of insights emerged in contemporary virology between the Sixties and Seventies. First, the suggestion of the existence of “slow viruses”, i.e., viruses responsible for pathological conditions arising long after infection.\textsuperscript{29} HIV has been clearly taken as being a slow virus in this sense.\textsuperscript{30} Second, the involvement of viruses in the pathogenesis of some forms of cancer;\textsuperscript{31} and third, the birth of human retrovirology.\textsuperscript{32} HIV is itself a retrovirus, and among AIDS-defining conditions there are oncological pathologies, some of which are thought of as being virus-induced.

As far as pathogenetic mechanisms are concerned, however, early hypotheses have been quite traditional. Many well-known viral diseases develop because the agent causes target host cells’ death as a consequence of active infection, the typical case being that of direct cell-destruction by cytolysis during the productive phase of the viral life cycle. From the beginning, it was clear that AIDS patients lacked immunocompetence and, as we have already seen, two specific kinds of experimental data drew much attention from the researchers:

\textsuperscript{25} Blattner, Gallo, and Temin (1988); Weiss and Jaffe (1990); Cohen (1993); Maddox (1993a; 1995a); O’Brien and Goedert (1996).

\textsuperscript{26} Ascher \textit{et al} (1993); Maddox (1993b); Schechter \textit{et al} (1993); Darby \textit{et al} (1995); Maddox (1995b).

\textsuperscript{27} For a last statement of this position, see the Durban Declaration 2000.

\textsuperscript{28} For more extensive treatments of the history of AIDS, see Epstein (1996), Grmek (1990), and Hellman (2001, ch. 10).

\textsuperscript{29} Gajdusek, Gibbs, and Alpers (1965).

\textsuperscript{30} See, for instance, Levy (1993, p. 185).

\textsuperscript{31} Emmelot and Bentvelzen (1972); Tooze (1973).

\textsuperscript{32} Blattner (1990).
it turned out that disease progression is associated with loss of CD4+ T-lymphocytes in blood; and

HIV was found to exhibit a strong tropism for these very immune system cells and to display some cytopathic activity against them.

Taken together, these data seemed to suggest a natural framework for pathogenesis, which can be summarized in two basic assumptions:

the pathogenetically crucial consequence of infection is that HIV enters CD4+ T-cells and destroys them;

does a general CD4+ lymphocytopenia, which progressively impairs physiological immune system functions, thus exposing the organism to classical opportunistic infections and other AIDS-related pathologies.

Over the years, a wide range of different mechanisms for CD4+ T-cells’ destruction in AIDS have been considered and investigated (including cytolysis, formation of syncytia, induction of apoptosis, and various immune and autoimmune host responses), and evidence has been reported of damages occurring in immune system cells of AIDS patients quite independently from active infection. However, even if some alternative accounts have been proposed, the most influential approach to pathogenesis has been for long the acceptance of the working hypothesis that the major event in AIDS is the destruction of immune system cells, largely due to active infection by HIV and causing their subsequent depletion.

Yet this point of view had to face a serious anomaly: according to early estimates, mainly based on blood sample measurements, the ratio of actively infected T-cells, even in clinically compromised individuals, was very low. Figures ranged from a minimum of about 1 out of $10^5$ to a maximum of about 1 out of $10^3$. On the basis of these numbers, the primary focus on direct cytopathic mechanisms did not allow a convincing account of immunological collapse even assuming that all actively infected cells are invariably killed in vi-

---

33 For reviews and further references, see Weiss and Jaffe (1990), Levy (1993), Stevenson (2003).

34 Ascher and Sheppard (1988); Nowak et al. (1991); Habeshaw, Hounsell, and Dalgleish (1992); Sheppard and Ascher (1992a, b); Adleman and Wofsy (1993); Margolick et al. (1993); Margolick et al. (1995).


36 Harper et al. (1986); Schnittmann et al. (1989).
by HIV. As a consequence, a “HIV hunting” phase started. Ingenuity, determination and improvements in observational techniques yielded two partially encouraging results. First, it turned out that the virus was biologically active and significantly more widespread in lymphoid tissues.\(^{37}\) Second, by ultrasensitive methods of detection (such as PCR) it was estimated that large quantities of viral RNA – and, therefore, high levels of “free floating” viral particles (viral load) – were present in plasma.\(^{38}\)

The latter results, dating the beginning of the Nineties, were readily received as good news for research in AIDS pathogenesis\(^{39}\) and soon incorporated into pathogenetical hypotheses and speculations.\(^{40}\) Yet, according to these studies (as well as more recent ones),\(^{41}\) even in lymphoid tissues actively infected T-cells are typically no more than 1 out of 100 – still not enough to be reconciliated with the then prevailing trends in AIDS pathogenetical research given the regenerative capacity of the immune system. Moreover, the overwhelming majority (~99.9%) of detected “free” viral particles appeared to be defective, i.e., unable to successfully infect cells.\(^{42}\)

This puzzling state of affairs – i.e., evidence of low levels of active HIV infection despite substantial loss of immunocompetence and of circulating CD4+ T-cells in AIDS patients – has been labeled the “central paradox of HIV infection”\(^{43}\) and has represented a major challenge in the study of AIDS pathogenesis. Some have observed that, assuming the view that AIDS is mainly caused by infection-mediated killing of immune system cells by HIV, it seems one is facing a “murder scene with more bodies than bullets”.\(^{44}\)

This was the situation when one of the most significant episodes in the history of the viral programme took place.

### 4. The sink model

In January 1995 David Ho’s and George Shaw’s research teams published two articles on *Nature* and shaped the “sink model” of immune cells “dynamics” in
AIDS pathogenesis. Here is a summary reconstruction of the proposal, based on Ho et al.’s paper.

AIDS seems to be characterized by a pathological dynamics in immune cells populations. In its final stage, in particular, it develops through a severe decrease in counts of circulating CD4+ T-lymphocytes, which supposedly reflects a more general depletion (see statement B.2 in paragraph 3). If \( x \) denotes the total number of CD4+ and \( t \) a time-variable, then \( \frac{dx}{dt} \) will be the rate of change of CD4+ levels in the organism. Then let \( P \) and \( K \) be, respectively, the rate of cell production and that of cell death. The basic equation of Ho’s et al.’s model states that

\[
(E) \quad \frac{dx}{dt} = P - K.
\]

This simply means that the rate of change of CD4+ T-cell total count is a function of cell production rate and cell death rate. According to the standard view, in the final stage of AIDS \( \frac{dx}{dt} \) typically assumes consistently negative values. However, before that, a long period of “incubation” or “latency” occurs during which CD4+ levels appear relatively stable. Suppose we idealize the incubation period as a “steady state” in which

\[
(S) \quad \frac{dx}{dt} = 0.
\]

Clearly, (E) along with (S) imply that in the steady state \( P = K \), but what is their value? The viral aetiology grounding the HIV-AIDS research programme suggests that there should be some biologically damaging activity by HIV leading to the final collapse of the immune system. As a consequence, Ho et al. conjecture that the value of \( K \) during the incubation period, modelled by the steady state, is not the purely physiological cell death rate. If so, it follows from (E) that the relatively constant levels of CD4+ in the incubation period must in fact be a surface effect of an underlying abnormal turnover induced by HIV infection.

The experimental intervention reported in the paper consisted in the administration to previously untreated patients, starting from time \( t_0 \), of a then new powerful kind of drugs (protease inhibitors) contrasting viral replication. Blood samples measurements obtained soon after \( t_0 \) suggested that HIV was indeed effectively being halted, showing a relatively unsurprising steep decrease of viral load. If HIV typically kills CD4+ T-cells by infecting them, one would reasonably expect fewer and fewer of them being killed, and therefore overall CD4+

---

45 Ho et al. (1995); Wei et al. (1995).
levels to rise, i.e., $dx/dt > 0$ soon after $t_0$. Now consider the following important auxiliary assumptions:

**(A.1)** blood sample measurement are highly representative of overall CD4+ T-cell population;

**(A.2)** $P$ remains constant before and soon after $t_0$, i.e., cell production rate is not influenced by drug administration.

**(A.1)** directly excludes major effects of redistribution among different compartments of the CD4+ T-lymphocytes pool; in particular, it excludes that an increase observed in the blood compartment be compensated by a decrease somewhere else (e.g., in lymphoid tissues). Moreover, since it is commonly estimated that overall CD4+ population is about $0.5 \times 10^2$ times CD4+ population in blood, **(A.1)** implies that increase in CD4+ levels in blood at any given time should approximately amount to the increase in overall levels (i.e., $dx/dt$) divided by $0.5 \times 10^2$.

On the other hand, **(A.2)** states that, after $t_0$, $dx/dt > 0$ only because $K$ drastically drops down, i.e., because, by having halted HIV, fewer and fewer CD4+ T-cells are being killed. Assuming that soon after $t_0$ $K$ virtually reduces to 0, by **(A.2)** the model implies that $dx/dt$ soon after $t_0$ approximates $P$ (i.e., overall CD4+ production rate). In particular, **(A.2)** implies that the increase in CD4+ levels soon after $t_0$ quite faithfully reflects the rate of cell production that, before $t_0$, was required to compensate for the HIV-induced cell destruction and keep CD4+ levels stable. Thus, **(A.1)** and **(A.2)** together imply that increase in CD4+ levels in blood soon after $t_0$ estimated by blood sample measurements, should amount to about $P$ divided by $0.5 \times 10^2$, where $P$, in turn, equals $K$ in the steady state (by **(E)** and **(S)** above).

By statistical analysis on raw data from 18 patients, Ho et al. estimated that, soon after $t_0$, CD4+ increase in blood is on average $3.51 \times 10^7$ per day, and used this figure to fix the value of parameter $P$ in the model at $1.8 \times 10^9$ per day ($3.51 \times 10^7$ times $0.5 \times 10^2$). This number is meant to provide a measure of CD4+ turnover rate (daily production and destruction) in the steady state, that is, in the “incubation” or “latency” period in untreated HIV infection, when the virus is active and undisturbed.

According to the sink model, then, CD4+ T-cells dynamics during the incubation period is in fact characterized by a very high turnover consisting in continuous virus-mediated cell-destruction compensated by an ongoing effort of replenishment by the immune system. And here is the suggestion proposed in the often quoted last paragraph of the paper:
The CD4+ T-lymphocytes depletion seen in advanced HIV infection may be likened to a sink containing a low water level, with the tap and drain both equally wide open. As the regenerative capacity of the immune system is not infinite, it is not difficult to see why the sink eventually empties.\footnote{Ho et al. (1995, p. 126).}

The sink model implies that the development of AIDS is backed by continuous CD4+ T-lymphocyte destruction and suggests that it is precisely this process that leads, through exhaustion, to the final depletion of this crucial population of cells. The proposal of this model offered a concrete, although still partial and tentative, insight as to the mechanisms leading to the collapse of the immune system.

5. Theory and evidence

The sink model drew much attention within as well as without the community of researchers. The \textit{Time}, for instance, awarded David Ho with the title of Man of the Year in 1996. According to the magazine, “his pioneering experiments with protease inhibitors helped clarify how the virus ultimately overwhelms the immune system”.\footnote{\textit{Time}, 30 Dec. 1996.} And in 1997 some critics defined the rise of the sink model as “spectacular”, while complaining “that there is hardly any visible debate over this versus alternative theories” in the viral pathogenesis of AIDS and noting that, after the appearance of the model, previously well-known approaches seem to “have been fading away rather silently”.\footnote{Grossman and Herberman (1997a, p. 936).}

Remarkably, commenting on the “new view” of HIV infection soon after the publication of the 1995 papers, the then editor of \textit{Nature} John Maddox claimed that the “central paradox” had for the first time a plausible solution. In fact, assuming a mechanism of killing by infection as driving HIV infection to overt AIDS (and this assumption, although not explicitly involved, certainly inspired the construction of the sink model) along with a typically very short time-lag from cell-infection to cell-killing, there might be some hope of explaining why so few infected cells are detected and how, if so few are found to be infected, the virus can possibly destroy the immune system: large amounts of the CD4+ population in the blood at any given time may have been freshly created and not yet infected. In Maddox’s words:
In essence, the new developments resolve the paradox by showing that the T-cells in an infected person’s blood are likely to have been created only in the few days previously. There will not have been time enough for more than a small proportion of them to have become infected, while those that harbour virus will be killed off very soon. So the scarcity of T-cells from which virus can be recovered in test-tube experiments is consistent with the assertion that the immune system is in overdrive from the onset of infection by HIV.49

First reactions among AIDS researchers, collected in the “Scientific Correspondence” section of the May 1995 issue of Nature, were by and large less enthusiastic. On the whole, critics did not question the experimental data reported by Ho’s and Shaw’s research teams, but were apparently reluctant to recognize those very results as genuinely supporting the sink model against other possible interpretations of the same data. Accordingly, substantial and recurrent doubts were raised about the assumptions involved, a major target being statement (A.1) above (see paragraph 4). In absence of direct evidence of T-lymphocytes’ abnormal replication rates – so the argument run – increasing levels of T-cells counts in blood can well, and even more plausibly, be explained as an effect of redistribution from different compartments, in particular from lymphoid tissues into circulation.50 This alternative reading amounts to a straight rejection of (A.1): in this perspective, Ho et al.’s blood samples measurement were clearly not representative of overall T-cell population, since increase in blood levels did not reflect a more general proliferation, but rather was compensated by a decrease in other compartments harbouring T-cells.

However, the sink model shared at least one of the typical features of good and promising scientific hypotheses: it provided new empirically testable predictions on the basis of which its acceptance or rejection could be rationally evaluated. Although the sink model has been widely discussed, it seems plausible that its value had to be ultimately assessed by its capability to bear additional and confirmed empirical content.51 The following are two particularly straightforward consequences (predictions) of the model:

(P.1) due to their rapid loss and the necessity of their ready replacement required to sustain the observed constant levels at the steady state, CD4+

51 See Popper (1963) and Lakatos (1978).
production rate in naïve (untreated) HIV-positive patients should be higher than in HIV-negative controls; (P.2) as a direct consequence of the suppression of viral replication by effective antiretroviral therapy in HIV-infected subjects, CD4+ T-cells should live, on average, significantly longer.

Several methods for investigating immune cells dynamics and testing the empirical predictions of the model have been devised and employed. Arguably, this process culminated in 1999 with the publication on *Nature Medicine* of a sophisticated experimental study by Hellerstein and colleagues, reporting results obtained by a research team based in San Francisco. The observational technique involved allows “direct” monitoring of *in vivo* cell dynamics in humans. The procedure runs as follows. First, glucose or water are administered (either intravenously or orally) which have been labeled by means of deuterium, a safe and stable isotope of hydrogen which is incorporated in dividing cells by DNA synthesis. Then peripheral blood (or tissue) samples are obtained at various points in time, cell populations of interest (for instance, CD4+ T-lymphocytes) are purified, and isotopic enrichment of cellular DNA is assessed. By mathematical analysis, the time-dependence of the fraction of labeled DNA can be determined and this, in turn, allows the calculation of dynamically relevant data, such as production rate and survival time.

The 1999 CD4+ labeling study clearly showed both (P.1) and (P.2) empirically incorrect: CD4+ production rate has *not* been found to be significantly higher in naïve HIV-positive subjects than in healthy seronegative controls, and CD4+ survival time in HIV-positive previously untreated subjects was *not* significantly extended after 12 weeks of effective antiretroviral therapy. As the authors point out, even if “a definitive biological interpretation of the [...] results cannot be made at present”, “some models [...] can be excluded”. In particular, according to AIDS researcher Giuseppe Pantaleo, commenting on the paper, the reported outcomes virtually “put an end to four years of exciting (although often harsch) debate about the CD4+ T-lymphocyte production/destruction hypothesis” – i.e., the sink model.

---

52 Wolthers *et al.* (1996); Fleury *et al.* (1998); Sachsenberg *et al.* (1998); Zhang *et al.* (1998); Wolthers *et al.* (1999).
6. Shifting the paradigm? From killing by infection to chronic immune activation

The construction of the sink model has been a major, and possibly the last, upshot of the view of AIDS as a relatively traditional viral disease mainly driven by the cytopathic activity of HIV. Beyond the observations quoted in the previous paragraph and directly disconfirming the sink model, a growing body of evidence has shown general limitations of this view. In particular, a serious problem has been the demonstration that in AIDS patients a different family of T-lymphocytes, called CD8+, which do **not** represent a natural target for HIV infection, suffer from abnormalities in biological behavior and population dynamics which are strikingly similar to those affecting CD4+ T-cells.56 Worse still maybe, even among CD4+ T-cells, a major cell-killing process, i.e., apoptosis, predominantly occurs in uninfected cells.57

Some observers have identified a paradigm shift in recent research on AIDS pathogenesis.58 The rise and fall of the sink model seems, in fact, to have come along with, and even to have stimulated, a fundamental change in perspective. A proposal which is gaining attention and consensus sees in an abnormal and chronic immune activation the crucial process associated with progression to AIDS,59 and much recently reported experimental evidence seems to fit in a quite natural way into this framework but not into more traditional views. According to this emerging perspective, a crucial step is the inclusion into AIDS pathogenetical models of a more accurate and sophisticated version of our current knowledge of physiological immune system processes. Both CD4+ and CD8+ circulating T-lymphocytes include functionally distinct subpopulations. Essential components are represented by a large subset of long-lived “resting” cells consisting in pools of so-called “naïve” and “memory” cells, which regenerate and reproduce in a slow and relatively stable fashion. Upon antigenic exposure, a portion of (both naïve and memory) resting cells become activated, thereby starting a process of rapid proliferation and differentiation into so-called “effector” cells over a period of days or weeks. A large majority of activated cells typically die soon by activation-induced apoptosis, while a small fraction meets the pool of long-lived memory cells and serves as a persistent

56 See, for instance, Roederer (1998); Hazenberg et al. (2000); Kovacs et al. (2001); Lem-picki et al. (2000); McCune et al. (2000).
58 Grossman et al. (2002); Silvestri and Feinberg (2003).
59 Grossman and Herberman (1997b); Grossman et al. (2002).
reservoir for subsequent antigen-induced activation. It has been repeatedly reported that HIV-infected persons typically exhibit abnormal, chronic and up-regulated levels of immune system activation.  

Focussing on pathological immune activation as the basic process underly-ing progression to AIDS is providing researchers with several new insights, and gathers into a unified framework a cluster of intriguing experimental results. For instance, a marked preferential biological activity by HIV in activated CD4+ T-cells has been reported.  

Consistent with these data, the immune activation approach suggests that it is precisely increased immune activation that sustains high HIV replication and viral load levels in (untreated) progression to AIDS. In other words, “activation is the machine driving virus production”.  

Moreover, the fact that antiretroviral therapy may impact very quickly on viral load without immediately increasing average survival time of T-cells suggests that, even if HIV is cytopathic in vivo to some extent, T-cells’ death in HIV infection occurs largely independent of HIV. Rather, it may reflect apoptosis in a pathologically expanded population of activated T-cells. On the same basis, the finding of a typical susceptibility to apoptosis in circulating CD8+ cells and, in general, uninfected “bystanders” in HIV infection and AIDS can be quite simply explained. In fact, in a further labeling study in 2003, Hellerstein and colleagues reported that in HIV/AIDS untreated patients the absolute number of circulating short-lived activated CD4+ cells is significantly higher than in healthy controls, while the number of circulating long-lived “resting” cells is drastically lower.  

Many aspects of the interplay between the immune activation model and experimental evidence are currently under scrutiny. Here I just would like to point out that the paradigm shift (assuming it is indeed occurring) has substantial, and partly puzzling, consequences on both old issues and further directions of inquiry. As a major example of the former case, it should be noticed that, from the standpoint of the new approach, inferring the basic pathogenetical hypotheses (B.1) and (B.2) from initial data (D.1) and (D.2) (see paragraph 3) seems to have taken AIDS research on a blind alley for years. For instance, AIDS researcher Mario Roederer has claimed that, contrary to the interpretation prevailing in the early times, “the fact that HIV uses CD4 as its primary receptor

---

60 Gougeon et al. (1996); Giorgi et al. (1999); Sousa et al. (2002); Hunt et al. (2003).
61 Roederer et al. (1997); Spina et al. (1997); Woods et al. (1997).
63 Hellerstein et al. (1999); Kovacs et al. (2001).
64 Hellerstein et al. (2003).
and that CD4+ T-cell numbers decline during AIDS are only an unfortunate coincidence that have led us astray from understanding the immunopathogenesis of this disease.” In fact, the very idea of an overall depletion of CD4+ T-cells as the hallmark of AIDS has been called into question in favour of the statement of a “selective depletion of ‘resting’ naïve and memory cells” on the basis of the recent observation that, at least during asymptomatic infection, in an allegedly reliable animal model of AIDS CD4+ (and CD8+) T-cells’ total counts seem actually to increase.

As far as future prospects are concerned, it is fair to say that a satisfactory account of two crucial links in the causal chain from HIV infection to AIDS via immune activation still fail: in a recent review, while promoting the paradigm shift, Silvestri and Feinberg point out that “we still lack an explanation of why HIV appears to be uniquely powerful in inducing a chronic state of immune activation [...], and why the HIV-induced immune activation is so disruptive of the proper overall functioning of the immune system”. In view of documented observations that AIDS-like immune activation may occur without HIV infection and that effective clinical improvement in AIDS patients on antiretroviral treatment can obtain despite evidence of modest inhibition of HIV replication, investigation on these “missing links” seems a particularly urgent task for future research.

Acknowledgements
I would like to express my gratitude to Sharyn Clough, Gilberto Corbellini, Roberto Festa, Franz-Peter Griesmaier, Jonathan Kaplan, Diego Marconi, Pier-paolo Marrone, Matteo Motterlini, Alfred Tauber, Paolo Vineis, John Worrall, the participants to the LSE 2001/02 Research Seminar in the Philosophy of the Natural Sciences and to the 2001/02 Seminar on Cognition, Choice, Decision of the Laboratory of Cognitive Sciences in Rovereto (Italy) for useful and sometimes usefully critical comments on several previous presentations of material merged into this work. I also thank Raffaella Campaner, Edoardo Camurri, Gabriele Contessa, Francesca Guidi, Matteo Morganti, Silvia Pessione and Claudia Vittori for various helpful discussions on relevant issues. Any mistake falls, of course, under my own responsibility.

---

67 Sopper et al. (2003).
69 Kalinkovich et al. (1998).
70 Deeks et al. (2002).


HAZENBERG, M.D. et al. (2000): “T-Cell Division in Human Immunodeficiency Virus (HIV)-1 Infection Is Mainly Due to Immune Activation: A Longitudinal Analysis in Patients before and during Highly Active Antiretroviral Therapy (HAART)”, Blood, 95, pp. 249-255.


SALAHUDDIN, S.Z. et al. (1985): “Isolation of Infectious Human T-Cell Leukemia/Lymphotropic Virus Type III (HTLV-III) from Patients with Acquired Immunodeficiency Syndrome (AIDS) or AIDS-Related Complex (ARC) and from Healthy Carriers: A Study of Risk Groups and Tissue Sources”, Proceedings of the National Academy of Sciences of United States of America, 82, pp. 5530-5534.


