

A MULTIFACTORIAL MODEL FOR THE DEVELOPMENT OF AIDS IN  
HOMOSEXUAL MEN

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The existence of a specific transmissible AIDS agent was proposed as an explanation for the syndrome very soon after its first description among homosexual men in 1981. This proposal appeared to receive support when manifestations resembling those seen in homosexual men were reported in intravenous (i.v.) drug users, in recipients of blood, and in Haitians.<sup>1</sup> The implication was that the AIDS agent was transmitted among and between the groups by sexual contact or by contaminated blood.

I will present an alternative view regarding the development of AIDS, proposing that there is no specific AIDS agent. I will present a model illustrating how AIDS could have developed in homosexual men as a result of an interaction of the known or likely effects of repeated exposures to specific environmental factors. With respect to the other groups, rather than invoke a single common infectious etiology, it is suggested that different pathways may lead to similar disorders of immune regulation. Of necessity, the model I will present includes a more rational description of the homosexual men at risk, in terms of exposure to environmental factors, rather than merely in terms of sexual orientation.

Since AIDS was first recognized, it rapidly became apparent that the risk for developing the syndrome was not uniformly shared by all homosexual men. AIDS was occurring in a probably rather small subgroup of men characterized by having had sexual contact with large numbers of different partners<sup>2</sup> in settings where there was a high prevalence of carriage of cytomegalovirus (CMV), particularly in the semen,<sup>3</sup> and where other sexually transmitted infections were also highly prevalent. Such conditions were met in New York City, San Francisco, and Los Angeles in the mid-1970s.

What is presented here is a multifactorial model on two levels. It considers the interaction of an individual with multiple environmental factors, and it also considers how the multiple biologic effects generated in the individual interact to produce the disease.

The environmental factors that are important are (1) repeated exposure to multiple allogeneic semens, (2) repeated infections with CMV, and (3) infection with other sexually transmitted pathogens, particularly those associated with immune complex formation. Active Epstein-Barr virus (EBV) infections are also important, but we believe that these represent reactivated infections.<sup>20</sup>

The new element is the remarkably high prevalence of CMV carriage, particularly in the semen of sexually active homosexual men in large cities in the United States during the past decade. The prevalence of CMV carriage in the semen may now approximate 35% in some settings,<sup>4</sup> and this is undoubtedly the consequence of lifestyle changes already alluded to, which permitted the expansion of the pool of men carrying cytomegalovirus.

It is proposed that the disease develops in two stages. There is a reversible stage of disease acquisition followed by a self-sustaining stage of disease progression. Promiscuity is important in the first stage as it is associated with an accumulation of effects that will eventually lead to the second, self-sustaining stage. Cumulative effects occur in men exposed to multiple allogeneic semens who are frequently reinfected with CMV and experience episodes of reactivation of Epstein-Barr virus. Thus, we expect to see some immunologic changes in tests on some apparently healthy men.

Exposure to multiple allogeneic semens is of course not new, and therefore, unlikely in itself to be associated with substantial morbidity. Dr. Witkin has described some humoral immune responses to semen, which include the appearance of antisperm antibodies, of both IgA and IgG isotype, and of circulating immune complexes containing sperm-related antigen.<sup>5</sup> There are antigens expressed on cells in the ejaculate that are shared by T lymphocytes<sup>6,7</sup> and natural killer (NK) cells. Asialo GM<sub>1</sub> is a ganglioside expressed on spermatozoa<sup>8</sup> and NK cells.<sup>9</sup> Dr. Witkin found antibodies to asialo GM<sub>1</sub>, more frequently in patients with AIDS and lymphadenopathy than in healthy homosexual men,<sup>10</sup> and it is possible that these antibodies contribute to the diminished NK activity found in some patients." Another possibility is that exposure to many different allogeneic semens may lead

to the appearance of antibodies reactive with T lymphocytes. It is also predictable that anti-HLA antibodies will be found in homosexual men who have never received a blood transfusion.

It is clear that immunologic changes can be seen in men exposed to allogeneic semen that in itself has not been associated with any obvious morbidity, but this may provide a background not only promoting CMV infections, but exacerbating the resulting immunologic disorders. In addition to its immunizing effect, semen can have direct immunosuppressive effects.<sup>12</sup>

Infection with CMV has several adverse effects on the immune system.<sup>13,14</sup> There is an activation of T8 suppressor cells, with a reduction in the ratio of helper to suppressor cells. A population of monocytes with suppressor activity is induced, and CMV infections have also been associated with the appearance of autoantibodies and immune complexes.<sup>15</sup> Cytomegalovirus-infected cells also express Fc receptors,<sup>16,17</sup> which may be significant in a host with circulating immune complexes.

The frequency with which an individual will be reinfected with CMV will be a function of the number of different sexual partners, the prevalence of CMV carriage in the population with whose members the individual interacts, and the specific nature of the sexual practice. Anal exposure to the large inocula that may be found in semen is probably the greatest risk.

The environment in which the patient has been sexually active places him at considerable risk for acquiring other sexually transmitted infections. These may add to the immunosuppressive burden. Syphilis and hepatitis B are highly prevalent in these men, and these infections can be associated with immune dysfunction and with immune complex formation.

Epstein-Barr virus plays an important role. Reactivated infections not only contribute to disordered immune regulation, but some specific manifestations are associated with this virus, the B-cell lymphomas occurring in AIDS is an example.<sup>20</sup> The hyperimmunoglobulinemia characteristically seen in patients may be due to EBV, as this is seen in some patients who have virtually no T-cell help. Epstein-Barr virus is a T-cell independent polyclonal B-cell activator.<sup>21</sup> Some autoantibodies may also derive from EBV-driven B cells. Purtilo has shown that in these patients at least, EBV serology is an unreliable indicator of reactivation. The EBV genome has been found in the lymph nodes of patients with lymphadenopathy in quantities indicative of an active infection; these patients, however, did not show a serological reactivation pattern.<sup>20</sup> Epstein-Barr virus probably plays a major role in the patients with lymphadenopathy. Anti-viral capsid antigen (VCA) IgA responses were noted in patients with lymphadenopathy and AIDS.<sup>20</sup> It is of interest that patients with nasopharyngeal carcinoma frequently show anti-VCA IgA responses even before onset of the tumor.<sup>21</sup> In men with lymphadenopathy and AIDS, EBV receptors were diminished on the surface of B cells as were proliferative responses to EBV in homosexual men with lymphadenopathy and AIDS.<sup>20</sup> These men also had an impairment of EBV specific T-cell cytotoxicity.<sup>20</sup> This is yet another EBV association in AIDS that resembles those seen in renal transplant recipients.<sup>23</sup>

We have described multiple biological effects in patients at risk for developing AIDS and have identified environmental factors that can produce such effects. What remains is to describe a process by which these effects can interact to produce AIDS. The repeated infections with CMV, the reactivation of EBV, exposure to multiple allogeneic semens, and infection with other sexually transmitted pathogens result in an accumulation of effects that interact either additively or synergistically to result in a switch to a self-sustaining condition.

The central defect in this stage is an inability of cytotoxic lymphocytes to clear CMV-infected cells. We thus postulate that an important target would be the HLA-restricted antigen-specific T-cell cytotoxicity for CMV-infected cells. The factors that accumulate to result in the functional impairment of these cells are the following. (1) There is an increasing level of CICs that may react with some T lymphocytes and interfere with cytotoxic or regulatory function. Herpes viruses, including CMV-infected cells express Fc receptors,<sup>16m</sup> and thus may bind CICs and block target recognition by cytotoxic lymphocytes. (2) There is the appearance, in increasing concentrations, of antibodies that are cross-reactive with T cells and NK cells. The specific targets may be regulatory of effector T cells. The consequence is impaired cytotoxicity. Antibodies reactive with T lymphocytes and NK cells may result from polyclonal B-cell activation or from immunization by cross-reactive antigens present in the ejaculate. (3) There is a loss of T-helper cells and a diminishing ratio of T4 helper to T8 suppressor cells.

Thus, both humoral factors (CICs and autoantibodies) and cellular factors (diminished T4/T8 ratios, depressed NK activity) conspire to inhibit an effective cytotoxic response to CMV-infected targets (FIGURE 1). These factors might act additively or synergistically, and the relative contribution of each may vary from patient to patient.

The process described could, by its nature, become self-sustaining, as it does have features characteristic of positive feedback systems (FIGURES 1 and 2). For example, if cytotoxic function becomes further inhibited, expansion of the total CMV antigenic load will result in yet further immunosuppression. An intercurrent viral infection, for example, could precipitate a self-sustaining and possibly progressive condition. It is also possible that a specific circumstance moves the disease into an irreversible state, such as thymic destruction.

AIDS in groups other than homosexual men may also arise as a result of exposure to multiple environmental factors. Among Haitians, for example, the risk is obviously not

shared by the population at large. An analysis of those environmental exposures of those Haitians affected might reveal that the operative influences are such that the disease might be found throughout the world where similar conditions prevail. Poverty and malnutrition, tropical infections, and malaria in particular, could be important contributing factors. Similarly, an examination of the environmental exposures of those i.v. drug users with and without AIDS could clarify the risk factors. The setting in which the drugs are used with respect to the possibility of a transfer of blood may vary in different populations and may prove to be important. AIDS is certainly not uniformly distributed among the population of i.v. drug users. A good deal of the confusion surrounding AIDS comes from the assumption of homogeneity among the risk groups. Another assumption is that AIDS is new in all the designated risk groups. I believe this can only be said with any confidence for the disease in homosexual men, and even here some qualification is needed. It is the epidemic that is new. Isolated cases may well have been seen before.

The dispersal of the elements of the immune system, the variety of different specific and nonspecific effector and regulatory functions, as well as the chemical diversity of the short and long-range signals employed, implies a great number and variety of vulnerable targets, and therefore, a susceptibility to many different influences. The model I have presented is an illustration of how the interaction of known or likely effects of specific environmental exposures can lead to the development of progressive immune dysregulation in homosexual men. In other groups, different but analogous mechanisms may also operate.

In conclusion, I believe that this multifactorial model lends itself to a formal epidemiologic analysis. This is true at two different levels. We must have a better understanding of the environment in which AIDS develops and the ways in which affected individuals have interacted with that environment. But this is not the only way in which epidemiology can contribute. The analysis of the interaction of the various biological effects generated by these exposures is also an appropriate and important epidemiological undertaking.

[NOTE ADDED IN PROOF: A substantial effort has been made to identify a unique, new microbial agent that may account for the appearance of AIDS. The lymphadenopathy-associated virus described first by Montagnier and colleagues at the Pasteur Institute<sup>24</sup> may be an important agent in the final stages in the immunopathogenesis of AIDS. It would appear that the vast majority of the individuals in the high-risk groups who become infected with this virus already have immune perturbation prior to the infection by the agent. Perhaps this may allow the virus to proliferate in the host as it escapes immune surveillance." Only time will tell whether the lymphadenopathy-associated virus (HTLV-III, synonymous) is the sole agent responsible for AIDS. We doubt that this is possible and hence continue to predict that interaction with Epstein-Barr virus, cytomegalovirus, and other agents contributing to immune perturbation are required to permit the virus to induce AIDS.]

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" This work was supported by the AIDS Medical Foundation.

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