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The HIV Seropositive State and Progression to AIDS:

An Overview of Factors Promoting Progression

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We have considered factors that predispose to infection by the human immunodeficiency virus as well as the clinical consequences of infection. We have also reviewed what is known about the virological status of the asymptomatic carrier, particularly the female, and the fact that pregnancy may be a cofactor for progression of HIV disease in seropositive women. Additionally, we have discussed several other cofactors that may promote the progression of HIV infection. These include intercurrent infection, excessive use of recreational drugs and alcohol, malnutrition, and stress. With respect to stress, we have reviewed evidence indicating that certain personality factors, by buffering the effects of stress, may play a role in determining the outcome of HIV disease. Possible neuromodulators that may mediate the effect(s) of stress on the immune system are considered. Also discussed is the potentially complicating role of HIV infection of the brain of asymptomatic carriers on psychosocial studies, as well as the possible dysregulation of neuromodulator levels which might result from such infection. The possibility that HIV infection of the brain may act to enhance progression of HIV infection is proposed.

One of the major issues concerning AIDS is knowledge of the virological state and infectivity of the person who has seroconverted to HIV and remains healthy — the so-called asymptomatic carrier. Equally important is the subject of cofactors — those factors which may enhance or promote the asymptomatic carrier's progression to AIDS. In this article, we shall present an overview of these topics and some implications for seropositive women who become pregnant.

Infection by the Human Immunodeficiency Virus

Upon exposure to HIV, the virus that causes AIDS, a person may develop an acute infectious mononucleosis-like syndrome with or without meningitis. Generally, these infections subside, an immune response occurs in relationship to the disease, and the patient

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becomes seropositive (Group I, see table 1).¹ Other people who are exposed to the virus may not develop signs or symptoms of illness, and seroconversion may take weeks to months to occur (Group II, table 1). Little is known about the factors that determine whether an acute infectious disease occurs or whether a person seroconverts asymptotically. Moreover, relatively little is known regarding the extent of exposure necessary for seroconversion.² In some studies, 50 to 60 percent of male homosexual partners of infected persons become infected, as judged by antibody testing;³ approximately the same figure applies to male-to-female transmission from HIV-infected intravenous drug users or male bisexuals.⁴ Female-to-male transmission appears to be much lower, probably owing to the lower infectivity by this route.⁵ Other studies reveal that four out of eight women who were artificially inseminated from an infected donor seroconverted,⁶ and 50 percent of hemophiliac patients who received a contaminated Factor VIII preparation seroconverted.⁷ Thus it is likely that about half of the people exposed to infectious individuals and materials will seroconvert. Factors such as the amount of virus in the infectious fluid, route of infection, or host factors, or a combination of these, must certainly be operative in determining whether seroconversion occurs after exposure to HIV.

Once an individual is infected with HIV and seroconverts, he or she is potentially infectious for the rest of his or her life. We know that the genetic material of the virus (RNA) is able to make DNA and that this DNA becomes associated with the cell's genes. This integrated proviral DNA becomes a cellular gene and, as long as the cell lives, will be a permanent part of its genetic endowment. Approximately 70 to 80 percent of asymptomatic, seropositive carriers, in whom the infectious virus cannot be found, will have the latent viral genes activated from their blood cells by various cocultivation and activation techniques. This finding indicates that most asymptomatic carriers have the capacity to synthesize the infectious virus but that it is still present in most cells in a latent state. Little is known as to the actual levels of infectious virus produced by asymptomatic carriers; however, most evidence suggests that only small amounts of infectious virus are present. Despite this, a large amount of evidence indicates that a seropositive person, symptomatic or asymptomatic, is infectious and can transmit the virus.⁸

Asymptomatic individuals can transmit the virus by means of genital secretions or blood or through transmission to the fetus. The virus is certainly in the blood cells in a latent state. Data are very sparse as to whether the virus in the genital secretions, for example, the ejaculate of males and the cervical secretions of women, is contained within cells or is free in bodily fluids in the asymptomatic individual. Some evidence indicates that the virus resides intracellularly in a latent state in cervical secretions.⁹ Transmission to the fetus by the asymptomatic carrier presumably occurs through the blood, although in certain unusual circumstances newborns appear to have become infected through nursing.¹⁰

Asymptomatic Female Carrier

Although the virus has been recovered from the cervical secretions of asymptomatic female carriers by means of cocultivation techniques throughout the menstrual cycle, little is known about the relative levels of virus in the cervical secretions of women during various phases of the menstrual cycle or during pregnancy.^{11, 12} Retroviruses in mice can be activated by certain female sex steroids.¹³ This discovery raises a question as to whether female sex hormones activate virus replication in cells in the cervical secretions which harbor the virus, such as lymphocytes and macrophages and, if so, which are the activating hormones. We know very little about these phenomena in humans, but they are important, since the type and level of sex steroid vary during different phases of the menstrual

Table 1

Summary of Classification System for HIV

Group I. Acute infection
Group II. Asymptomatic infection
Group III. Persistent generalized lymphadenopathy
Group IV. Other disease
Subgroup A. Constitutional disease
Subgroup B. Neurological disease
Subgroup C. Secondary infectious disease
Category C-1. Specified secondary infectious diseases listed in the CDC surveillance definition for AIDS
Category C-2. Other specified secondary infectious diseases
Subgroup D. Secondary cancers
Subgroup E. Other conditions

Category C-1 and Subgroup D include those patients whose clinical presentation fulfills the definition of AIDS used by the Centers for Disease Control for national reporting.

cycle and these factors may be operative in regulating the amount of virus present as well as its intracellular or extracellular location in urogenital secretions. This possibility is of obvious importance with respect to heterosexual transmission, since it is the infectious virus in cervical secretions which passes from the female to the male and transmits the disease. Many of these questions can be addressed by utilization of various techniques that have been shown to activate or stimulate virus production in vitro. For example, one could treat infected lymphocytes or macrophages, or both, with various sex steroids and measure the production of infectious HIV.

Pregnancy and the Asymptomatic Female Carrier

Of the fetuses born from women who are infected with HIV prior to pregnancy, approximately 50 percent are infected with HIV. For subsequent pregnancies, the percentage is even higher. Current evidence indicates that virus is generally passed from mother to fetus during the intrauterine residence of the fetus rather than perinatally.¹⁴ This evidence stems from the fact that Caesarean section does not protect the fetus from infection.¹⁵ Moreover, the virus can be recovered from the fetal compartment in cases of elective Caesarean section at twenty and thirty-six weeks.¹⁶ Thus, most evidence indicates that the virus passes from mother to fetus transplacentally. There are reported cases, however, in which virus has been passed to the neonate via the milk.¹⁷

That pregnant positive women may pass the virus to the fetus in approximately 50 percent of pregnancies and that pregnancy may influence the course and progression of the disease in infected women raise many issues regarding testing for HIV positivity and counseling women who are found to be seropositive.

One important question concerns the progression of disease during pregnancy. Does pregnancy enhance the progression of disease in a healthy female carrier? There is evidence at present to suggest that HIV-infected women who have already given birth to an infected child have an increased risk of developing AIDS during the subsequent pregnancy or soon thereafter.¹⁸ It is possible that exposure to paternal antigens of the fetus triggers an immune response that is likely to activate latently infected immune cells. Viral replication is more likely to take place in such stimulated cells. It has been suggested that these events have a cumulative effect, since the risk of AIDS does not seem to increase in the first pregnancy of an HIV-infected woman in some studies.¹⁹ In still other studies,

progression was evident in women during the first pregnancy.²⁰ Obviously, studies must be carried out to resolve this important issue, but it seems clear that pregnancy can be a cofactor for progression, which poses the question as to whether such progression is due to enhanced viral activation or to the immunosuppressed state that accompanies pregnancy. This subject will be discussed below.

Infection of the Brain

At what point the brain, which is affected in 85 to 95 percent of AIDS cases, is seeded with virus is not known at the present time.²¹ It is entirely possible that the brain may be seeded with virus at the time of initial infection. This is what occurs with visna, a disease in sheep caused by a subgroup of retroviruses, the lentiviruses, a group to which HIV belongs. In visna infection, the virus is brought to the brain in a monocyte; presumably this happens with HIV infection, since the virus infects monocytes, and monocytes are the cells most frequently infected in the brains of AIDS patients. These monocytes may appear as multinucleated, syncytial giant cells, and viral replication has been documented in these cells. Evidence indicates that the brain is seeded with HIV in healthy, asymptomatic, seropositive individuals.²² These conclusions are based on studies carried out with the cerebrospinal fluid (CSF). If antibody to a virus is present in the CSF, it is extremely likely that virus is replicating in the brain. In most chronic virus infections of the brain, such as measles and visna, replication of virus in the brain evokes antibody production in the brain, and the antibody subsequently appears in the CSF. Other tests can be carried out to detect viral antigen in the CSF, which is also indicative of brain infection. That the brain is seeded by the virus, possibly very early, is important, since the brain may act as a reservoir for virus replication. The brain frequently harbors chronic, subacute, and latent virus infections. Why various virus infections persist in the brain is not known. It is known that the brain is an immunologically privileged site, probably owing, in no small part, to the blood brain barrier and the lack of lymphatic supply to the brain. The fact that HIV persists in the brain will make eradication of the infection very difficult indeed, since most drugs pass the blood brain barrier poorly, if at all.

In the preceding sections, we have considered the likelihood of becoming infected with HIV as well as the consequences of infection with respect to the development of acute disease or seroconversion without clinical disease. We have also considered the viral status and infectivity of the asymptomatic carrier, particularly the woman. Pregnancy as a factor promoting progression of disease and the possible mechanisms implicated in maternal to fetal spread were also discussed. The likelihood of invasion of the central nervous system by CNS HIV was considered. The HIV carrier may feel completely well for many years, or he or she may experience progression of the disease. We will now consider the factor(s) that may influence the outcome of HIV infection.

Progression to AIDS

In table 1, a summary of the new Centers for Disease Control (CDC) classification system for HIV is presented. We define progression as the development of disease in asymptomatic individuals (Group II), which may be minor (persistent generalized lymphadenopathy [PGL], Group III) or severe (Group IV). It should be noted that in the CDC classification, several distinct symptomatic presentations of HIV infection are now included. Within Subgroup A of Group IV, for example, fall cases formerly termed AIDS-related complex, or ARC.

What, then, is the likelihood of progression? Various studies indicate that at least 50 percent of seropositive individuals will experience progression of HIV infection to a disease included in Group IV. The likelihood that progression will occur is strongly related to the length of the HIV infection.²³ Several studies suggest that the incidence of progression of persons in Group III, or PGL, is similar to that of persons in Group II.²⁴ What percentage of asymptomatic carriers will remain so, without progression clinically or immunologically, is not known for certain. These individuals must, of course, be followed for longer periods.

The question of whether the persistently asymptomatic state reflects containment of the replication of HIV by means of certain unspecified factors or through specific immune mechanisms, or both, remains unanswered. Although it is not known for certain, it is likely that a slower rate of progression in some individuals reflects a relative lack of cofactors; put another way, it is likely that cofactors enhance progression. We postulate that the cofactors act by increasing viral replication or by altering the capacity of the immune system to contain the infection, or by doing both. This proposed mechanism of progression is untested at present and likely will remain so for years. Nevertheless, we would assume that anything that activates viral replication or that diminishes the immune response would favor progression.

The likelihood that cofactors influence the development of AIDS is of paramount importance. We have already pointed out that pregnancy may increase the risk of developing AIDS in an asymptomatic carrier. There is much current feeling that other cofactors such as intercurrent infection, malnutrition, excessive use of recreational drugs and alcohol, and stress may all play a role in the development of disease in people infected with the HIV agent. We will discuss these factors after briefly reviewing the question of genetic predisposition.

Genetic Influence

Susceptibility to HIV infection as well as rates of disease progression may depend on genetic characteristics, for example, a predisposition for acquisition of the disease; the evidence for this, however, is very preliminary. Some data have been presented linking HIV infection with a certain genetic phenotype (group specific component [Gc]) in homosexual men.²⁵ Yet, in a series of seropositive hemophiliac patients, no significant difference was found between patient and control populations with respect to this genetic marker.²⁶

Other studies, mainly from New York, indicate that the HLA-DR5 antigen is positively associated with Kaposi's sarcoma as a manifestation of AIDS.²⁷ The significance of these preliminary studies is unknown, and more studies must be done. However, the notion that there may be a genetic influence on susceptibility to, or progression of, HIV infection remains a fascinating one.

Intercurrent Infection

A large body of evidence indicates that replication of HIV may occur only in an activated cell. The infectious viral cycle generally does not proceed to virus production, but proceeds only to proviral DNA synthesis and integration in a resting lymphocyte. Upon lymphocyte activation, viral replication occurs and progeny virus is produced.²⁸ In a latently infected cell as well, virus synthesis may occur only after cell activation with varying agents that stimulate lymphocytes to divide, such as various antigens or infectious agents.²⁹ Elegant molecular biological studies have identified a factor produced by acti-

vated T-cells, a subset of lymphocytes, which enhances the expression and replication of HIV.³⁰ This factor is a protein that binds to the regions of the viral genome which enhance the expression of viral genes. Such studies indicate that stimulation of lymphocytes associated with another infection can activate HIV virus replication both during an acute infection and in a latently infected cell.

Infectious processes, by activating HIV replication, may promote the infection of a greater number of target cells and cause their ultimate destruction. Through this amplification, the threshold for clinical disease might then be reached. Tuberculosis and generalized viral infections have been thought to act as cofactors for HIV progression in this way.³¹ There is, however, much more evidence that intercurrent sexually transmitted infections such as gonorrhea, syphilis, primary herpes simplex, hepatitis B, and nonspecific urethritis acquired after HIV infection are strongly associated with the development of symptomatic disease in two separate cohort studies.^{32, 33} It has been suggested that intercurrent sexually transmitted disease may also act to promote seroconversion in the following way:³⁴ HIV may have infected relatively few T-lymphocytes and/or macrophages (the cells of the immune system most susceptible to HIV infection) at the site of entry of the virus, and thus may not have provided sufficient viral antigens to illicit an immune response. Such latently infected cells, when activated as part of a local, or systemic, response to infection, may then release sufficient viral particles to induce a primary specific immune response. Pinching further speculates that this phase of required HIV replication may explain the relatively long latency period between exposure and seroconversion (generally six weeks to three months; however, lag periods of up to twelve months have been reported), longer than with most other infections or immunizations.³⁵ One would want to have more data as to how often seroconversion is triggered by intercurrent infections, although this information might be difficult to obtain. Whether or not this hypothesis can be substantiated, the epidemiological evidence of the association of intercurrent infection and progression of HIV disease suggests that intercurrent infections are an important cofactor. Moreover, other studies indicate that the presence of lesions in the genital area which are associated with sexually transmitted diseases may be a risk factor for HIV infection, since such lesions may provide a portal of entry for the virus.³⁶

Malnutrition

Many studies have indicated that severe protein calorie malnutrition and a variety of single nutrient deficiencies are causes of defective-cell-mediated immunity and of other defective immune functions.³⁷ Stated another way, deficiencies in calories in general as well as specific vitamins or minerals can lead to deficiencies in immune function. Malnutrition as a result of persistent diarrhea and malabsorption may contribute to further impairment of immunity and the progression of AIDS. Some evidence indicates that nutritional status decreases as the severity of HIV-related illness increases from an asymptomatic seropositive state to AIDS.³⁸ It is likely that malnutrition plays an important role in the progression of HIV infections in central Africa.

Recreational Drugs and Alcohol

The excessive use of alcohol or recreational drugs, or both, can cause immunosuppression.^{39, 40} The contribution of alcohol and drug use to HIV-related disease is uncertain at this time, however, as recent studies were unable to demonstrate that the use of these substances contributes significantly to disease progression.^{41, 42} Chronic use of alcohol, which

may result in cirrhosis of the liver and diminished host resistance, could certainly act as a cofactor for disease progression.

Stress

A growing literature suggests that mental attitudes and emotions may influence the progression of infectious diseases, including those associated with HIV. Such studies, together with those dealing with psychosocial aspects as predictors of which infected individuals will progress to AIDS, are attempting to determine the relationship between mental processes and the immune system. This is a new field of study, which has been called psychoneuroimmunology.⁴³ Such studies are extremely important, since they may reveal mechanisms that will aid in determining whether and how stress and associated dysphoria may be cofactors in the progression of HIV infection to AIDS.

If distress is such a cofactor, it becomes important to determine the personality factors and interventions that may be instrumental in buffering the effects of stress. A number of reports have indicated that hardiness is associated with less illness in highly stressed individuals.⁴⁴ Hardy individuals are defined as those who make commitments, welcome challenge and change, and tend to feel that they can exercise control over their lives. Psychological tests to measure hardiness have found that men who are "most hardy" on the control subscale have a greater longevity following diagnosis of *Pneumocystis carinii* pneumonia.⁴⁵

Another study has indicated that patients with Kaposi's sarcoma who are following a macrobiotic regimen have survived with their disease for as long as three to five years.⁴⁶ These patients have shown some improvement in their immunologic profile without medical therapy. Survival patterns such as these in patients with Kaposi's sarcoma are not frequently encountered. As the choice to practice a macrobiotic way of life and the ability to continue with it involve many changes and require a strong commitment, one would predict that the individuals in the study are quite hardy. In addition, an important component of the practice of a macrobiotic regimen is the belief that health can be controlled by diet. This belief presumably reduces the sense of hopelessness associated with AIDS. In animal studies, helplessness and hopelessness are associated with immune suppression. The extent to which the clinical improvement is due to the macrobiotic diet per se or the psychological involvement in the macrobiotic way of life or the particular "mind set" of those who choose an alternative therapy is not completely understood at present.

The aforementioned studies suggest that certain personality characteristics indicative of "psychological health" and a feeling of involvement and commitment may influence the course of HIV infection. It would not seem unlikely that stress and dysphoria influence progression of disease in HIV-infected persons. Numerous studies have revealed that the immune function can be diminished by many of the chemicals released from the brain or nerves, which are called neuromediators, neurohormones, and neurotransmitters and which mediate the effects of stress.⁴⁷ Furthermore, the psychological depression experienced by many people who have seroconverted to HIV may itself be immunosuppressive.⁴⁸ Although it is likely that any progression of HIV infection which is caused by stress is brought on by the immunosuppressive effect(s) associated with stress, it is also possible that the virus is directly activated in cells by certain of the neuromediators just referred to. HIV production is, for example, stimulated by corticosteroids. Activation of other viruses by several of these substances has been demonstrated in animal cells in vitro as well as in vivo.⁴⁹ In humans, certain neurohormones can also activate viruses; for example, epineph-

rine can activate latent herpes simplex virus infection in the rabbit eye.⁵⁰

The effect(s) that the mind has on the HIV disease process are complicated by the possibility of the presence of HIV in the brain of asymptomatic carriers. As we have mentioned, the time when the brain is seeded with HIV is not known. It is evident that central nervous system seeding occurs eventually in most patients who progress, since the vast majority (85 to 95 percent) of patients with AIDS have pathological evidence of AIDS encephalopathy at autopsy.⁵¹ Indeed, evidence indicates that of those diagnosed with AIDS, 20 percent may initially present with a psychiatric or neurological syndrome. Therefore, psychological or psychosocial studies on asymptomatic carriers may be complicated by the presence of HIV in the brain of an asymptomatic carrier. It is known, however, that the brain may contain HIV without psychiatric or neurological signs or symptomatology.⁵² Thus, infection of the CNS may remain asymptomatic. One can determine whether the brain is seeded with HIV by examination of the CSF for HIV antigen or antibody to HIV (see above), but performance of such studies may be difficult to justify because of the risk associated with spinal tap. Recently, neuropsychological testing has been developed to identify subjects with "likely early" or "early" AIDS-related dementia.⁵³ This finding should allow researchers in this area to analyze their data for a possible confounding effect of organically induced alterations in mood and personality.

Although few studies have been carried out so far, it is possible that production and levels of neurotransmitter substances are altered in an HIV-infected individual who has seeded the brain. At present, there is no evidence that neurons are infected by HIV. However, the cells in the brain known to be infected by HIV (monocytes, endothelial cells, and certain glial cells)⁵⁴ elaborate substances that have been shown to affect certain neurotransmitter substances in neurons.⁵⁵ Similarly, monocytes and T-lymphocytes can also secrete factors that influence brain function. Altered neurotransmitter substances in the CNS may, in turn, affect immune function.⁵⁶ Thus, a complex interaction exists whereby products of cells of the immune system or other cells capable of secreting similar products influence the levels of neuromediators in the brain.⁵⁷ Whether HIV infection alters the function of CNS cells with respect to production of, or response to, neurotransmitter or immunomodulatory substances, respectively, is currently unknown. We speculate that because of these alterations, progression may occur more rapidly in an asymptomatic person who has HIV infection of the brain. Much work must be done to delineate further the relationship between the central nervous and immune systems, the ways in which emotions affect the immune system, and whether and how HIV infection in general, and of the brain in particular, alters these interactions. Such studies may help determine whether and how stress may be a cofactor in either the development or the progression of AIDS.

Summary

We have attempted to present an overview of the factors that may play a role in determining whether progression occurs in the HIV-positive asymptomatic person. Pregnancy, intercurrent infection, malnutrition, excessive use of recreational drugs and alcohol, and stress, as well as certain genetic factors, may influence the progression of disease. It will be important to determine whether progression occurs more rapidly in a seropositive individual with CNS infection by HIV.

Although our knowledge about the factors predisposing to the progression of HIV infection is not extensive, it is extremely likely that cofactors play an important, if not a

determining, role. Thus, modifying behavior could presumably influence the outcome of an HIV infection. Present data suggest that by avoiding the use of recreational drugs and alcohol, and reducing stress or buffering its effects, one would be maximizing the host potential to combat infection. Since there is no cure for HIV infection at present, a better understanding of the psychological, biological, and behavioral influences that act as cofactors is of great importance. Research is urgently needed in these areas, so that accurate information can be used as a basis for devising more effective treatment strategies, setting public policy, and educating persons at risk. More specific knowledge could thus be used to develop adjunctive intervention directed at cofactors rather than at the virus itself. 🐼

Notes

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Provirus.

This is DNA made from an RNA template (of an RNA virus) by the enzyme reverse transcriptase, and it is required for replication of the virus. This DNA becomes permanently associated with the DNA of the cell and, as long as the cell lives, will remain associated with the cell's genes.

Seroconversion.

The development of antibody to an infectious agent is termed seroconversion. This occurs during acute infectious diseases. It may also occur without obvious clinical disease or symptoms. In the latter case, the seroconversion may be termed silent or asymptomatic. Most infections and seroconversions with HIV are of the asymptomatic variety.

T-lymphocytes.

Lymphocytes are a class of white blood cells responsible for specific immunity. T-lymphocytes are a subclass of lymphocytes and include cells that can kill virally infected cells.

“ I have no immune system. You people are much more likely to give me something than I am ever likely to give you something. And I don't think very many people think in those terms, that we're the ones at risk. Just being in a room, people coughing and sneezing, could put me in the hospital, and you have virtually nothing to fear from me, so I mean, that reversal of roles has to be brought home. ”

Glossary

Ataxia.	A loss of the power of muscular coordination.
Autonomic neuropathy.	A disorder of the autonomic nervous system which manifests in abnormalities of functions governed by the autonomic nervous system, such as temperature regulation and maintenance of blood pressure.
Cat scan.	Computerized axial tomography, a special radiographic examination consisting of a series of x-rays.
Cortical atrophy.	A shrinkage of the outer tissues of the brain (known as the cortex of the brain).
Histopathology.	The science or study dealing with the cytologic and histologic structure of abnormal or diseased tissue.
Hyperreflexia.	A condition in which the deep tendon reflexes are exaggerated.
Methylphenidate.	A medication that acts as a stimulant on the central nervous system.
Neuroleptic.	An antipsychotic medication.
Nonfocal encephalopathy.	Diffuse disease of the brain.
Obtundation.	A diminished state of alertness.
Postural hypotension.	A form of low blood pressure which occurs when the subject stands.
Subacute encephalitis.	Inflammation of the brain which progresses at a moderate rate.