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The Acquired Immunodeficiency Syndrome (AIDS) first recognized in 1981, has been extensively studied, and the most recent studies have demonstrated that its defects extend well beyond the apparent deficient cell-mediated immunity to include humoral immunity, autoimmunity, and abnormal immunoregulation. The recent discovery of a retrovirus, HTLV III, as a possible etiologic agent is discussed in relation to other viruses known to cause immunodeficiency. Simian AIDS, an animal model of virus-induced immunodeficiency, is also discussed. Recommendations are made regarding the interpretation and limitations of immune testing in AIDS, including a discussion of how apparently healthy homosexuals and groups at risk develop an immunologic profile which mimics that of patients with AIDS.

Since late 1981, an unexpected outbreak of opportunistic infections and unusual neoplasms has been noted, described, and studied (1-4). This outbreak appears to have had its onset in the United States in 1978-1979. The affected patients lacked the usual congenital or acquired immunosuppressive background illnesses that would be expected to predispose to such infections as pneumocystis pneumonia and such neoplasms as disseminated aggressive Kaposi's sarcoma. The term "acquired immunodeficiency syndrome" (AIDS) is partially inaccurate, since it does not really differentiate the current syndrome from many known *acquired* immunodeficiency states such as leukemia, lymphoma, systemic lupus erythematosus, and malnutrition. In addition, exogenous factors such as treatment with corticosteroids and other immune suppressing medications can cause acquired immunodeficiency. Perhaps a more descriptive (albeit, more cumbersome) term could be the "idiopathic" acquired immunodeficiency syndrome. This report will attempt to summarize and review the immunologic abnormalities that have been described in AIDS and its apparently related disorders. We will also review such immunologic data as are available in normal healthy controls and high-risk groups, eg, homosexual men, intravenous drug users, and hemophilia patients.

General Overview of the Immune System

The immune system is complicated, and concepts of its origins, functions, controls, and derangements are continuously changing. Newer tools, such as hybridoma-produced monoclonal antibodies to cell surface markers on lymphocytes and other effector cells have provided more information, yet raised more questions. The simplified outline of the immune system which follows will serve as a ground for the discussion that follows.

The immune system has "surveillance" functions to protect humans (and other vertebrates) from infections and cancer. Multipotential stem cells arise during embryogenesis and develop further into two major populations of lymphoid stem cells (5-8). One of these, pre-T cells, leaves the bone marrow, enters the epithelial thymus, and matures there into mature T-cells under the influence of local thymic hormones. Mature T-cells leave the thymus and populate the paracortical and medullary areas of lymph nodes, the central regions of the periarterial lymphoid sheaths of the spleen, and other sites. T-cells recognize foreign antigens and self because of receptors on their surfaces. This system is genetically controlled. A variety of T-cell surface antigens can be identified using monoclonal antibodies, and these antibodies can define T-cell subpopulations (5).

B-cells mature in the bone marrow of mammals. The cell membrane of these cells incorporates IgD and IgM, and these serve as recognition units for antigen(s). After specific antigenic stimulation, B-cells, usually under the influence of helper T-cells, undergo blastic transformation, proliferate, and differentiate further. Diversification occurs, and the five classes of immunoglobulins are produced and secreted. The B-cells mature further into plasma cells which secrete either IgG, IgM, IgA, IgD, or IgE in varying quantities.

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T-cells recognize antigen(s) and a self marker, Ia, coded by the HLA-D region in the major histocompatibility system. This encounter results in the blastic transformation and proliferation of specific T-cell clones. However, in contrast to the change described for the B-cells, several T-cell subpopulations have specific functions, eg, memory, suppressor activity, helper activity, cytotoxicity, and lymphokine production. A number of lymphokines (soluble mediators or hormones released by lymphocytes that influence other immune cells) have been identified, including interferons, migration inhibiting factor (MIF), and transfer factor.

Monocyte-macrophages are involved in these processes in at least two steps (7). Early on, these cells encounter new antigens, "process" them, and present them to wandering T- and B-cells. Once "activated" by these antigens, the T- and B-cells undergo the changes described earlier. Eventually, the lymphokines (eg, MIF and others) released by these activated lymphocytes further influence the monocyte-macrophages to perform their effector functions in a more vigorous manner (turned on, "angry," activated macrophages). One such specialized cell in the epidermis, the Langerhans cell, serves as the antigen-presenting cell in the skin. Other types of these cells are found in important areas in the lymphoid tissues and organs.

A review of the immune system organization requires more detailed mention of the chemical signals that regulate cell growth and differentiation (8). A major lymphokine is interleukin-2, which was originally described in the mid-1970s and named T-cell growth factor. Interleukin-2 is produced by T-cells, and it in turn stimulates the division of T-cells. In addition, interleukin-2 stimulates T-cells to produce gamma (immune) interferon which also serves as a lymphokine with several defined important functions. Interleukin-2 seems to have a limited range of sources and targets. Only T-cells that are antigenically stimulated will respond to interleukin-2. In contrast, interleukin-1 has a wide range of effects on non-lymphocytic cells which contribute to inflammation. Evidence has accumulated to suggest that interleukin-1 and endogenous pyrogen are the same molecule!

The sequence of events can be oversimplified and summarized as follows: macrophages release interleukin-1, which stimulates the production of interleukin-2 by T-cells that have been activated by antigen. Receptor-bearing T-cells are stimulated to divide by interleukin-2. Gamma interferon is produced, and it then enhances the cytotoxic activities of T-lymphocytes, macrophages, and natural killer (NK) cells. Immune interferon also amplifies the response of macrophages to specific antigens by increasing the expression on their surface of certain class II histocompatibility molecules that are needed for the presentation of foreign antigens.

B-cell activation cell division requires B-cell growth factor which is produced by T-cells and interleukin-1. Additional lymphokines, called B-cell differentiation factors, are then needed to stimulate the B-cells to a state where they can produce antibodies.

In the peripheral blood, approximately two thirds of the circulating lymphocytes are T-cells, and one third are B-cells. Of the T-lymphocytes in the blood, approximately two thirds are helper T-cells and one third suppressor T-cells, giving the "normal" helper-to-suppressor ratio of approximately 1.2:2.2 in normal, healthy adults (5). In other tissues, T-cells constitute more than 75% of the lymphocytes in lymph and lymph nodes, and B-cells more than 75% of the lymphocytes in the bone marrow. The proportion of T- and B-lymphocytes in the spleen is approximately 50% of each.

Immunologic Findings in AIDS with Routine Screening Techniques

In view of the complexity of the immune system, the many tests available for use or abuse, and the need for accurate, timely, and cost-effective diagnostic tests in patients at risk for AIDS, it is very important for clinicians to be aware of the office and laboratory clues that can be readily obtained without a sophisticated immunology laboratory. It should be reemphasized that AIDS is a syndrome; even with the most expensive technology available today, the diagnosis cannot be made with laboratory testing alone.

Patients who meet the rigorous Centers for Disease Control (CDC) criteria (2,3) for the diagnosis of AIDS will almost invariably have evidence of cellular immunodeficiency. Opportunistic infections with microorganisms (especially viral, fungal, mycobacterial, and parasitic) and/or the presence of certain tumors against which cellular immunity (T-cell mediated immunity) is considered most vital remain the essential components in the diagnosis of AIDS. In these patients, and in several groups that have been identified as being at increased risk, immunologic testing is indicated.

The minimum evaluation that should be done on patients at risk for AIDS would include (see Table I): complete history and physical examination, complete blood cell count with differential white blood cell and platelet count, erythrocyte sedimentation rate, liver function tests, serologic test for syphilis, mononucleosis spot test, hepatitis A and B markers, immunoglobulin quantitation, delayed hypersensitivity skin

TABLE I

Evaluation of the Patient at Risk for AIDS: Screening with Routine Office Procedures

1. Complete history and physical examination
2. Complete blood count with differential count: peripheral blood
   a) Total absolute lymphocyte count
   b) Peripheral blood morphology
   c) Platelet count
3. Liver-related tests
   a) Liver enzymes, bilirubin
   b) Hepatitis viral markers
      1. IgG and IgM-specific hepatitis A antibodies
      2. Hepatitis B surface antigen, surface antibody, and core antibody
4. Venereal diseases-related tests
   a) Complete genital examination
   b) VDRL
5. Mononucleosis-related tests
   a) Monospot test
   b) Save sera for EB virus and CMV titers
6. Autoimmune-related tests
   a) ANA
   b) Coombs'
   c) Urinanalysis (for nephritis)
7. General immunologic testing
   a) Immunoglobulins: quantitation of IgG, IgM, and IgA levels
   b) Delayed hypersensitivity skin tests with at least 3 antigens, eg, candida, mumps, trichophyton, and tetanus toxoid
8. Gastrointestinal tract-related testing
   a) Stool specimens for ova and parasites
   b) Stool specimens for routine C & S
   c) Stool specimens (with throat and rectal) for gonorrhea
   d) Stool for occult blood
   e) Proctosigmoidoscopy if any GI symptoms or history of anal receptive intercourse
9. Chest X-ray

tests, and chest x-ray. In patients with gastrointestinal complaints, especially in homosexual men, an extensive search should be made for infectious agents in stool specimens. Abnormalities of the skin should be evaluated by a dermatologist, and biopsies should be performed on any suspicious lesions. Persistent, unexplained, enlarged lymph nodes should also be biopsied to rule out lymphoma, Kaposi's sarcoma, and infection, and also for prognostic purposes (9).

Recently, Kalish, et al (10) reported that leukopenia was found in 45% of 11 patients with AIDS, 23% of 39 patients with the AIDS-associated lymphadenopathy syndrome (LAS), 9% of 32 mildly symptomatic homosexual men, 4% of 57 asymptomatic homosexual men, and none in 39 asymptomatic heterosexual controls. Similar incidences of anemia and thrombocytopenia were reported in the same series. Cutaneous anergy was identified in 88% of 8 patients with AIDS, 62% of 39 patients with LAS, 37% of 27 mildly symptomatic homosexual men, 18% of 60 asymptomatic homosexual men, and 23% of controls. Elevated levels of IgG, IgA, and IgM were found in 56% of 9, 67% of 9, and 22% of 9 patients with AIDS, respectively. Elevated immunoglobulin levels were found less often in the LAS patients and infrequently in the other groups. Elevated levels of IgM were found, however, in 37% of 30 mildly symptomatic homosexual men, 24% of 59 asymptomatic homosexuals, and 11% of 37 controls. Mean values for the total lymphocyte counts were significantly different among five study groups already described; the mean number of cells was lowest for the AIDS patients and was stepwise increased in the LAS patients, the mildly symptomatic male homosexuals, and the asymptomatic homosexual men.

The values of these routine laboratory tests have been similarly altered in AIDS patients who were not male homosexuals, eg, intravenous drug abusers, hemophilia patients, and sexual contacts and infants in households of AIDS patients (1,4). Generally, these patients have high incidences of titers to hepatitis A, hepatitis B, cytomegalovirus (CMV), and Epstein-Barr virus (EB virus).

T-cell Changes in AIDS, Patients at Risk for AIDS, and Related Disorders

The T-cell changes in AIDS include changes in number (lymphopenia), type (suppressor-helper), and function (decreased response to antigen and mitogen). The most publicized and familiar change is the decreased helper/suppressor ratio. Normally approximated, 64% of T-cells are helper, and 36% are suppressor. The normal ratio, therefore, is 1.5-2:1. This ratio provides a useful index of immunologic stance, but it can be deceptive if taken alone. Recent studies (10,11) reveal that absolute changes in T-helper cells and T-suppressor cells are more important than changes in the ratio.

In AIDS, for example, the dominant change is in the T-helper cells. Suppressor T-cells are often normal or increased, and there is a profound drop in the ratio as well (usually ≤ 0.5 in patients with opportunistic infection). In healthy homosexual men, the ratio is decreased but to a lesser degree; in most cases the decrease is due to an increase in T-suppressor cells. This same pattern is noted in healthy hemophiliacs on Factor VIII replacement therapy. In these two situations, T-helper cells may be normal or increased. The LAS is a mixed group. In 30% there is a definite decrease in T-helper cells, and in 20% an increase in T-suppressors. The combination, therefore, of the profound absolute

decrease in T-helper cells with an associated decrease in ratio is relatively specific for AIDS but does occur in 30% of patients with LAS. Even given this combination, it is not possible to make the diagnosis of AIDS with these laboratory tests alone.

Changes similar to those seen in patients with AIDS (decreased T-helper cells with decreased ratio) are seen in patients during the acute phase of several viral, mycobacterial, and fungal infections (12). This is usually a transient phenomenon, however, and T-suppressor cells are often markedly increased. The T-helper cell depletion resolves quickly, but the T-suppressor cell increase may persist for months. Because cytomegalovirus (CMV) infection is common in the groups at risk for AIDS and is known to decrease the T-helper/T-suppressor cell ratio, it was suspected earlier to be the etiologic agent in AIDS (13). It is more probable that CMV is an opportunist that potentiates rather than initiates the immunosuppression. The AIDS patient is unable to clear the CMV infection and remains in an "acute phase" with prolonged decrease in T-helper cells and ratio.

Although the changes in T-cell subsets are strongly emphasized in the literature, the more important change in AIDS is loss of function (14). Thus, not only are there fewer cells, but the remaining cells fail to respond in normal fashion to foreign antigens or mitogens. Skin tests for delayed hypersensitivity are weak or negative, and the T-cells fail to respond when they are stimulated in vitro with mitogen. Several attempts have been made to define and reverse the T-cell defect, but the first and most basic question is whether this is reversible at all. Addition of interleukin-2 has been shown to improve lymphocyte responses in vitro, but in vivo studies are still in progress. Again, studies of viral infections reveal that similar functional defects occur. Lymphocytes were taken from patients infected with CMV and immediately stimulated with mitogen but failed to respond. When the same lymphocytes were cultured for seven days and restimulated, they responded appropriately (13). This reaction suggests that in CMV infections, at least, the defect is probably not in the T-cell itself but is mediated by suppressor substances that the T-cell can shed. One hope is that AIDS patients may either block the suppressor substance(s) or provide enough activator to overcome the defect.

As stated above, CMV probably potentiates but does not initiate the changes in T-cell number and function. As in renal transplant patients, CMV can act only against a background of immunosuppression. What, then, is the infectious agent "equivalent" of cyclosporin-A which initiates the AIDS process? Recently, a virus related to the human T-leukemia/lymphoma virus (HTLV) has been isolated from a number of AIDS patients (15,16). This virus is known to preferentially attack T-helper cells, but instead of leading to the neoplastic proliferation seen in T-cell leukemias and lymphomas due to HTLV-I and II, this new virus, HTLV-III, appears to destroy the T-helper cells, initiating the profound and sustained immunosuppressant characteristics of AIDS. For this reason, it has been proposed that HTLV stands for human T-cell *lymphotropic* virus instead of *leukemia/lymphoma* virus.

B-cell Changes in AIDS

Until 1983, most references on AIDS reported that humoral immunity was intact. This conclusion was based on the fact that immunoglobulin levels are normal or increased in patients with AIDS and that such patients are plagued more by life-threatening infections usually controlled by cell-mediated immunity rather than by humoral immunity. The findings of Lane, et al (17) and Ammann, et al (18) were somewhat surprising, for they reported severe B-cell dysfunction in AIDS patients. In spite of decreased T-helper cells, the AIDS patients had hyperactive B-cells, with fewer B-cells in the resting state and many more B-cells spontaneously secreting immunoglobulin. However, these B-cells failed to produce adequate antibody response to specific new and recall foreign antigens, even those not requiring T-helper cell function. Thus, the B-cells were "turned on" in one sense but unresponsive in another. The mechanism of this B-cell defect is not known at present, but a viral infection, EB virus mononucleosis, may provide a model of what may be happening in AIDS patients. In fact, EB virus reactivation may even be the cause of the B-cell defect in AIDS. Lane, et al (17) were able to culture EB virus from every patient displaying the B-cell changes. B-cells have a receptor for EB virus: The virus acts as a mitogen, directly stimulating the B-cell to mature, proliferate, and secrete immunoglobulin (19). As part of the host response to this B-cell proliferation, T-suppressor and cytotoxic cells increase markedly. The atypical lymphocytes seen in infectious mononucleosis are largely T-suppressor and cytotoxic cells.

In summary, in AIDS the unchecked EB virus or other viruses may drive the B-lymphocytes to secrete immunoglobulin, but this is a nonspecific, generalized response, and the ability to respond to other specific foreign antigens is severely impaired.

The Lymphadenopathy Syndrome

The immunologic aspects of the LAS represent the full spectrum of the T- and B-cell changes discussed above. Histologically, there are two extremes (9). The majority of lymph node biopsies reveal follicular hyperplasia. The follicle is the node area usually occupied by B-

lymphocytes. This pattern is identical to the pattern seen in early mononucleosis when B-cells are driven to proliferate by the EB virus infection. At the other extreme, the follicles atrophy and are surrounded by a hypertrophied parafollicular area composed of T-suppressor cells, which presumably have halted the B-cell overgrowth. This pattern is similar to the pattern in resolving mononucleosis. Some homosexuals with the LAS do not have a mild or prodromal form of AIDS, but rather seem to have a prolonged mononucleosis-like illness which may be due to EB virus or CMV. To date, between 1-25% of LAS patients will develop frank AIDS. The histologic type most associated with progression to AIDS is the follicular atrophy type. It has been suggested that in their attempt to shut down the B-cell proliferation, the T-suppressor and T-cytotoxic cells are finally victorious, but the victory is pyrrhic. The massive outpouring of T-suppressor cells contributes further to the already intense immunosuppression of AIDS. Supporting the view that the lymph node represents a kind of summation of T- and B-changes is the significant reduction of T-helper cells in the lymph nodes of patients with LAS and Kaposi's sarcoma (20).

Malignancy and AIDS

The same immunosuppression which allows opportunistic infections may allow the emergence of malignancy in patients with AIDS. The most common malignant tumor in AIDS is Kaposi's sarcoma, a tumor of endothelial cell origin. The same aggressive form of Kaposi's sarcoma is seen in renal transplant patients. Perhaps the most interesting aspect of Kaposi's sarcoma in the setting of renal transplant recipients is the complete remission that can be seen after withdrawal of immunosuppression. Unfortunately, the immunosuppression cannot be conveniently decreased in AIDS, and meaningful remissions have not been recorded.

CMV and EB virus may play a central role in the pathogenesis of the common malignant tumors seen in AIDS patients. DNA from CMV has been identified in biopsy specimens of Kaposi's sarcoma (21). Several theories have been proposed to explain the relationship. CMV infects many cells and may directly cause proliferation of endothelial cells, or it may infect and convert a "reactive proliferation" into a neoplastic one, with the CMV acting as an oncogene.

The B-cell lymphomas seen in patients with AIDS are probably related to EB virus (22). As discussed above, EB virus drives B-cells to polyclonal proliferation, and a malignant clone may emerge from this stimulated pool (23). Whether or not the virus is responsible for this transformation to malignancy is not clear, but undoubtedly the initial proliferation is driven by a virus. Burkitt's lymphoma, another EB virus-related tumor, has also been seen in AIDS patients.

Autoimmune Manifestations of AIDS

Similarities between AIDS and autoimmune disorders (Table II) have been noted in several reports (1,4). Among these are the general suppression of cellular immune reactions, polyclonal hyperglobulinemia, and an immune thrombocytopenia (24). Less often, positive tests for antinuclear antibodies and a Coombs-positive hemolytic anemia have been described. As noted earlier, leukopenia is common, and abnormalities of T-cell subsets are almost universally found.

TABLE II
Autoimmune-like Changes and AIDS

1. Suppression of cellular immunity
2. Polyclonal hyperglobulinemia
3. Immune thrombocytopenia
4. Antinuclear antibodies
5. Coombs' positivity (and hemolytic anemia)
6. Leukopenia
7. Circulating levels of acid-labile alpha interferon
8. Elevated blood levels of circulating immune complexes
9. Circulatory lymphocytotoxic antibodies
10. Systemic lupus erythematosus-like circulating anticoagulant
11. Elevated blood levels of beta-2 microglobulin
12. Immune complex nephritis and nephrotic syndrome

One particularly interesting finding, confirmed by several laboratories, is the high incidence of elevated circulating levels of a peculiar acid-labile form of human alpha (leukocyte) interferon (25). In the initial report, 0/22 normal controls had this abnormality, while 2/25 asymptomatic male homosexuals had small amounts (4-8 IU/ml) in their blood. In contrast, 10/35 patients with the LAS and 17/27 with Kaposi's sarcoma had between 4 and 60 IU/ml in their circulation. The only other medical condition known to date in which the blood has a high incidence and large quantities of this acid-labile alpha interferon is systemic lupus erythematosus.

Other abnormalities in AIDS and LAS patients which suggest "overlap" or common origins with autoimmune diseases include positive tests for circulating immune complexes, an SLE-like circulating anticoagulant, lymphocytotoxic antibodies, and elevated levels (1-4) of beta-2-microglobulin levels (26). The latter represents the light chain moiety of class I HLA-antigens on cell surface membranes. Increased beta-2-microglobulin levels may be found in several lymphopro-

liferative disorders and autoimmune diseases including infectious mononucleosis, Crohn's disease, rheumatoid arthritis, Sjögrens syndrome, systemic lupus erythematosus, acute and chronic hepatitis, primary biliary cirrhosis, and sarcoidosis.

A recent report described the nephrotic syndrome in 9/92 patients with AIDS (27). Two other patients in that series had azotemia and proteinuria of less than 3.5 grams in 24 hours. Five of these 11 patients were intravenous drug addicts, and nine patients (including six non-addicts) developed rapidly progressive uremia. Pathologic examination showed focal and segmental glomerulosclerosis. Immunologic staining of the renal tissue usually showed intraglomerular deposits of IgM and C3, suggestive of an immune complex nephritis.

Lastly, an inordinate and unexpectedly high incidence of adverse and/or allergic reactions has been noted in patients who had AIDS and were treated with trimethoprim-sulfamethoxazole. In one series (28), only 5/37 patients who were started on this drug were able to complete the therapy. Therapy had to be discontinued for the others because of fever, rash neutropenia, transaminase elevation, azotemia, and hypoglycemia. An analogy between this problem and the high incidence of ampicillin-induced rashes in patients with infectious mononucleosis has been suggested (29).

The significance of the autoimmune-like abnormalities in patients with AIDS and the AIDS-associated LAS is unknown. Ongoing active infection is known to trigger autoimmune types of changes, and these patients certainly are persistently and often heavily infected with a variety of viral and other organisms. Whether these changes represent merely a secondary effect of such uncontrolled (eg, viral) infection or indicate a more basic immunologic abnormality remains to be determined.

Miscellaneous Other Immunologic Changes and AIDS

In addition to the several alterations in immunity already described, a variety of other abnormalities have been noted (Table III). Almost all reports on AIDS or the LAS have described normal to increased numbers of NK cells but decreased NK cell activity (30). NK cells were first described about ten years ago as cells that are capable of an immediate cytotoxic (killer) response to tumor cells (31). It is probable that NK cells and macrophages do, in fact, represent the first line defense against cancer. Current information suggests that NK cells also may eliminate microbial agents by killing virus-infected host cells, parasites, fungi, and bacteria, and may contribute to graft-vs-host disease and/or autoimmunity.

TABLE III
Immunologic Changes in AIDS: Overview

1. Office (screening) tests
   a) Absent or diminished delayed hypersensitivity on skin testing
   b) Hyperglobulinemia
   c) Lymphopenia
2. Office (more advanced) tests
   a) Decreased T-helper cell: T-suppressor cell rates (≤1.2:1)
   b) Decreased absolute number of T-helper lymphocytes
   c) Decreased lymphocyte responses to mitogen stimulation
   d) Normal to increased numbers of NK cells but decreased NK cell activity
3. Autoimmune-like tests (see Table II)
4. Miscellaneous other immune tests (generally, research laboratory required)
   a) Decreased production of interleukin-1
   b) Decreased production of interleukin-2
   c) Suppressor factors in serum for production of interleukin-2
   d) Altered granulocyte function
   e) Defects in monocyte function
   f) Increased numbers of mast cells in transbronchial tissue and lymph nodes
   g) Increased neutrophils and polyclonal B-cell activation in bronchoalveolar lavage fluid
   h) Elevated thymosin alpha-1 blood levels
   i) Impaired production of gamma interferon and other lymphokines after antigen stimulation of lymphocytes
   j) Polyclonal B-cell activation in blood and inability of these cells to respond to new or recall antigens
   k) Decreased number of T-helper cells in lymph nodes
   l) Reduced Langerhans cell numbers in skin

Other abnormalities in AIDS include decreased production of interleukin-1, decreased production of interleukin-2, presence of suppressor factors in serum for production of interleukin-2 (32), altered granulocyte function (33), defects in monocyte chemotaxis and cytotoxic activity (34), increased numbers of mast cells in transbronchial tissue and lymph nodes (35), increased neutrophils and polyclonal B-cell activation in bronchoalveolar lavage fluid (36) (dichotomy between circulating and regional immunocompetent cells), and elevated serum thymosin alpha-1 levels (37). This last finding is interesting because thymosin alpha-1 is one of the thymic hormones that influences T-cell differentiation, including the induction of T-helper cells. The elevated circulating levels of thymosin alpha-1 could represent end organ failure or could result from the release of hormone from thymic epithelial cells under a viral attack. The biologic activity of these elevated levels also remains to be confirmed.

Impaired production of gamma interferon and other lymphokines upon exposure to antigens has recently

been described in patients with AIDS (14). Gamma interferon stimulates many components of host defenses: cytotoxic and NK cell activities, monocyte-macrophage activity against intracellular pathogens, lymphocyte antiviral activity, antiviral activity of other cells (fibroblasts, epithelial cells, etc), expression of HLA-DR (class II HLA or Ia antigens) and F receptors, release of interleukin-1, priming for tumoricidal activity, and induction of interleukin-2 receptors.

Although viral infection of T-helper cells currently represents the most likely theory for the etiology of AIDS, the report of reduced Langerhans cell numbers in the skin of AIDS patients is interesting (38). T-cell abnormalities can be secondary to generalized B-cell activation or defects in the antigen-presenting cell system. It is possible, therefore, that the T-helper cell abnormalities are not primary in AIDS and that the Langerhans cells (and other dendritic cells) might be the target of a virus attack; a deficiency in these cells might then result in a cascade of secondary T-cell abnormalities. The result would be a severe and possibly irreversible immunodeficiency state. Gamma interferon and interleukins-1 and -2 can, in vitro, correct similar deficiencies in Langerhans cells induced by ultraviolet light exposure.

So far as sexual practices and immune changes are concerned, much interest has been generated by the finding of antisperm antibodies in 19/26 homosexual men who were anal sperm recipients and smaller percentages of antisperm antibodies in sexually active male homosexuals who were not anal sperm recipients (39). Human seminal plasma has been found to suppress NK activity (40,41). The risk of AIDS among male homosexuals appears to be greatest for those who are anal sperm recipients and who have the largest number of sexual partners (39).

The use of amyl nitrate has not been shown to correlate statistically with the development of AIDS in the at-risk groups. Although opioids and stress do transiently alter T-cell function and lower the T-helper/T-suppressor cell ratio (42), there is no evidence that these factors play any more than an adjunctive role, if any, in the genesis of AIDS.

Simian AIDS (SAIDS)

An acquired immunodeficiency syndrome has been noted in monkeys in New England and California (43). Endemic immunodeficiency with consistent immunologic abnormalities occurred in macaques in the New England colony. In California, four separate outbreaks of SAIDS have occurred in two species of macaque monkeys. The latter illnesses were characterized by malignant lymphomas and opportunistic infections including Mycobacterium avium-intracellulare, Herpesvirus simiae, and progressive multifocal leukoencephalopathy. In other outbreaks, encephalitis, candidiasis, lymphadenopathy, splenomegaly, persistent diarrhea, chronic wasting, and cutaneous fibrosarcomas developed. As in human AIDS, the outbreaks in primates carried a high mortality (44).

Immunologic testing in SAIDS has revealed varying incidences of the following: lymphopenia, granulocytopenia, thrombocytopenia, diminished-to-absent delayed hypersensitivity on skin tests, depressed stimulation indices of lymphocytes with mitogens, and high titers to CMV. SAIDS differs from human AIDS in the lesser incidence of pneumocystis, the hypoglobulinemia, and the more normal helper/suppressor T-cell ratios that characterize the non-human primate syndrome (43,44). Later studies in SAIDS have shown somewhat depressed T-helper/T-suppressor cell ratios.

A new type D retrovirus has been isolated from the peripheral blood lymphocytes and pharyngeal secretions of monkeys with SAIDS but not from healthy monkeys using a co-cultivation technique with Raji cells, a lymphoblastoid cell line of human origin (45,46). Early reports suggest that the type D retrovirus of SAIDS does not appear to be closely related to the human T lymphoma-leukemia virus (HTLV-III) that is currently the leading candidate for the viral etiology of human AIDS (15,16).

Summary and Conclusion

Much confusion has occurred because seemingly healthy homosexuals may acquire an immunologic profile similar to that of AIDS patients. This can be related to the ability of viral infections other than the "AIDS agent" to cause immunosuppression. In fact, parasitic, viral, mycobacterial, and fungal infections are all capable of causing an immunologic profile similar to AIDS, but the effect is usually transient. In AIDS, the suppression is more severe and more sustained, leading finally to a state of immunologic "shock," at which point even the most passive, easily controlled organisms such as Pneumocystis carinii can act as a virulent, deadly pathogen. The development of malignancies and autoimmune changes are also evidence of the profound alterations in the immunoregulation system of these patients.

The etiologic agent in AIDS may be a new type T-cell lymphotropic virus, HTLV-III, which infects and destroys T-helper cells, creating the profound immunosuppression characteristic of the syndrome. The virus apparently can create the syndrome in people outside the recognized risk groups. In homosexual men, the immunosuppression presumably induced by

this virus is aggravated by infection with ubiquitous pathogens, such as CMV and EB virus, which cause further immunosuppression and the other manifestations discussed above.

A similar abnormal immunologic profile is seen in many healthy hemophiliac patients (47), intravenous drug abusers (48), and patients who have received multiple transfusions (49). The cause, again, may be repeated exposure to common viruses and foreign antigen(s) resulting in subclinical immunosuppression. Clearly, this does not lead to AIDS as was once suspected, but it does lead to an immunologic profile simlar to AIDS which creates confusion and makes it necessary to define AIDS clinically rather than by immunologic tests. If the accumulating data relating HTLV-III is confirmed, serologic tests for this virus may simplify the diagnosis and, perhaps, lead to the development of a vaccine.

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