Acquired Immunodeficiency Syndrome: Epidemiologic, Clinical, Immunologic, and Therapeutic Considerations

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The acquired immunodeficiency syndrome is a new disease whose cause is unknown but is almost surely due to a transmissible agent, most likely a virus. The disease is clearly spread by sexual contact, particularly homosexual activity. Blood-borne transmission appears to be responsible for the spread of the disease, although it is highly likely that the disease is not readily spread through casual, nonsexual, non-blood-borne contact. The disease is still highly concentrated in the United States. It is now seen in several countries throughout the world. The common denominator of the disease is a profound suppression of cell-mediated immunity, specifically a quantitative and qualitative defect in the T4 inducer or helper subset of T lymphocytes. Hyperactivity of B lymphocytes is also characteristic. The clinical manifestations are those of severe and life-threatening opportunistic infections and unusual neoplasms, particularly Kaposi’s sarcoma. The mortality may well approach 100%, making this one of the most extraordinary transmissible diseases in history.

DR. ANTHONY S. FAUCI (Chief, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases): In the summer of 1981, the Centers for Disease Control (CDC) alerted the medical community to the unprecedented occurrence of Kaposi’s sarcoma, Pneumocystis carinii pneumonia, and other severe opportunistic infections in apparently previously healthy homosexual men in the United States (1, 2). What has followed has been the evolution of a new and extraordinary syndrome whose underlying defect is an acquired immune deficiency caused almost surely by a transmissible agent. The disease is no longer confined to the male homosexual population, and the numbers of patients are increasing at an alarming rate. The syndrome has been termed the acquired immunodeficiency syndrome and for surveillance purposes has been empirically defined by the CDC (Table 1).

Epidemiology

SCOPe OF THE SYNDROME

Initially, in June and July 1981, 5 cases of P. carinii pneumonia were reported in previously well homosexual men in Los Angeles (1), and 26 cases of Kaposi’s sarcoma were also reported in previously well homosexual men in New York and Los Angeles (2). By August 1983 there had been over 2000 cases reported from 39 states and the District of Columbia as well as 122 cases from at least 20 other countries (CDC weekly update on the acquired immunodeficiency syndrome). Every 6 months there has been a doubling of the number of patients affected. Because the incubation period for adults is generally felt to be greater than 1 year, the full scope of the syndrome has not yet been realized. However, the syndrome’s pattern of transmissibility suggests that it will remain largely confined to the groups already affected, with minor intrusions into other populations at high risk.

RISK GROUPS

There are four major risk groups for the acquired immunodeficiency syndrome (Table 2). Clearly, homosexual or bisexual men constitute the largest risk group, accounting for 71% of all the cases reported in the United States. Intravenous drug abusers with no history of homosexuality comprise 17% of the total patients. The first reports of the disease in this latter group (3) added extra credence to the theory that this disease was caused by a transmissible agent and, together with reports of the acquired immunodeficiency syndrome in other risk groups, discounted the erroneous assumption that there was something intrinsic to homosexuality itself that was causally related to the syndrome.

The appearance of the acquired immunodeficiency syndrome in Haitians in the United States with no admitted history of homosexuality or intravenous drug abuse has been extremely puzzling and has led to wide speculation on the potential connections between Kaposi’s sarcoma in Africa and the acquired immunodeficiency syndrome in Haiti as well as the connection between visits to Haiti of male homosexuals from New York, Los Angeles, and San Francisco, and the appearance of the acquired immunodeficiency syndrome in the United States. This speculation is based on no data, however, and of interest is the fact that a substantial proportion of Haitians with this disease may in fact be homosexual because Haitians rarely admit to homosexual activity (4). At present the "Haitian connection" remains unexplained. Together with the appearance of the disease in intravenous drug abusers, the syndrome is best grouped into the following four risk categories: (1) homosexual and bisexual men, (2) individuals with a history of intravenous drug use but no history of homosexuality, (3) Haitians with no history of homosexuality, and (4) individuals with a history of frequent sexual contacts with gay men.
Table 1. Centers for Disease Control Surveillance Definition of the Acquired Immunodeficiency Syndrome

<table>
<thead>
<tr>
<th>Presence of reliably diagnosed disease at least moderately indicative of underlying cellular immunodeficiency (Kaposi’s sarcoma in a patient under &lt;60 years of age, Pneumocystis pneumonia, other opportunistic infections)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of known causes of underlying immunodeficiency and of any other reduced resistance reported to be associated with the disease (immunosuppressive therapy, lymphoreticular malignancy)</td>
</tr>
</tbody>
</table>

Although the problem cannot be dismissed because it appears possible that the syndrome is transmitted via blood and blood products, it is generally agreed that given the small number of suspected transfusion-associated cases the risk of not accepting a needed blood transfusion far outweighs the risk of contracting the disease from transfused blood.

Recently, either full-blown acquired immunodeficiency syndrome, generalized lymphadenopathy syndrome (see below), or severe immunodeficiency has been reported in the female sexual partners of a few patients with the syndrome (11). The significance of this finding may be substantial because it raises the possibility of heterosexual spread of the disease outside the usual risk groups. In this regard, it should be pointed out that there have been no recognized cases of the syndrome being transmitted by sexual contact from a woman to a man.

The recent reports of an unexplained immunodeficiency syndrome with many characteristics of adult acquired immunodeficiency syndrome occurring in infants born in families with recognized risks for the acquired immunodeficiency syndrome (12, 13) has caused considerable concern regarding the danger of the spread of the syndrome to household contacts of high-risk groups. However, if the children did have the acquired immunodeficiency syndrome and contracted it from within the family, it is likely that the disease was transmitted from mother to infant either pre- or perinatally (14). There is no evidence that the acquired immunodeficiency syndrome can be transmitted by routine household or social contact.

Table 2. Hierarchical Order of Acquired Immunodeficiency Syndrome Risk Groups, August 1983

<table>
<thead>
<tr>
<th>Homosexual or bisexual†</th>
<th>Intravenous drug user</th>
<th>Haitian</th>
<th>Hemophiliac</th>
<th>Non-apparent or unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>Cases</td>
<td>Percent</td>
<td>Cases</td>
<td>Percent</td>
<td>Cases</td>
</tr>
<tr>
<td>Homosexual or bisexual†</td>
<td>1427</td>
<td>76.0</td>
<td>0</td>
<td>0.0</td>
<td>1427</td>
</tr>
<tr>
<td>Intravenous drug user</td>
<td>273</td>
<td>14.5</td>
<td>66</td>
<td>10.8</td>
<td>339</td>
</tr>
<tr>
<td>Haitian</td>
<td>91</td>
<td>4.9</td>
<td>14</td>
<td>10.8</td>
<td>105</td>
</tr>
<tr>
<td>Hemophiliac</td>
<td>15</td>
<td>0.8</td>
<td>0</td>
<td>0.0</td>
<td>15</td>
</tr>
<tr>
<td>Non-apparent or unknown</td>
<td>72</td>
<td>3.8</td>
<td>38</td>
<td>28.4</td>
<td>110</td>
</tr>
<tr>
<td>Total</td>
<td>1878</td>
<td>100.0</td>
<td>130</td>
<td>100.0</td>
<td>2008</td>
</tr>
</tbody>
</table>

* Data are courtesy of the Centers for Disease Control.
† The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.

Patient Profile

The profiles of patients with the acquired immunodeficiency syndrome reflect the populations within the risk groups (Table 2). The race and ethnicity pattern of these patients are: white non-Hispanic, 58%; black non-Hispanic, 27%; Hispanic, 14%. The age distribution shows...
that virtually all of the patients are between ages 20 and 49 years. As of August 1983 there have been 130 reported cases of women with the syndrome out of the total of 2008 cases (CENTERS FOR DISEASE CONTROL. Unpublished observations).

**Clinical Syndromes**

**Classic Acquired Immunodeficiency Syndromes**
The classic acquired immunodeficiency syndromes are: opportunistic infections, Kaposi's sarcoma, and other lymphoid malignancies. Clearly, the commonest opportunistic infection is *P. carinii* pneumonia. The breakdown of disease patterns and manifestations in patients with the syndrome regarding *P. carinii* pneumonia versus Kaposi's sarcoma shows that the commonest manifestation of the syndrome comprising 51% of patients is *P. carinii* pneumonia without Kaposi's sarcoma. Kaposi's sarcoma without *P. carinii* pneumonia forms the next largest group with 27% of patients, whereas 7% of patients have both Kaposi's sarcoma and *P. carinii* pneumonia, and 16% of patients have other opportunistic infections without *P. carinii* pneumonia or Kaposi's sarcoma (CENTERS FOR DISEASE CONTROL. Unpublished observations).

**Chronic Lymphadenopathy Syndrome**
The CDC has defined the chronic unexplained lymphadenopathy syndrome in homosexual men as lymphadenopathy of at least 3-months' duration involving two or more extraglandular sites and confirmed on physical examination; absence of any current illness or drug use known to cause lymphadenopathy; and presence of reactive hyperplasia in a lymph node, if a biopsy is done (16). The relationship between this syndrome and full-blown acquired immunodeficiency syndrome is unclear at present. It is possible that the lymphadenopathy syndrome represents an entirely different syndrome from the acquired immunodeficiency syndrome; this seems unlikely given its temporal relationship to the appearance of the latter. On the other hand, investigators fear that the syndrome may actually represent a prodrome of acquired immunodeficiency syndrome and that patients will ultimately have the classic syndrome. Indeed, a substantial number of patients have been reported, who ultimately developed classic acquired immunodeficiency syndrome with Kaposi's sarcoma, *P. carinii* pneumonia, or other opportunistic infections, who had initially presented with chronic lymphadenopathy (3, 17-22).

**Mortality Rate**
The overall mortality of the disease is 38% of the 2008 patients reported as of August 1983 (CENTERS FOR DISEASE CONTROL. Unpublished observations). However, if one breaks down the mortality according to the year of diagnosis, the ultimate mortality may well approach 100%. It is clear that many more people have been exposed to the putative etiologic agent than have developed the syndrome. Therefore, it is highly likely that a significant number of persons have been infected but have not developed the disease and probably have developed immunity. However, once the full-blown clinical manifestations of the disease set in, the course is likely one of inexorable fatality.

**Infections in the Acquired Immunodeficiency Syndrome**
Dr. Abe M. Macher (Staff Fellow, Microbiology Service, Department of Clinical Pathology, Clinical Center): Over the past 2 years, we have had the opportunity to follow and prospectively study 53 patients with the acquired immunodeficiency syndrome and have paid particular attention to the nature and extent of their infectious disease complications. The following discussion is based on this experience.

The commonest etiologic agents of serious infections in our patients are shown in Table 3. Oral candidiasis is commonly seen and extension of lesions distally leads to esophageal erosions; patients have dysphagia, odynophagia, and retrosternal burning. Barium studies (esophagrams) show mucosal ulcerations, and samples from esophageal biopsies show invasive candidiasis.

 Patients with the acquired immunodeficiency syndrome often have manifestations of herpes virus infection. Both primary and recurrent herpes simplex virus infections may appear as vesicular lesions on erythematous bases in oral, genital, and perineal areas. The recurrences often present as extensive genital and perirectal ulcerations but may also involve the esophageal and tracheobronchial mucosa. Cytomegalovirus has been isolated from several sites, including throat washings, urine, or blood, from nearly all the patients studied at the National Institutes of Health (NIH) Clinical Center. Fevers, granulocytopenia, lymphocytopenia, thrombocytopenic purpura, maculopapular rashes, interstitial pneumonia, chorioretinitis, esophagitis, and ulcerative gastrointestinal lesions are all potential manifestations of cytomegalovirus infections in patients with this syndrome. Epstein-Barr virus has been isolated from the throat washings and peripheral blood lymphocytes of virtually all of our patients. The clinical significance of this finding is still unclear; however, it may relate to the propensity of these patients to develop lymphoid malignancies.

*Mycobacterium avium-intracellulare* is a ubiquitous environmental saprophyte that, in the past, had rarely been shown to be a cause of disseminated disease. However, *M. avium-intracellulare* has been a common pathogen in patients with the syndrome (20, 23), suggesting

<table>
<thead>
<tr>
<th>Infection</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus*</td>
<td>31</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>29</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td>26</td>
</tr>
<tr>
<td><em>Mycobacterium avium-intracellulare</em></td>
<td>15</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>8</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>7</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>5</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>5</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>4</td>
</tr>
</tbody>
</table>

* *Positive blood culture or tissue histopathology.
that they have an unusual immunologic lesion that selectively predisposes them to this heretofore rare mycobacterial pathogen. Mycobacterium avium-intracellulare is typically shown in and cultured from bone marrow, lymph node, and liver biopsy samples from patients with this syndrome. More strikingly, eight patients at the NIH Clinical Center have grown M. avium-intracellulare and these patients are, therefore, mycobacteremic (24). Histopathologic findings from biopsy samples commonly show a histiocytic process as true granulomata are often poorly formed or absent. Acid-fast stains show large clusters of mycobacteria within the cytoplasm of the histiocytes (Figure 1). These clusters, or "globi," of acid-fast mycobacteria are reminiscent of those seen in patients with lepromatous leprosy.

Diffuse pneumonitis is another common manifestation of the acquired immunodeficiency syndrome and may be caused by cytomegalovirus, Cryptococcus neoformans, M. avium-intracellulare, and even Kaposi's sarcoma when intra-alveolar hemorrhage is associated with pulmonary Kaposi's sarcoma. However, the commonest cause of diffuse pneumonitis is P. carinii (17, 21).

Pneumocystis carinii pneumonia in patients with the acquired immunodeficiency syndrome differs from the disease seen in other groups of immunosuppressed patients (Kovacs JA. Personal communication). Pneumocystis carinii pneumonia in patients with the syndrome is characterized by a subacute and insidious onset as the patient complains of a mild cough or chest discomfort of 2- to 10-weeks' duration. Chest radiographs show subtle infiltrates, and often the patient presents with minimal hypoxemia with arterial blood gases in the range of 80 to 95 mm Hg on room air. Histopathologic findings show pneumocyst organisms in large numbers, and we have not uncommonly found them in large numbers in the bronchial lavages of our patients. Furthermore, P. carinii pneumonia frequently presents in the setting of other concomitant opportunistic infections. Thus, in addition to bacterial, mycobacterial, fungal, and viral cultures, we have regularly used rapid special stains including toluidine blue O (25), Gram Weigert (26), or methanamine silver (27).

Central nervous system disease affects many patients and may present as a progressive idiopathic encephalopathy, relapsing cryptococcal meningitis, mass lesions due to Toxoplasma gondii, progressive multifocal leukoencephalopathy, and central nervous system lymphoma.

The idiopathic encephalopathy is characterized by a slowly progressive dementia that often becomes incapacitating. Computed tomographic examination of the brain often shows no focal lesions, but the lateral ventricles may be enlarged. Results of brain biopsy or autopsy show nonspecific inflammation often with demyelination but no etiologic agent. In patients with progressive multifocal leukoencephalopathy, computed tomography may show intra-axial hypodense focal lesions, and tissue from brain biopsy samples will show characteristic inclusion cells using an immunohistochemical staining technique (28).

Cryptococcal meningitis is a relatively common complication in patients with the syndrome. However, cryptococcal meningitis is often part of a disseminated process with positive blood and bone marrow cultures. The disease often recurs despite apparently adequate therapy. Toxoplasma gondii and lymphoma are the commonest causes of mass lesions in the central nervous system in patients with the syndrome. Patients with toxoplasma infection present with fever and focal neurologic signs. Computed tomographic examination with contrast typically shows single or multiple enhancing intra-axial mass lesions (29). Unfortunately, serologic findings have not been useful diagnostically using the Sabin Feldman dye test of IgM-enzyme-linked immunosorbent assay titers. Therefore, definitive diagnosis requires showing the tachyzoite in tissue sections or by isolating the organism through intraperitoneal mouse infections from a tissue that does not ordinarily contain the dormant cyst.

Chorioretinitis is also common in these patients. Although occasional patients will present with T. gondii retinitis (diagnosed by vitrectomy), the commonest cause of progressive chorioretinitis is cytomegalovirus (30). Initially, the lesions are asymptomatic as perivascular exudates and hemorrhages are seen. However, as the lesions enlarge and begin to involve macula, vision be-
comes compromised (Figure 2). At autopsy, numerous cytomegalovirus inclusion cells are shown in the necrotic retinal, choroidal, and optic nerve tissues.

Persistent or recurrent diarrhea is a frequent problem among patients with the acquired immunodeficiency syndrome. Although some patients have several loose stools per day, others may have copious volumes of watery diarrhea that can reach 15 litres per day. Homosexuals with acquired immunodeficiency syndrome may have a range of bowel problems due to the enteric organisms that cause symptomatic disease in the general homosexual population, including Entamoeba histolytica, Giardia lamblia, and Shigella, Salmonella, and Campylobacter species. Appropriate antimicrobial treatment that eliminates these pathogens often fails to eliminate the copious watery diarrhea. Some patients with persistent watery stools have cryptosporidiosis. Cryptosporidium is an enteric coccidia that attaches to the epithelial surface of the small and large intestine; it ordinarily infects animals but occasionally causes a self-limiting diarrheal illness in immunocompromised humans (31). The oocyst form of the protozoan is found in stool specimens using a sucrose flotation method. Although thorough evaluation has in some patients shown celiac disease, cytomegalovirus lesions, M. avium-intracellulare infiltration of the bowel wall, or gastrointestinal Kaposi's sarcoma, many patients with persistent diarrhea have no demonstrable pathogen despite careful stool examination, endoscopic examination, small bowel biopsy, and autopsy.

Finally, we have done autopsies on 16 patients with the acquired immunodeficiency syndrome at the NIH. The commonest life-threatening infection found at autopsy was disseminated cytomegalovirus in 14 patients. Disseminated M. avium-intracellulare infections were shown in 9 patients, disseminated Cryptococcus neoformans in 6, P. carinii pneumonia in 3, and intracerebral T. gondii in 1.

Kaposi's Sarcoma and Other Neoplasms

Dr. Dan L. Longo (Head, Experimental Immunology Section, Medicine Branch, National Cancer Institute): To date, two types of malignancy have been seen in increased frequency in patients with the acquired immunodeficiency syndrome: Kaposi's sarcoma (22) and malignant lymphomas of several histologic types including Burkitt's lymphoma (32), immunoblastic lymphoma (33), a subtype of Rappaport's diffuse histiocytic lymphoma), lymphoblastic lymphoma (34), and Hodgkin's disease (Longo DL, Stites R, Gelmann EP. Unpublished observations). These lymphomas are histologic subtypes with diverse cells of origin including B cells, T cells, and dendritic cells (monocyte-macrophage). Rarely do patients have both Kaposi's sarcoma and malignant lymphoma (34). In addition, the incidence of two other malignancies is increased in one of the groups at high risk of developing the acquired immunodeficiency syndrome, namely, male homosexuals. These malignancies are squamous cell carcinoma of the tongue and cloacogenic carcinoma of the rectum. Cancer of the tongue has been a disease of elderly men with a history of tobacco and alcohol abuse (35) and cloacogenic carcinoma of the rectum, which arises in the transitional epithelium at the anorectal junction and accounts for 3% of all rectal cancer, has the same epidemiology as rectal cancer of other histologic types (36). The occurrence of these two malignancies in young homosexual men was recognized in the early 1970s before the appearance of the acquired immunodeficiency syndrome in the same group (Ziegler JL, personal communication). Therefore, it is felt that tongue and rectal cancers are not related to the acquired immunodeficiency syndrome but coincidentally occur in a common risk group, male homosexuals.

The magnitude of the problem of Kaposi's sarcoma in patients with the acquired immunodeficiency syndrome can be estimated by examining the data in Table 4 collected by the CDC. About 34% of these patients have developed Kaposi's sarcoma and nearly 28% of those patients have died. When the incidence of lymphoma in these patients (3% to 4%) is added to that of Kaposi's sarcoma, nearly 40% of the victims have developed a malignancy. This number is over twice the incidence of malignancy in patients with other primary and secondary immunodeficiency states (37, 38). Four clinical subtypes of Kaposi's sarcoma are recognized based on the degree of local invasiveness and organ or node involvement. Nodular Kaposi's sarcoma consists of blue or brown nodules or plaques confined to the skin (usually starting on the legs); however, lesions may be numerous and widespread. Autoimmunization has been shown (39) and Koeber's phenomenon (spread to sites of trauma) may be seen (40). Florid and infiltrative Kaposi's sarcoma subtypes are locally destructive lesions, with the former usually causing fungating skin lesions and the latter deep tissue and bone invasion by direct extension from the skin. Disseminated or lymphadenopathic Kaposi's sarcoma subtype is defined as any distant spread to visceral organs or lymph nodes.

There are two essential features of the histopathologic

<table>
<thead>
<tr>
<th>Case</th>
<th>Percent of All Acquired Immunodeficiency Syndrome Cases Reported (2008)</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi's sarcoma</td>
<td>533</td>
<td>26.5</td>
</tr>
<tr>
<td>Kaposi's sarcoma with Pneumocystis carinii pneumonia</td>
<td>148</td>
<td>7.4</td>
</tr>
<tr>
<td>Total</td>
<td>681</td>
<td>33.9</td>
</tr>
</tbody>
</table>

*Data are courtesy of the Centers for Disease Control.*
mechanism of Kaposi's sarcoma regardless of the clinical syndrome: vascular proliferation (vascular spaces need not be lined by endothelium), and spindle-shaped neoplastic cells in a network of reticulin fibers that appear to be of endothelial origin by virtue of their binding of antibody to factor VIII (41) and proliferating in vitro in response to endothelial growth factor (ARMSTRONG G. Unpublished observations). Tumors may be subcategorized based on the atypia of the cells and the abundance of vascular formations. Skin involvement tends to be intra- dermal and lesions occurring in other epithelial-lined organs tend to be in the submucosa.

In addition to patients with the acquired immunodeficiency syndrome, Kaposi's sarcoma is also seen in elderly Jewish and Italian men (incidence, 0.03 cases per 100,000 people), African children or young adults in the same regions where Burkitt's lymphoma is prevalent, and transplant recipients. These non-epidemic forms of disease considered together have only about a 10% incidence of extranodal organ involvement (40). In contrast, the epidemic form of the disease has about a 72% incidence of organ involvement. Lymph nodes (81%) and the gastrointestinal tract (81%) are most often involved, and lung involvement (11%), though relatively uncommon, can result in severe physiologic compromise. All segments of the gastrointestinal tract from mouth to anus can be involved, and there is a correlation between the presence of oropharyngeal lesions and other gastrointestinal sites of disease (42). About 5% of patients have extranodal organ system disease in the absence of skin involvement.

The treatment of the non-epidemic forms of Kaposi's sarcoma has generally been localized radiotherapy with x-rays (43) or more extended field or total body electron beam radiotherapy (44) because most patients have localized disease. This treatment achieves a complete response in 93% to 100% of patients. Those patients with more aggressive or advanced disease have shown high response rates to a wide range of chemotherapeutic agents used singly and in combination (45) (Table 5).

Table 5. Treatment of Nonepidemic Kaposi's Sarcoma

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patients Tested</th>
<th>Complete Responses</th>
<th>Complete + Partial Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop iatrogenic immunosuppression</td>
<td>8</td>
<td>5 (63)</td>
<td></td>
</tr>
<tr>
<td>Single agent chemotherapy*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinblastine</td>
<td>26</td>
<td>11 (42)</td>
<td>23 (88)</td>
</tr>
<tr>
<td>Daunomycin</td>
<td>46</td>
<td>14 (30)</td>
<td>40 (87)</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>10</td>
<td>0 (0)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>ICRF-139</td>
<td>18</td>
<td>1 (5)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>BCNU</td>
<td>21</td>
<td>4 (19)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>6</td>
<td>0 (0)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>DTIC</td>
<td>10</td>
<td>3 (30)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>10</td>
<td>1 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Combination chemotherapy†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daunomycin + vincristine</td>
<td>52</td>
<td>31 (60)</td>
<td>47 (90)</td>
</tr>
<tr>
<td>Daunomycin + vincristine + DTIC</td>
<td>39</td>
<td>37 (95)</td>
<td>39 (100)</td>
</tr>
<tr>
<td>Vinblastine + bleomycin</td>
<td>1</td>
<td>1 (100)</td>
<td></td>
</tr>
</tbody>
</table>

* ICRF-139 = Kasabian (Imperial Cancer Research Fund); BCNU = Bisanthracene (carmustine); DTIC = dacarbazine; 5-(3',3'-diamethyl-1-riothio) imidazolinone-4-carboxyl.
† See reference 45 for primary references.

however, the rarity of the tumor has meant that most treatment reports involve a small number of patients. The median survival of patients with nonepidemic Kaposi's sarcoma is 13 years (range, 2 months to 50 years), and the common causes of death are heart failure, second malignancy, sepsis from infected skin lesions, and hemorrhage. Up to 37% of patients develop a second tumor (46).

The treatment of the epidemic form of Kaposi's sarcoma, that associated with the acquired immunodeficiency syndrome, has not been as successful as the treatment of the nonepidemic form of Kaposi's sarcoma (Table 6). Over 60 patients have received some type of interferon. Only about 10% of the patients have had complete responses, and another 20% have had short-duration partial responses. Two small series of patients treated with chemotherapy have been reported using single agents and combinations (49, 50). The studies have not been randomized, and, in general, patients with more aggressive disease have been given the combinations. Responses are common, but 30% of all reported patients have died and the projected 2-year survival in only 30%. There have been no long-term, disease-free survivors (longest remission, 12 months). The causes of death in most patients are overwhelming opportunistic infections and irreversible cachexia and wasting. Tumor-related deaths comprise only about 25% of the total.

The cause of Kaposi's sarcoma is unknown. The disappearance of the disease in patients where the immunodeficiency can be reversed links the cause to immune depression and supports the proposition that the disease may be reactive rather than a malignant transformation. Abundant data link cytomegalovirus to the nonepidemic forms of the disease (51, 53). The high frequency of the HLA-DR 5 allele in one series (22) of Kaposi's sarcoma related to the acquired immunodeficiency syndrome (63% of patients versus 23% in the normal male homosexual population) implies that immune response gene phenomena may be contributing to the development of the disease (54). The analysis of Kaposi's sarcoma cell lines may
clarify the pathogenesis of this complication of the acquired immunodeficiency syndrome.

Finally, physicians managing patients who develop malignant lymphoma should make a vigorous attempt to induce complete remission with combination chemotherapy regimens successful in the particular lymphoma (55-59). The ultimate success in controlling the malignancies associated with the acquired immunodeficiency syndrome most likely depends on reversing the immune dysfunction.

Immunologic Abnormalities

Dr. H. Clifford Lane (Senior Investigator, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases): The acquired immunodeficiency syndrome is one of the most devastating diseases of the adult immune system (3, 17, 18, 19, 60). Abnormalities of immune function that have been reported in patients with the syndrome are shown in Table 7. It should be stressed that these abnormalities are characteristic of patients with the acquired immunodeficiency syndrome, do not necessarily occur in all patients with the syndrome, and are not by themselves in any way diagnostic of the syndrome.

One of the most striking features of the immune system of patients with the acquired immunodeficiency syndrome is profound lymphopenia with total lymphocyte counts often below 500/mm³. This lymphopenia is predominantly due to a loss from the peripheral blood of T lymphocytes that bear the helper/inducer phenotype defined by the monoclonal antibodies OKT 4 or Leu 3 (61). These subsets can be quantitated through the use of fluorescein-conjugated monoclonal antibodies and the use of the fluorescence-activated cell sorter. A typical fluorescence-activated cell sorter analysis of a patient with the syndrome and a control are shown in Figure 3. As can be seen from the figure, the patient has a marked decrease in the number of cells capable of binding the OKT 4 monoclonal antibody. It is this depletion in helper/inducer T lymphocytes that results in a lowering of the helper/suppressor ratio. It is not currently known whether the immunologic dysfunction in this syndrome is due to the imbalance between help and suppression or more directly due to the depletion of T cell help.

Patients with Kaposi's sarcoma alone have a higher absolute number of T4 lymphocytes than those initially presenting with life-threatening opportunistic infections. This is the immunologic correlate of the observation made in the statistics compiled by the CDC (Table 4) that showed that patients with Kaposi's sarcoma alone have a longer life expectancy than those with opportunistic infections. Thus, those patients who initially present with Kaposi's sarcoma alone may be doing so earlier in

Table 6. Treatment of Epidemic Kaposi's Sarcoma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients Tested</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Institution*</th>
<th>Reference</th>
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<td>6</td>
<td>9</td>
<td>MSK</td>
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<td>36-54 × 10⁴ U im every day × 28 d</td>
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<td>1</td>
<td>UCSF</td>
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<td>1 × 10⁶ U/m² iv every day × 5 d, every other week</td>
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<td>4</td>
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<tr>
<td>15 cycle repeats every 21 days</td>
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<tr>
<td>VP-16 (Elcosamide) 150 mg/m² body surface area iv every day × 3 every 28 days</td>
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<td>10</td>
<td>9</td>
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<td>Adriamycin (40 mg/m² body surface area · iv day 1) + vinblastine (6 mg/m² body surface area · iv day 1) + bleomycin (15 mg/m² body surface area · day 1)</td>
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<td>15 cycle repeats every 21 days</td>
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* MSK = Memorial Sloan-Kettering, UCSF = University of California in San Francisco; NCI = National Cancer Institute; NYU = New York University.
† Hoffman-LaRoche, Inc., Nutley, New Jersey.
‡ Schering-Plough Corp., Kenilworth, New Jersey.
¶ Lastrow DL, Unpublished observations.
the course of a progressive immunodeficiency than those initially presenting with a life-threatening opportunistic infection such as P. carinii pneumonia or cryptococcal meningitis.

Although the cause of the basic immunologic lesion remains unknown, the end result, a profound alteration in T-cell function both in vivo and in vitro, is quite evident. In vivo, this alteration in T-cell function may be manifested as the development of neoplasms, the development of opportunistic infections, or the inability to mount a delayed-type hypersensitivity response (cutaneous anergy). Less than 10% of patients have shown the ability to develop a positive skin test when tested with appropriate recall antigens (3,17-21). This inability reflects a profound degree of cellular immune dysfunction. However, as has been pointed out by Siegal (62), this function may be variably intact in early stages of the syndrome.

Virtually all in-vitro measurements of T-lymphocyte function are decreased in patients with the syndrome. These measurements include the responses to nonspecific signals delivered by mitogens (63) as well as responses to the specific signals delivered by soluble antigens such as tetanus toxoid or alloantigens expressed on the surface of allogeneic lymphocytes (mixed lymphocyte reaction) (3, 64).

The T-lymphocyte competence can also be assessed in vitro by the measurement of certain T-cell effector functions such as providing help to B lymphocytes or eliciting a virus-specific cytotoxic lymphocyte response. In both of these variables, patients have been shown to be markedly deficient (63-65). When assayed in a system for measuring immunoglobulin production in which normal helper/inducer cells were present, the suppressor/cytotoxic subpopulation of lymphocytes from the patients appeared to function normally. Similarly, cytotoxic lymphocyte function could be restored to normal simply by the addition of interleukin-2 to culture. Phenotypically, however, these cytotoxic/suppressor lymphocytes have been shown to be activated in vivo because they express certain surface antigens associated with an activated stage of the cell cycle. Whether this in-vivo activation of suppressor/cytotoxic T lymphocytes is related to the immunopathogenesis of the syndrome or is simply part of the normal in-vivo response to viral infection remains to be determined.

The peripheral blood B-lymphocytes of patients with the syndrome are characterized by an enormous degree of polyclonal activation. This activation is shown serologically as elevated levels of total immunoglobulin, predominantly IgG and IgA. In addition, immune complexes have been shown in the serum of most patients with the syndrome (3,17,18,22,60). Finally, there is an increased number of peripheral blood B-cells that spontaneously secrete immunoglobulin reflecting a polyclonal activation. The B cells in such an activated state are refractory to subsequent primary activation signals (65). We feel these findings are most likely due to the activation and transformation of peripheral blood B-lymphocytes by an agent such as Epstein-Barr virus in the absence of the normal regulatory T-lymphocyte influences.

Paradoxically, this polyclonal B-cell activation is accompanied by an inability to mount a de novo serologic response to the primary protein antigen keyhole limpet hemocyanin (63). This fact has important clinical implications regarding the ability of patients to either develop specific humoral immunity or to use the development of such immunity as a clinical test for infection (serologic diagnosis). Serologic responses to recall antigens appear to be highly variable.

In addition to these abnormalities of T- and B-cell function, patients have other serologic markers of altered immune function. These markers include the presence of a heat-labile form of alpha interferon (66), elevated alpha-1 thymosin levels (67), and the presence of substances capable of suppressing the in-vitro immune responses of normal lymphocytes (64).

Host Responses to Viral Infections

Dr. Alain H. Rook (Research Investigator, Division of Virology, National Center for Drugs and Biologies, Food and Drug Administration): Cytomegalovirus and Epstein-Barr virus infections may simulate the clinical and immunologic abnormalities seen in this syndrome. For example, lymphadenopathy and prolonged fever are com-

![Figure 3. Non-gated fluorescence-activated cell sorter analysis of the peripheral blood mononuclear cells from a patient with acquired immunodeficiency syndrome (AIDS) and a healthy control subject. Cells are first incubated with mouse monoclonal antibody OKT 4 or OKT 8 and then with goat antinonbody conjugated to fluorescein isothiocyanate. Fluorescence intensity (y-axis) is then plotted as a function of the number of cells with that intensity (x-axis). Nonspecific binding of goat antibody by monocytes is seen as the peak in the background profiles. The patient with the syndrome has a profound decrease in the number of cells reacting with the OKT 4 monoclonal antibody, indicative of a decrease in the number of helper/inducer T lymphocytes.](image-url)
mon during either cytomegalovirus or Epstein-Barr virus infection. In patients with cytomegalovirus infection, there was an enhanced susceptibility to other opportunistic infections (69). Also, transplant patients with cytomegalovirus infection have an enhanced susceptibility to other opportunistic infections (70).

In our present study, at initial presentation patients with the acquired immunodeficiency syndrome, chronic lymphadenopathy syndrome, and asymptomatic cohorts had throat, urine, blood, and any suspicious skin or mucous membrane lesions cultured for cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and varicella-zoster virus. In addition, virus-specific antibody determinations were done, including anti-cytomegalovirus IgM and IgG and anti-Epstein-Barr virus capsid antigen, early antigen, and nuclear antigen.

Results of attempted virus isolations are shown in Table 8. Cytomegalovirus was isolated from one or more sites from nearly all patients with the acquired immunodeficiency syndrome or chronic lymphadenopathy, but cytomegalovirus viremia was found only in the group with the syndrome. Anti-cytomegalovirus IgM, indicative of recent onset cytomegalovirus infection, was found in 15 of 16 serum samples from patients with the syndrome. 4 of 7 samples from those with lymphadenopathy, and none of 5 samples from asymptomatic homosexual men. Combining the results of culture and IgM serologic findings, all patients with the acquired immunodeficiency syndrome or chronic lymphadenopathy had evidence of active or recent onset of cytomegalovirus infection.

Similarly, active Epstein-Barr virus infection was nearly universal in these same patients. Twenty-five of twenty-seven patients had Epstein-Barr virus isolated from throat washings. Antibody to Epstein-Barr virus early antigens, detectable only during primary or reactivation infection, was found in the sera of 50% of these patients, including one of the two patients who were culture negative, thus providing culture or serologic evidence of active Epstein-Barr virus infection in 96% of patients with the acquired immunodeficiency syndrome. The Epstein-Barr virus infections must have resulted from reactivation of latent virus, because all of these patients had antibodies to Epstein-Barr virus nuclear antigen (71).

In contrast, infection with herpes simplex virus or varicella-zoster virus was much less common, being documented in 6 of 28 and 1 of 28 patients, respectively. With regard to relative frequency of herpesvirus infections, patients with the acquired immunodeficiency syndrome do not resemble other populations with depressed cell-mediated immunity. For instance, among bone marrow transplant recipients who have a high frequency of all herpesvirus infections (72), herpes simplex virus and varicella-zoster virus are more frequent, whereas cytomegalovirus and Epstein-Barr virus are significantly less frequent than in the patients with the acquired immunodeficiency syndrome whom we studied. These findings imply that immunosuppression alone is unlikely to account for the prevalence of cytomegalovirus and Epstein-Barr virus infections in the acquired immunodeficiency syndrome.

In view of the universal occurrence of cytomegalovirus infection in patients with the acquired immunodeficiency syndrome, we studied the integrity of specific and non-specific antiviral cellular immune responses. In bone marrow and renal transplant patients, HLA-restricted cytotoxic T cells and natural killer cells are the cells whose immune functions correlate most significantly with recovery from cytomegalovirus infections (73-75). During acute cytomegalovirus infection, there is usually an increase in this cytotoxicity mediated by both enhanced natural killer cell activity and cytotoxic T cells, the latter cell type being found in the circulation only during acute infection.

In light of these observations, it is noteworthy that all of the patients with the acquired immunodeficiency syndrome that we have studied have had absent cytomegalovirus-specific cytotoxic T cell activity in the presence of active infection with cytomegalovirus, and most have had depressed natural killer cell activity as well (FREDERICK WR, MASUR H, ROOK AH, et al. Unpublished observations). This deficiency in cytotoxic T cell activity may underlie the heightened susceptibility of persons with the acquired immunodeficiency syndrome not only to cytomegalovirus but also to other opportunistic infectious agents.

To understand the basis for the deficient cytotoxic T cell activity, we have examined the capacity of lymphocytes of patients with the syndrome both to produce and to respond to various immunoregulatory lymphokines that are important for the normal differentiation and

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<th>Study Group</th>
<th>Subjects Studied</th>
<th>Viral Isolations</th>
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<tr>
<td>Acquired immunodeficiency syndrome</td>
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<td>Cytomegalovirus</td>
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<td>Kaposi's sarcoma</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Opportunistic infections ± Kaposi's sarcoma</td>
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<td>13</td>
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<tr>
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<td>Asymptomatic without lymphadenopathy</td>
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Table 8. Isolations of Herpesviruses from Healthy Homosexual Men and Persons with the Acquired Immunodeficiency Syndrome or Chronic Lymphadenopathy
maturation of cytotoxic T cells. Phytohemagglutinin stimulation of these lymphocytes resulted in markedly reduced release of interleukin-2 and gamma interferon compared to the levels produced by the lymphocytes from healthy heterosexual subjects. In addition, although the natural killer cell activity of normal lymphocytes, using K562 cells as targets, was consistently augmented by beta interferon or alpha interferon, as is commonly seen (76), lymphocytes of patients with the syndrome were refractory to this immune-enhancing effect of the interferons. In contrast to the lack of effect of beta or alpha interferon, cytokine-mediated antiviral activity with highly purified interleukin-2 resulted in a marked augmentation of both natural killer cell and cytomegalovirus-specific cytotoxic activities and was associated with a restored ability to release gamma interferon (65, 77). Although the mechanism through which interleukin-2 enhances these important antiviral immune responses is uncertain, it may include the effect of interleukin-2 on gamma interferon release because gamma interferon is known to be required for cytotoxic T cell differentiation (78).

At the present time, it is clear that patients with the acquired immunodeficiency syndrome have clinical effects due to a profound defect in T-cell immunity. Our data suggest that if an exogenous source of interleukin-2 were provided, abnormalities in important cell-mediated antiviral immune responses would be corrected. Potentially, this action could lead to recovery from the many devastating opportunistic infections that commonly afflict these patients.

Treatment of Infections and Immune Defects

Dr. Henry Masur (Deputy Chief, Critical Care Medicine Department, Clinical Center): Because patients with the acquired immunodeficiency syndrome die primarily due to opportunistic infection, prognosis could presumably be improved either by developing more effective antimicrobial treatment or by reconstituting the defective immune response. Given the broad range of life-threatening infections to which these patients are susceptible, the latter approach has more theoretical appeal. Unfortunately, to date no patient has successfully regained immunocompetence either spontaneously or due to a therapeutic manipulation. Thus, treatment must be directed at controlling infections and neoplasms until a means for achieving immunologic reconstitution can be developed.

Treatment for some opportunistic infections, such as P. carinii pneumonia, t. gondii encephalitis, candidiasis, and mucocutaneous herpes simplex disease, is often effective in these patients. These infections can be fatal, however, and even when effectively treated, they tend to recur. In contrast, several of the frequently occurring infections are treatable with currently available regimens. These include disseminated M. avium-intracellulare, disseminated cytomegalovirus, and cryptococcosis.

A comparison of P. carinii pneumonia in patients with and without the syndrome between 1979 and 1983 has shown that mortality in these two patient groups is almost identical at 30% (Kovacs J, Hiemenz J. Unpublished observation). If the rapidity of response to drug therapy is compared in the two patient groups, there is no major difference in the number of days required for the patients to defervesce or for the chest radiograph to begin to clear. However, patients with the acquired immunodeficiency syndrome are much less effective in completely resolving their infection and often manifest cough, shortness of breath, substantial hypoxemia, and disease relapse after 10 to 14 days of pentamidine or trimethoprim-sulfamethoxazole treatment which is rarely the case in patients with malignancies, and are highly refractory to this immune-enhancing effect of the drug. Unpublished observations). Adverse reactions appear to be unusually frequent when prophylactic doses are used as well, limiting this drug's potential for preventing this major infectious complication (81).

Oropharyngeal candidiasis and candida esophagitis in patients with the acquired immunodeficiency syndrome have been relatively amenable to conventional antifungal treatment. Oral candida may resolve when nystatin liquid or clotrimazole troches are used every 4 hours. Often, however, oral ketoconazole or intravenous amphotericin B are needed to resolve the lesions. Oral candidiasis usually recurs as soon as treatment is stopped; therefore, patients need to be maintained on oral ketoconazole or nystatin for the duration of their lifetime.

Candida esophagitis responds to either oral ketoconazole or intravenous amphotericin B quite promptly. Symptoms resolve within several days, and after 14 days, endoscopic examination usually shows complete resolution of lesions. Relapses appear to be particularly common after ketoconazole therapy.

Mucocutaneous herpes simplex virus usually responds promptly to a 7- to 10-day course of intravenous acyclovir. Viral shedding ceases within several days and lesions epithelialize. Recurrences in the same area are very common in patients with the acquired immunodeficiency syndrome.

Cryptococcal disease is difficult to treat in the acquired immunodeficiency syndrome. Many patients are leukopenic and cannot tolerate flucytosine therapy without developing even more serious decreases in leukocyte production. Treatment with amphotericin B (0.6 mg/kg
body weight or 0.3 mg/kg body weight) for long courses up to a total dose of 2 to 3 g is usually associated with a symptomatic response, sterilization of blood and spinal fluid, and reduction in cryptococcal antigen titers. However, after amphotericin B is stopped, relapses are quite common, and at autopsy, active cryptococcal disease can usually be found despite apparently adequate treatment.

Infections due to M. avium-intracellulare, cryptosporidiosis, cytomegalovirus, and Epstein-Barr virus currently cannot be treated successfully. Mycobacterium avium-intracellulare is almost always resistant to isoniazid and rifampin and is usually resistant to other commonly used antituberculous agents (20, 22). The best in vitro activity is shown by the experimental compound antamycin (Montedison Company, New York, New York) and by the antileprosy drug clofazamine (National Hansen’s Disease Center, Carrville, Louisiana). Various multiple drug regimens have been tried, but none has succeeded in producing a clinical or microbiologic cure.

Cryptosporidiosis had been treated with over 30 different drugs, including metronidazole, quinacrine, trimethoprim-sulfamethoxazole, and tetracycline (30). None of these compounds has succeeded in decreasing the volume of diarrhea or the quantity of cryptosporidia being passed. Symptomatic relief can be obtained in some patients by using tincture of opium, diphenoxylate, or perhaps cholestyramine. In many patients with cryptosporidiosis, however, the diarrhea does not abate despite aggressive symptomatic therapy.

As in other patients, disseminated cytomegalovirus disease has not responded to intravenous acyclovir or vidarabine. The quantity of circulating virus is not substantially diminished, and organ dysfunction, such as chorioretinitis, is not ameliorated.

Sulfadiazine and pyrimethamine have appeared to be effective in limiting the progression of toxoplasmosis in some, but not all, patients with the acquired immunodeficiency syndrome. Because these drugs suppress bone marrow, they are administered with great difficulty to many patients with the syndrome who are leukopenic to begin with. For patients who do respond, antitoxoplasma therapy probably needs to be continued for life.

Because antimicrobial treatment is often ineffective in patients with the acquired immunodeficiency syndrome, a major thrust of current investigations is to find effective means to reconstitute immunologic competence. Figure 4 shows potential sites for immunologic intervention. If a virus or other infectious agent attacks cells that are immunologically competent, such as lymphocytes, one possible intervention would be to treat the patient with an antiviral drug or an interferon product to abolish the causative agent, if the immune defect was caused by the persistence of this agent. To date, a few patients have been treated with prolonged courses of acyclovir or vidarabine, but improved immunologic response has not resulted.

Interferon products have been used to prevent viral infection of leukocytes and thus to potentially restore immunocompetence. Trials of alpha interferon have not yet been uniformly successful in restoring immune function, though some trials have shown modest antitumor effect (47).

As mentioned above, the lymphocytes from patients with the acquired immunodeficiency syndrome are deficient in their ability to produce gamma interferon or interleukin-2. Gamma interferon has the ability to enhance cytotoxic lymphocyte function. Interleukin-2 has a role in the proliferation and differentiation of T lymphocytes, and it also stimulates gamma interferon production. Therapeutic trials with these compounds are currently underway in our attempts to restore immunocompetence.

If rejection phenomena could be overcome, it would seem more fruitful to provide patients with immunocompetent cells that could populate the appropriate sites and exert the proper biologic effects on immune response, thus obviating the need to identify and quantitate all of their humoral products. An unusual opportunity to assess transplantation was provided by a patient at the NIH who had a healthy identical twin. Transfer of 3 × 10¹⁰ mature lymphocytes to the patient without previous immunologic ablation resulted in a modest increase in sev-
eral immunologic parameters, including skin test hypersensitivity and absolute OKT 4+ lymphocyte count. However, this increase was transient. Subsequent transfer of $3 \times 10^6$ bone marrow cells with periodic transfers of mature peripheral lymphocytes resulted in a more sustained increase in skin test hypersensitivity and OKT 4+ T lymphocytes, but these increases were also only temporary, and the patient subsequently developed Kaposi's sarcoma, progressive cytomegalovirus chorioretinitis, and repeated bouts of P. carinii pneumonia, which lead ultimately to his death, proving that from a clinical standpoint, he had not been immunologically reconstituted. Clearly, this patient had persistent infections or immunologic abnormalities that prevented normal cells from restoring immunocompetence.

Possible Role for Retroviruses

Dr. Edward P. Gelmann (Senior Investigator, Medicine Branch, National Cancer Institute): Much of the epidemiologic research that has been directed at characterizing the acquired immunodeficiency syndrome suggests that this disease is caused by an infectious agent. For some time, workers have been intrigued by the notion that a retrovirus may be involved in the etiology of the acquired immunodeficiency syndrome. I will describe some of the arguments both for and against this hypothesis and review the evidence that has accumulated thus far. Retroviruses represent only one of several groups of viruses that have been proposed as possible etiologic agents. The high incidence of human cytomegalovirus, Epstein-Barr virus, and adenoviruses of specific subgroups in the acquired immunodeficiency syndrome have led all three to be proposed as being involved in the cause of this disease. On the other hand, a recently described human parvovirus (82) is an intriguing agent theoretically because there is an animal model where a strain of the minute virus of mice causes a T cell-specific immunosuppression analogous to the abnormalities described in patients with the acquired immunodeficiency syndrome (85). However, it has thus far been difficult to find evidence of parvovirus infection in these patients.

Retroviruses are enveloped viruses best known as agents that can cause malignant tumors in various vertebrates (84). At least one class of retrovirus, feline leukemia virus, can cause immunosuppression in the absence of malignant disease (85). Feline leukemia virus is horizontally transmitted among cats and is not infectious for humans. Studies of naturally occurring feline leukemia virus disease have shown that equal numbers of animals suffered from either a panleukopenia syndrome or from opportunistic infections in the absence of leukemia as those who suffered from leukemia and lymphoma. The two previously described human retroviruses, human T-leukemia virus I and II, are T-cell tropic agents (86) that are associated with acute (87) and chronic (88) T-cell leukemia. The acute leukemias are largely proliferations of cells with the OKT 4-reactive surface antigen (89). The acquired immunodeficiency syndrome is a disease in which the underlying abnormality appears to be the depletion of a specific subset of T cells, those that are OKT 4-positive. It is this predilection of human T-leukemia virus for OKT 4+ T cells that supports the notion of an association with the acquired immunodeficiency syndrome. The findings of this syndrome in Haitians both in the United States and in Haiti further supports the association because Haiti is an area endemic for human T-leukemia virus (90). It is conceivable that a T-cell tropic retrovirus underwent a mutation that conferred on it a toxic rather than a proliferative influence on the host cell. Such minute genetic changes can be responsible for differences in pathogenicity, as in the case of the murine leukemia viruses where nucleic acid sequencing of the genomes of closely related retroviruses has shown differences in leukemogenic potential to be attributable to alterations of a very few nucleotides in specific regions of the viral genome.

Testing of the hypothetical association between a human retrovirus and the acquired immunodeficiency syndrome is a challenging task. The acquired immunodeficiency syndrome presents potential difficulties in trying to find evidence of retroviral infection. The patients do not mount normal antibody responses to new antigenic challenge; therefore, one may have difficulty scoring newly infected patients by serologic means. A definitive method for detecting retrovirus infection is finding a DNA copy of the viral RNA genome integrated into the chromosomal DNA of the infected cell. This integration is part of the infectious process of retroviruses. However, because the acquired immunodeficiency syndrome appears to be a disease of cellular depletion, a sufficient number of infected cells may not be recoverable from a patient at a given time to allow detection of the viral genome.

The evidence of human T-leukemia virus infection in the acquired immunodeficiency syndrome has come from the laboratories of Dr. Myron Essex at the Harvard School of Public Health and Dr. Robert Gallo at the National Cancer Institute. Essex and associates (91) have used sera from patients with the acquired immunodeficiency syndrome and controls to react in an indirect immunofluorescence assay against two different human T-leukemia virus-infected cell lines. Using 50% of the cells that fluoresce as a cut-off for a positive result, they reported that approximately 25% of sera associated with the acquired immunodeficiency syndrome were positive, but none of the sera from the controls. Since that report, the use of fresh serum from one institution has improved the positivity score to approximately 85%, and the reaction continues to appear to be specific (Essex M. Personal communication).

Gallo's laboratory has surveyed sera associated with the syndrome for antibodies to disrupted whole virus by an enzyme-linked immunosorbent assay. This assay is probably less sensitive for viral infection in patients with the syndrome, because one would predict that they may not have had highly productive human T-leukemia virus infections. Productive infection is required to provide enough antigen for the formation of antibodies detectable by the assay. There appears to be a correlation of positive results with this assay and the cases scored by Essex as highly positive. However, the cases less strikingly positive...
as shown by immunofluorescence do not have detectable anti-HIV antibodies. Whether the immunoreactivity between sera associated with the syndrome and human T-leukemia virus-infected cells represents evidence of viral infection or detection of a human T-leukemia virus-induced or human T-leukemia virus-like protein remains to be determined.

Experiments designed to identify the integrated human T-leukemia virus genome in lymphocytes of patients with the syndrome and to try to recover the virus from cultured T cells have been done in Dr. Gallo's laboratory (92, 93). Evidence for active human T-leukemia virus infection in this syndrome has been found in two black male homosexuals in the United States. One patient was identified after the serologic detection of antibodies to human T-leukemia virus structural proteins. A cell line was established from the patient's cultured T-lymphocytes. These cultured cells produced a virus identified as human T-leukemia virus I. The patient had no evidence of human T-leukemia virus disease; however, he did develop a cerebral lymphoma, possibly of B-cell origin, that was treated with radiation.

The second patient had the human T-leukemia virus proviral genome integrated in the DNA of his uncultured peripheral blood lymphocytes. He also had serum antibodies to human T-leukemia virus structural proteins. Further analysis showed that at the time of blood sampling, approximately 10% of his peripheral blood lymphocytes had the human T-leukemia virus genome. This finding represented a monoclonal proliferation of a single infected cell. However, the proliferation was not sustained, as shown by the laboratory's inability to identify the human T-leukemia virus genome in lymphocytes sampled 2 months after the first specimen. The patient from whom the producer cell line was derived also did not have a sustained detectable circulating population of human T-leukemia virus-infected cells. This finding is consistent with the notion that the retrovirus infection was in some way toxic to the infected cells and resulted in their depletion. Further survey of peripheral blood lymphocytes from 123 patients with the syndrome, 20 healthy homosexuals, and 34 healthy hemophiliacs has failed to provide further cases of a detectable human T-leukemia virus genome in peripheral blood lymphocytes from these individuals.

A virus with reverse transcriptase activity has been recovered from the cultured lymphocytes of a patient in France (94). This virus can perpetuate and be propagated in blood T-lymphocyte cultures and buds from the cell surface like a retrovirus. The virus does not appear to be related to human T-leukemia virus I or II (Gallo RC. Personal communication), but appears morphologically and serologically to be related to the equine infectious anemia virus, a member of the retrovirus family (Montagnier L. Personal communication). The significance of this putative third human retrovirus and its relationship, if any, to the acquired immunodeficiency syndrome remains to be determined by further characterization of the isolate.

The significance of the association between human T-leukemia virus and the acquired immunodeficiency syndrome is not known. There are no data to disprove that there may be an etiologic role for this virus in the syndrome. The elucidation of this role is hindered by the low levels and transient nature of virus expression. Molecular analysis of the cloned viral genome from one of the patients described may shed further light on the significance and pathogenic potential of this isolate. On the other hand, human T-leukemia virus may represent another new or reactivated opportunistic infection in persons predisposed by the underlying immunodeficiency.

Future Directions

Dr. Fauci: Although the putative agent of this disease may not yet have been isolated, we know a good deal about the disease's epidemiology, clinical manifestations, and immunologic defects. It would be helpful to recapitulate our future directions and goals for dealing with the acquired immunodeficiency syndrome (Table 9). Of particular importance is maintaining a rational approach to the disease and to the risk groups by persons who are not in the risk groups in order to avoid unnecessary ostracizing of persons merely because they fall into a risk group. In this regard, epidemiologic data strongly indicate that simple precautions, such as avoiding intimate sexual contact, and exposure to blood, such as by sharing needles with victims of the syndrome or members of the risk groups, will most likely obviate any chance of transmissibility from a risk group to a non-risk group.

Finally, it should not be forgotten that despite the fact that the scientific and intellectual aspects of this disease are exciting and stimulating, a large number of young people are suffering and dying. It is the realization of this terrible tragedy that should inspire all of us working on this problem to apply our utmost energy and whatever talents we may have to the ultimate control of this extraordinary disease.

References


