SUMMARY OF THE WORKSHOP ON KAPOSI'S SARCOMA

Sponsored by:

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THE ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS): UPDATE ON THE DISEASE AND ON NCI RESEARCH ACTIVITIES

Background

Since late 1978, a new disease of unknown cause and great virulence has appeared. This disease has affected more than 600 people; almost half have died, and the ultimate fatality rate may reach 70-80%. The disease has been reported from 27 states, and while the great majority of the patients have been American, 34 cases in 9 other countries (many with American contacts) have been reported. The rate of attack is increasing: In 1981, an average of one new case was reported each day, but in June 1982, about 3 new cases were reported each day. Almost half of the patients have been from New York City, and 22% from Los Angeles or San Francisco.

One-third of the AIDS patients have developed Kaposi's sarcoma, a hitherto rare form of cancer, and other types of cancer (e.g., Burkitt's lymphoma) are becoming apparent as well. A second major way in which the disease manifests itself is through infection by any of several types of organism. The most common infection is caused by Pneumocystis carinii, a protozoan which produces a severe pneumonia. The underlying problem in this disease, however, is a defective immune system which leaves the patients unable to resist infections and cancer. Thus, AIDS is a serious public health hazard, but may offer a profound insight into the normal functions of the immune system and the origins of cancer.

Most investigators now believe that AIDS is caused by an infectious agent, in all likelihood a virus. The agent may be a new virus, a new variant of an existing virus, or a virus which has long existed in a very confined population and only recently been introduced into a much larger population. The spread of AIDS resembles that of the hepatitis B virus ("serum hepatitis"), but there is no evidence that hepatitis viruses are in fact the cause of AIDS.

Seventy-five percent of AIDS patients are young (25-45), white, urban homosexual or bisexual men, who are very active sexually. Homosexuals with AIDS have averaged about 1,100 sexual partners during their lifetime, but homosexual men without any manifestations of AIDS average about 500.

The second largest group of AIDS patients (about 14%) are mainly black or Hispanic heterosexual men from New York or New Jersey who are users of intravenous drugs, e.g., heroin. As with sexually hyperactive homosexual men, drug users are known to have a high incidence of hepatitis B infections, with the virus spread via sexual contact or by contaminated needles.

Hepatitis B is also transmitted through transfusion of whole blood or blood products. Within the past few months, three men with hemophilia have developed AIDS; the appearance of AIDS in this third group is a cause for particular concern because it suggests that the disease was acquired from an infectious agent which contaminated the blood product (a clotting

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OVERVIEW

Kaposi's sarcoma (KS), a rare form of cancer, has been the focus of heightened public and scientific attention in recent months because of the disease's sudden and markedly increased incidence and mortality among homosexual men in the United States. To bring together investigators from a variety of disciplines to shed some light on this "mini-epidemic," NCI's Division of Cancer Treatment and Division of Cancer Cause and Prevention, in cooperation with the Centers for Disease Control, sponsored a 1-day workshop on the Bethesda, Maryland, campus of the National Institutes of Health. Following formal presentations in the morning about various aspects of KS, attendees separated into three concurrent working group meetings in the afternoon. Recommendations were then presented for further studies in epidemiology, virology-etiology, and treatment.

I. INTRODUCTION

Dr. Bruce Chabner, Acting Director of NCI's Division of Cancer Treatment, described the current outbreak of Kaposi's sarcoma in the United States as one of the most fascinating problems in internal medicine in recent years. The disease is characterized by a unique lifestyle combined with interesting epidemiologic aspects, infectious problems, and immunologic compromise of the host, with a resulting malignancy rarely seen in the U.S. population. This disease offers the opportunity to learn more about the epidemiology and etiology of cancer in general, he noted.

Because there are not large numbers of KS cases in any one city, Dr. Chabner said a coordinated approach is needed to elucidate these aspects of the disease, as well as to facilitate diagnosis and treatment. He said NCI is awaiting the input of the scientific community regarding additional study into the problem. The Institute is available to serve as a statistical resource; to disseminate information about treatment; to arrange for further scientific meetings; and to conduct research in epidemiology and virology through its own intramural laboratories.

Dr. William DeWys, workshop organizer and Acting Chief of DCT's Clinical Investigations Branch, then noted that morning sessions would be for information exchange among investigators from various disciplines, and afternoon sessions for development of research protocols and prospective studies.

II. NATURAL HISTORY

Dr. John Ziegler, of the University of California at San Francisco, observed that the current epidemic of KS presents the same opportunities for unique research as did Burkitt's lymphoma 15 years ago. He then suggested that the workshop aim primarily at seeking, rather than generating, hypotheses.

Kaposi's sarcoma has two distinct incidence patterns, endemic and non-endemic. These are described below:

Endemic

This form of KS is commonly seen in tropical Africa, particularly Zaire, Tanzania, and western Uganda. It is a predominantly indolent and slowly progressive disease in this population--a chronic disorder which in some patients is completely compatible with a normal life span. Endemic KS is primarily a male disease (the male/female incidence ratio is greater than 9:1) which peaks in men in their 40's and 50's. There are four basic clinical types:

- Nodular--This form generally is chronic, indolent, and associated with some degree of edema, appearing in most cases on the extremities. Persons with nodular KS will not usually seek medical attention unless the nodules ulcerate, become somehow incapacitating, or undergo sarcomatous change and begin to invade deeper tissues and bones.

- Florid--This form features an exophytic sarcomatous transformation of a nodule which then becomes locally aggressive and invasive.

- Infiltrative--In this yet more serious form of KS, the tumor penetrates deeply and very often will involve underlying bone.

- Childhood or generalized--This last clinical form has been termed lymphadenopathic because it presents multiple lymph node enlargements. The disease is primarily associated with mucosal lesions, often becoming disseminated through the lungs and gastrointestinal tract. The prognosis is poor because of the generalized aggressive nature of this form of KS.

In the United States and Western Europe, KS is a much more dramatically violaceous type of lesion, resulting in large purple spots or bumps on the skin. A pseudo-Kaposi's lesion has also been recognized, probably a premalignant hyperplasia, which most often progresses to hemorrhagenic nodules seen throughout the skin and mucous membranes and in the lymph nodes.

Nonendemic

This incidence pattern of KS is associated with certain individuals of Jewish and Italian origin and occurs more commonly in Central European countries and Scandinavia. It is usually a chronic, indolent, benign type of disease with violaceous plaques and nodules seen on the skin in the extremities, usually with edema.

Unusual Occurrences

Dr. Ziegler noted that renal allograft recipients are 400 times more likely to develop KS than are individuals in the general population. These patients share important features:

- They are at greater risk for cancer in general, the most common type being histiocytic lymphoma. However, in one series of 600 malignancies in allograft recipients, about 4 percent were cases of KS. Interestingly, if immunosuppression is withdrawn or modulated in these patients, some lesions have been reported to regress spontaneously.

- Kaposi's sarcoma in patients with renal allografts occurs much earlier than other malignancies (the mean time from allograft to diagnosis of cancer is 16 months, or only half the time interval for diagnosis of most other cancers, notably lymphomas).

In his comments about immune defenses against KS, Dr. Ziegler made special mention of African studies in which Kaposi's tissue extracts injected into patients intradermally caused a delayed hypersensitivity reaction on the part of the host to his own tumor. Patients with positive reactions appeared to have a better prognosis than those with negative reactions. In general, the immune functions of KS patients in Africa are normal in that they mount no antibody responses and are capable of mounting delayed hypersensitivity responses to recall antigens and to DNCB. The DNCB reaction, however, tends to be more negative in patients with aggressive, florid, sarcomatous lesions. Once these lesions regress, the reaction becomes positive. Thus, Dr. Ziegler concluded that the delayed hypersensitivity impairment in these patients may be a function of the tumor burden, as it is with many other cancer patients, rather than an intrinsic immunologic defect.

In the few cases of KS he has seen among a select group of hospitalized homosexual men in the San Francisco area, Dr. Ziegler said, the disease is a unique, very aggressive form. Dermatologists in the area also have reported instances of an early, "pre-malignant" form of the disease, characterized by angiomatous hyperplasia and plaque-stage nodules. It is possible, then, that this clinical population is presenting a spectrum of the disease.

Dr. Ziegler concluded by outlining the evidence for predisposing factors associated with KS:

	Disease Forms	
Factors	Endemic	Nonendemic
Genetic	Ethnic origin	Ethnic origin
Environmental	No clues among Africans	Possibly carcinogens in the environment of allograft recipients
Host	Old age, maleness	Immunosuppression, with activation by virus and/or corticosteroids

During discussion, Dr. Ziegler said fever is not usually observed among patients with childhood endemic Kaposi's sarcoma unless infection is present. Nor are complications such as meningitis or herpes observed in African patients, who carry on normal village life unless the disease becomes incapacitating, fungated, infected, or bone-invasive.

III. EPIDEMIOLOGY

Dr. James W. Curran, coordinator of the Centers for Disease Control's task force on KS, reported on studies being conducted by CDC on the epidemiology of KS and pneumocystic pneumonia (PCP), diseases which have occurred both separately and in combination among homosexual men in the United States.

Key Epidemiologic Features

Kaposi's Sarcoma. The incidence of KS has been estimated to be extremely low—0.02 to 0.06 per 100,000 persons per year, or from 50 to 100 cases per year in the entire country. Dr. Curran said many cases are likely underdiagnosed since the disease is a chronic skin condition of elderly men which rarely causes death. The question is not whether the current outbreak of KS represents a national epidemic, he said, but rather whether it has become an epidemic among homosexual men or, alternatively, has become hyperendemic among homosexual men. Among all cancers, KS accounts for about 0.02 percent of cases, and the male-female ratio in the United States is 10:1 or 15:1. Transplant patients and other immunosuppressed patients are also at increased risk. The incidence in Africa is much higher, he noted—probably from 150 to 200 times that in America—and steadily increases with age. In some African cancer series, KS represents 10 percent of all cases. Also, the generalized form is proportionately more common in Africa, and regional differences are remarkable.

Pneumocystic Pneumonia. In the United States, PCP is also extremely rare—0.03 cases per 100,000 per year—even more so in persons who are not immunocompromised. Likewise, Dr. Curran said PCP is likely underdiagnosed because of the invasive procedures required and the insensitivity of some tests. In all cases examined by CDC between 1968 and 1978, only one case of PCP was found that did not have a serious underlying disorder. Exceptions to the U.S. pattern, besides among homosexual men, are the "endemic-infantile" form of the disease first described in Europe, for which prematurity and malnutrition are risk factors, and among patients with protein-calorie malnutrition, notably kwashiorkor. Recently, a milder form of PCP has been described in immunocompetent infants less than 3 months old, and PCP has also been linked to opiate addiction.

Active and Passive Surveillance Data

According to information collected by telephone from physicians, of the 124 cases of KS, PCP, and other serious opportunistic infections reported to CDC since June 1981, the following status table was constructed:

Disease	Status			
	Alive	Dead	Total	Percent Dead
KS	45	10	55	22.2
PCP	17	32	49	65.3
Both	7	4	11	36.4
Other	3	6	9	66.7
Total	72	52	124	41.9

Sex and Sexual Preference. Virtually all patients with these diseases were men, Dr. Curran reported; of the men with known sexual preferences, 94 percent were either homosexual or bisexual. Most of the heterosexual men were patients with PCP. Among opiate addicts with either KS or PCP, it was difficult to determine true sexual preference.

Race. About 80 percent of the patients with KS were white, whereas about 70 percent of the patients with PCP or other infections were black or Hispanic. Dr. Curran speculated that this finding is probably a result of a greater tendency among whites to seek earlier care, rather than a genetic difference.

Age and Residence. More than 80 percent of patients in each disease category were in the 25 to 45 age group, with the same median age among patients with different diseases. Dr. Curran argued, then, that CDC is dealing with a single epidemic.

Noting that patients are not distributed randomly across the country, Dr. Curran reported that more than 80 percent of them resided in New York, Los Angeles, and San Francisco; with the addition of Atlanta, the total becomes 85 percent. This situation is very difficult to understand from the perspective of a point-source outbreak. For example, many of the remaining patients have not visted or resided in these metropolitan areas in the past 5 years. Because not all homosexual men appear to be at equal risk, Dr. Curran said other factors—most likely lifestyle—must be involved. He said CDC's reporting techniques are inevitably biased, but not to the degree that the observed geographical variances are merely an artifact.

Dr. Curran added that increased awareness undoubtedly has contributed to the higher incidence reported for KS, but evidence for a real gain in incidence has been further strengthened by a rigorous search of NCI's SEER registry data, which showed no increase in cases up through 1979. Moreover, the increase in deaths--10 or 11 occurring in the past 3 months—is an ominous finding, he noted.

Diagnosis. The median time between diagnosis and onset of disease for KS is about 4-1/2 months; for PCP, about 3-1/2 months. Thus, both diseases appear to have a prodrome phase. Not all patients with KS had skin lesions before diagnosis, according to Dr. Curran. Lymphadenopathy, fever, diarrhea, and weight loss have been very common symptoms for patient both with KS and PCP, again suggesting a general debilitating prodrome.

Medical History. Uncontrolled information from 33 patient interviews with homosexual men (KS and/or PCP) in Atlanta, New York, and San Francisco revealed that over half had a history of hepatitis, gonorrhea, and syphilis, and over one-fourth had other sexually transmitted infections.

Interestingly, Dr. Curran reported, a preliminary CDC survey found that 88 percent of homosexual men interviewed in New York, Los Angeles, and San Francisco had used nitrite inhalants during the past 5 years, compared with only 14 percent of heterosexual men. This significant difference is confounded, though, by the fact that inhalant usage was highly correlated with the number of sex partners, an obvious factor in the spread of sexually transmitted microorganisms.

Future Studies

To resolve some of these problems, Dr. Curran said CDC will soon undertake a case-controlled epidemiologic study, continue its passive surveillance, and plan for a national active surveillance study of KS in combination with laboratory investigations. Because of the nature of the disease, he concluded, these efforts hold high promise for prevention of the epidemic in the next 2 years.

IV. VIROLOGY

Overview and Status

Dr. Alvin E. Friedman-Kien, of New York University Medical Center, first reviewed the current outbreak of KS. The first disseminated case in homosexuals was seen at NYU in September 1979; intermittently over the next year, seven more cases occurred--four of these eight patients have died. Suddenly, in late May to early June 1981, a cluster of cases occurred, and in late June, NYU alerted the homosexual population that an epidemic might be starting. The same pattern emerged on the West Coast. By comparison, between 1969 and 1979 in New York State, very few cases of KS were seen in men of age 15 to 49, suggesting that the recent cluster of diseases did not exist previously.

Reporting on his clinical experience, Dr. Friedman-Kien said skin lesions associated with the cancer can appear on any part of the body and are easily overlooked initially as bruises, moles, mosquito bites, eczema, psoriasis, or other common eruptions. Most patients appear healthy, except those with lymphadenopathy and a general feeling of malaise, including slight fever and weight loss.

All of these patients are immunologically suppressed, and each tumor has appeared de novo in multifocal distribution over the body--none are metastatic lesions. He said it appears almost as if the immunologic control over the mechanism that controls the growth of tumor cells has been lost or is defective. Following a brief discussion of histopathology, Dr. Friedman-Kien noted that the origin of KS almost appears to be from the precursor of mesenchymal blood cells or endothelial lining, rather than from the endothelial lining itself, and that the application of "sarcoma" to the disease is probably a misnomer.

All of the NYU patients had multiple sex partners, he noted, and as a group exhibited an extremely high use of all types of drugs; indeed, nitrites may prove to be a significant factor in the onset of KS. The frequency of organ involvement at disease presentation was, in order: skin, lymph nodes, gastrointestinal tract, spleen, and lung.

Dr. Friedman-Kien reported that there is a marked difference in the level of complement-fixing antibodies titered to cytomegalovirus (CMV) between homosexual patients and patients with classical (endemic) KS. The most recent and exciting finding, he said, is that titers of serum antibodies to Epstein-Barr virus (EBV) are extremely high in homosexual patients compared with patients with classical KS or mononucleosis, or normal controls. Immunologic response to mitogens was markedly depressed in these patients compared with normal subjects, and the ratio of T-helper cells to T-suppressor cells was totally inverted compared to controls, another exciting finding. He also noted that these patients have extremely high levels of immunoglobulins in their blood.

HLA-DR Antigens

Dr. Pablo Rubenstein, of the New York Blood Center, then commented on the positive aspects related to the DR series of antigens of the HLA system in patients with disseminated KS. Until now, a particular antigen--DR-5--has not been associated with any immunologic disease except very recent preliminary data that show it to be increased in juvenile rheumatoid arthritis. In seven patients with classical KS, five have been positive for this antigen. Only three of nine homosexuals suspected of having KS, but who did not, had DR-5 antigens. More studies are necessary to extend these data.

Association with CMV

Dr. Gaetano Giraldo, of Instituto Tumori in Naples, Italy, described his and others' research into whether an oncogenic virus plays a role in the development of KS. In recent work, he used the sensitive techniques of DNA-DNA reassociation kinetics, anticomplement immunofluorescence (ACIF), and ACIF-blocking tests to search for CMV gene products in KS biopsies and early cell cultures deriving from them. Three of eight tumor biopsies were positive for CMV DNA; CMV-related antigens, mainly localized in the nucleus, were found in cryostat sections of 7 of 31 tumor biopsies and 4 of 12 KS cell lines at early passage level. Dr. Giraldo concluded that the antigen is present in a high number of tumor cells, like the Epstein-Barr virus nuclear antigen in EBV-transformed cells.

Inevitably, he noted, the increasing data concerning the oncogenic potential of CMV lead on to consideration of the increasing evidence of its association with KS. Just as Burkitt's lymphoma has been the ideal situation for clarifying the biology of lymphomas, Kaposi's sarcoma—which shows epidemiological, biological, and clinical similarities to Burkitt's lymphoma—could represent the ideal model for a better understanding of the biology of soft-tissue tumors.

Even more recent studies have confirmed this report that CMV and its gene products can be demonstrated in KS. Similar to EBV and its association with Burkitt's lymphoma and nasopharyngeal carcinoma, there is a definite quantitative relationship in the antibody titers against CMV in KS patients. It might be that KS cells contain only certain fragments of the CMV genome, including the regions responsible for the initiation and/or maintenance of transformation (oncogene), reminiscent of HSV-2-transformed cells. The host cell-virus relationship of CMV in regard to oncogenesis might be more similar to HSV-2 in certain human cancers and experimentally transformed cells than when compared to EBV.

Nevertheless, other possibilities remain also to be considered for the CMV association with KS, such as latency or attraction of the virus after tumor inception. An important aspect would be to obtain KS passages in nude mice, particularly those with detectable CMV genomes, to see whether they grow and maintain virus sequences and to obtain a more favorable in vitro system by the establishment of a KS cell culture.

Dr. Giraldo concluded by presenting the following hypothetical cycle for the etiology of KS: (1) persistent infection, (2) combined with a susceptible genetic background, (3) immunodisbalance, and (4) persistent teratogenic stimulation, (5) induces a large number of defective virus particles, (6) which may induce the late part of the genome, (7) causing an amplification of antigens of CMV (oncogenes), (8) thereby inducing sarcoma in susceptible cells.

Virology of Homosexuals

Dr. Lawrence Drew, of Mt. Zion Hospital and Medical Center in San Francisco, reported on the serology and cultures of nine cases of KS among homosexual men in the San Francisco area (median age of 35). In all cases there was an IgG antibody in high titer, plus a high IgM titer, the significance of which is unclear in CMV--that is, titers can rise not only as a result of recent infection, but also chronically and during periods of reactivation.

Dr. Drew had assessed a year ago the titers of CMV antibody in homosexual men at a venereal disease clinic versus randomly selected blood donors at a city blood bank and heterosexual men at the same VD clinic. A striking incidence of antibody was found in the homosexuals, significantly higher than the other two groups. Even more interestingly, 93 percent of the homosexual men--even under the age of 30--were seropositive, and not much rise was noted

VIII. DISCUSSION

In general discussion, it was reported that the recovery rate in patients with PCP is now about 75 percent, whereas only 50 percent recovered when only pentamidine was available for these immunosuppressed patients. Dr. Curran stated, however, that these data are biased: pentamidine, available only through CDC, is usually requested by patients who have already failed treatment, and some of the PCP cases have been diagnosed at autopsy. It was also suggested that patients be placed on antibiotic prophylaxis (trimethoprim and sulfamethoxazole) to prevent PCP.

The question was raised, in light of the host of microorganisms that might be present in a patient, whether the diagnosis of KS should alone determine that the patient be placed on chemotherapy. It was expressed that in most cases, the earlier the treatment, the better; also, the tumor should be vigorously treated while taking concurrent measures to control infection. Relapse patterns cannot yet be determined for homosexual KS patients because of the short followup. Followup on African patients is limited as noted previously. It was also mentioned that among patients with Burkitt's lymphoma, immunosuppression quickly was reversed following initiation of treatment.

From discussion comments, it was unclear whether the wasting illness syndrome sometimes associated with KS and PCP was a result of infection and/or the tumor, or whether it was a contribution to later infection and/or cancer. In infantile PCP, for example, malnutrition can be a factor in immunosuppression. This "chicken and the egg" discussion also focused on the immunosuppression/oncogenesis cycle in KS.

IX. WORKING GROUP MEETINGS

In the afternoon, workshop attendees separated into three concurrent working group meetings to discuss specific topics raised during the morning sessions and to develop recommendations for further studies and future directions. Dr. Curran headed the epidemiology group; Dr. Werner Henle, of Children's Hospital of Philadelphia, led the working group on virology-etiology; and Dr. DeWys was chairman of the treatment group.

Epidemiology

Participants in the epidemiology working group began by considering three basic topics: (1) What should be done about the current epidemic as defined--that is, Kaposi's sarcoma and serious opportunistic infections--from an epidemiologic point of view? (2) What additional syndromes should be defined and studied further in groups at risk? and (3) What should the government's role (that is, NCI's and CDC's) be, if any, in facilitating these studies or stimulating interest in this topic?

An initial diagnosis of KS can be suspected if an accumulation of compressed cells is observed around the sweat glands. Additionally, many associated vessels are remarkably sclerotic, iron stains will show very early before the nodule develops, and many cells will contain inclusion bodies. After the appearance of nodules, Dr. Templeton described, diagnosis is unmistakable--the pattern is a mixture of spindle cells, a vascular portion, inflammatory cells, and lymphocytes intimately admixed with tumor cells around the edge of the lesion.

- Tuberculosis, leprosy, and Hodgkin's disease are the associations of KS in Africa, all of which involve substantial T-cell deficiency. The classic regression pattern of cutaneous nodules of KS is to undergo autoamputation, probably without an immunologic basis. But in some cases, a reaction around the nodule in the skin occurs that has all the hallmarks of immunologic rejection. A sizeable cuff of lymphocytes surround the tumor and invade tumor cells around the margin, highly reminiscent of a kidney transplant rejection.

VI. STAGING

Dr. Charles Vogel, of the University of Miami, presented the following clinical staging workup for KS:

A. General

1. History and physical examination
2. Detailed immunologic profile
3. Venereal disease culture and blood screen
4. CBC, platelet count, SMA, EKG, and clinical photography (standard tests for any type of chemotherapy trial).

B. Metastasized Sites (Classical)

1. Chest X-ray (lung biopsy if abnormal)
2. Abdominal CT scan (for liver and nodes)
3. Bone scan with confirmation bone X-rays
4. Lymph node biopsy (if adenopathy).

C. Metastasized Sites (Unique)

1. Indirect laryngoscopy

2. Upper GI tract and small bowel series

3. Barium enema

4. Sigmoidoscopy

5. Gastroscopy (if indicated)

6. Ophthalmological examination (to detect such problems as CMV retinitis).

Dr. Vogel then outlined possible treatment plans for patients with KS as suggested at a January 1980 symposium on KS. For generalized disease: hemi-body or total body irradiation versus the three-drug regimen of actinomycin D, vincristine, and DTIC. For localized disease: (1) surgery or radiotherapy, with adjuvant three-drug chemotherapy; (2) three-drug regimen versus some type of alternating drug combination with radiation; and (3) adjuvant immunotherapy. If ever there was a disease with potential for treatment by immunologic manipulation, Dr. Vogel said, KS is unmatched based on data so far reported. He added that the largest group of patients with aggressive disease treated in a uniform fashion is in Uganda, where patient followup (for cases brought into complete remission in the 1970's) has become problematic secondary to political unrest. If followup of these 100 to 200 patients could be accomplished, he said, the potential cure rate for the three-drug combination could be established.

VII. THERAPY

African Results

Chemotherapy. Dr. Ziegler said the drug trenimon, an inexpensive and orally administered alkylating agent, was first used against KS in developing countries. It produced dramatic and prolonged regression of the nodular form of the disease, the primary side-effect being hematologic suppression.

The first Ugandan trial compared actinomycin D (2 complete response, 7 partial response, 3 no response) versus cytoxan plus potassium iodide (1 complete response and 9 no response). Adding vincristine to actinomycin D resulted in a response rate of 94 percent (13 of 14), 10 of the 13 responses being complete. The response rate was further improved to 97 percent (31 of 32) by adding a third drug, DTIC; of these 31 responses, 30 were complete. This combination is now the primary therapy. In nonendemic areas, velban has produced a response rate of 80 percent (11 of 14), 2 of the 11 responses being complete; the drug is administered as a weekly injection.

Dr. Ziegler said the following drugs should be considered active for second-line treatment (in patients who have been heavily pretreated): BCNU (43 percent response rate), ICRF (57 percent), and bleomycin (60 percent), plus velban as an alkaloid. The distribution of responses for these drugs and other first- and second-line regimens is shown in the table below.

Chemotherapy and response rates in Kaposi's sarcoma in Uganda

Drug regimen	Evaluable	Response		
		Complete	Partial	None
Previously untreated patients:				
Acinomycin D	12	2	7	3
Cyclophosphamide	10	1	0	9
Actinomycin D Vincristine	14	10	3	1
Actinomycin D Vincristine DTIC	32	30	1	1
Patients with relapse:				
BCNU	21	4	5	12
Bleomycin	10	0	6	4
DTIC	10	0	5	5
MOPP	5	0	0	5
Daunorubicin	3	0	0	3
ICRF 159	47	10	17	20

Hormonal Therapy. Estrogen therapy for women with KS has not been studied in a controlled fashion, but nevertheless offers little promise. For example, two pregnant women developed a progressive form of KS despite their necessarily high levels of circulating estrogen, and one study indicated that estrogen had no effect on, and in one case worsened, the disease.

Immunotherapy. Similarly, immunotherapy results have been scattered. Two positive reports have been cited using intralesion injections of either BCG or PPD, resulting in regression of isolated nodules injected. Again, the immunologic sensitivity of KS warrants further study in this area. Suppressor cell excess in the disease, for example, might be an appropriate target for immunomodulation.

Dr. Ziegler noted a study of tumor cell kinetics that reported an extremely high cell lost rate from KS in nine Ugandan patients; in fact, the loss of tumor cells nearly matched the production of tumor cells in patients with the nodular form of the disease. In the florid form, the cell loss rate decreased only slightly. The investigators discovered a potential

doubling time in the nodular patients of 213 hours, and in the florid cases of 128 hours—but in both a very high output of dying cells.

Radiotherapy. Kaposi's sarcoma is very radiosensitive, although radiotherapy data are difficult to compare due to the highly individualized treatment given (doses, schedules, ports, etc.). About 1,000 rad is required for treatment of local disease, and the cure rate ranges between 20 and 40 percent depending on patient selection. The advent of hemi-body radiotherapy has been met with promising results, and this approach may offer a more logical strategy than conventional treatment with radiation.

U.S. Results

Dr. Linda Laubenstein, of NYU Medical Center, reported that of the eight homosexual KS patients seen at NYU between September 1979 and March 1981, five have died. The treatment regimens varied widely, and conclusions are difficult to draw. Patients were treated with velban, bleomycin, actinomycin D, DTIC, and vincristine combinations, and some were not treated at all because of late diagnosis and subsequent death. However, in this group two patients achieved complete remission by a combination of Adriamycin, bleomycin, velban, and DTIC, similar to the treatment given some patients with lymphoma or Hodgkin's disease.

Based on this experience, NYU investigators began two new regimens in May 1981. Twenty patients are now on treatment following extensive staging procedures. In patients with relatively minor disease, Phase 2 trials with VP-16 were begun, based on the drug's similarity to the alkaloids, lack of major toxicity, and activity in lymphoma and oat cell carcinoma of the lung. Of the six patient initiated, two developed progressive disease and were switched to the alternate regimen, and four have had objective responses, though data are very preliminary.

For patients with widespread disease, a regimen of Adriamycin, bleomycin, and velban was selected; DTIC was omitted initially because of its GI toxicity. Because the anthracyclines (such as Adriamycin) were developed after completion of the African chemotherapy studies, little data are available concerning their efficacy in KS. All nine patients on this three-drug schedule have had excellent responses with minimal toxicity, Dr. Laubenstein reported, resulting in good patient compliance. Because patients are young and anxious, tolerable and acceptable regimens are important. Other Phase 2 agents are being considered for use following completion of the VP-16 trial, she said, as are several immunologic approaches.

During discussion, Dr. Laubenstein noted that 17 of the 20 patients were totally anergic to skin tests and the remaining three were partially anergic.

VIII. DISCUSSION

In general discussion, it was reported that the recovery rate in patients with PCP is now about 75 percent, whereas only 50 percent recovered when only pentamidine was available for these immunosuppressed patients. Dr. Curran stated, however, that these data are biased: pentamidine, available only through CDC, is usually requested by patients who have already failed treatment, and some of the PCP cases have been diagnosed at autopsy. It was also suggested that patients be placed on antibiotic prophylaxis (trimethoprim and sulfamethoxazole) to prevent PCP.

The question was raised, in light of the host of microorganisms that might be present in a patient, whether the diagnosis of KS should alone determine that the patient be placed on chemotherapy. It was expressed that in most cases, the earlier the treatment, the better; also, the tumor should be vigorously treated while taking concurrent measures to control infection. Relapse patterns cannot yet be determined for homosexual KS patients because of the short followup. Followup on African patients is limited as noted previously. It was also mentioned that among patients with Burkitt's lymphoma, immunosuppression quickly was reversed following initiation of treatment.

From discussion comments, it was unclear whether the wasting illness syndrome sometimes associated with KS and PCP was a result of infection and/or the tumor, or whether it was a contribution to later infection and/or cancer. In infantile PCP, for example, malnutrition can be a factor in immunosuppression. This "chicken and the egg" discussion also focused on the immunosuppression/oncogenesis cycle in KS.

IX. WORKING GROUP MEETINGS

In the afternoon, workshop attendees separated into three concurrent working group meetings to discuss specific topics raised during the morning sessions and to develop recommendations for further studies and future directions. Dr. Curran headed the epidemiology group; Dr. Werner Henle, of Children's Hospital of Philadelphia, led the working group on virology-etiology; and Dr. DeWys was chairman of the treatment group.

Epidemiology

Participants in the epidemiology working group began by considering three basic topics: (1) What should be done about the current epidemic as defined--that is, Kaposi's sarcoma and serious opportunistic infections--from an epidemiologic point of view? (2) What additional syndromes should be defined and studied further in groups at risk? and (3) What should the government's role (that is, NCI's and CDC's) be, if any, in facilitating these studies or stimulating interest in this topic?

Dr. Curran said it was very difficult to separate epidemiology from virology and etiology, and group members occasionally lapsed into discussions of microbial agents. This points to the need, he said, that cognizance of risk factors and careful analysis and characterization of cases and controls accompany sophisticated laboratory tests. Some of the behavioral risk factors and epidemiologically identified risk factors may well direct laboratory studies, Dr. Curran noted, and vice versa.

In attempting to arrive at a denominator for the problem of KS, to determine the real risk for homosexual men, and to define the susceptible subpopulation, the working group developed a number of general recommendations:

- A case-controlled study should begin immediately and receive the maximum cooperation of all academic centers. There was some discussion about the coordination of laboratory studies with this case-controlled study, and that it would be desirable to obtain well-characterized laboratory data from controls for whom epidemiologic information is available. However, the consensus was that it would be difficult to coordinate these studies within the time limits at hand--about 2 weeks to startup. The government could assist by ensuring that all tests are done in selected centers, for example, or at a central site, to the extent that this would be possible.

- There should be a definition of an immunosuppressive syndrome beyond KS and PCP. Working group members expressed a strong feeling that these diseases are only part of the problem. Men who have milder forms of this syndrome or who have such disorders as lymphadenopathy, fever, or malaise should be tested immunologically and followed prospectively to determine the permanence of their particular immunologic markers.

- Having defined some risk factors in a profile of high-risk patients through case-controlled studies, investigators should conduct a prospective followup of high-risk patients. Much discussion focused on the feasibility of doing this, but several retrospective cohort approaches were mentioned. For example, there are approximately 3,000 homosexual men who have been characterized antigenically and behaviorally through various hepatitis B vaccine studies over the past 3 to 4 years. These patients might be recontacted, examined, and queried regarding both mild and serious illnesses over the past 24 months; those still at high risk might then be prospectively followed. Such a followup would be expensive, and funding would have to be secured.

- An even more expensive study would be a prospective study for a to-be-defined cohort that is at present less well-characterized, or any other prospective study of homosexual men over a long period of time. If large numbers of homosexual men, say 20,000 to 30,000, could be identified through some list (e.g., subscribers

to a publication for homosexuals) and crosstabulated with cancer registries, this might provide some approximate mortality data. Dr: Curran doubted that such an approach would be feasible, for reasons of privacy and other considerations.

- A study of classical KS and prospective epidemiologic studies of all cases of KS should be coordinated so that investigators studying classical KS are aware of the risk factors identified for the current outbreak, and vice versa. One example cited was the use of nitroglycerin in patients with classical KS as a possible risk factor.

- Similarly, studies of heterosexual persons with opportunistic infections without underlying disorders should be coordinated with those in this particular population to identify any potential risk factors.

- Consideration should be given to studies of heterosexual prostitutes, patients with Down syndrome and lymphomatous leprosy, and dialysis patients.

- A search of cancer registries should be conducted to identify possible excesses of other tumors among homosexual men. Although the working group did not specify how this should be done, presumably all registries would contain this particular information.

- In a social statement, the working group strongly voiced the need for investigators to serve patients, and warned against using patients as pawns. There are probably more people interested in attending this meeting than there are patients with KS and PCP combined, Dr. Curran noted, and their welfare must be placed first.

Virology-Etiology

Current evidence indicates that CMV is a prime candidate for causing or contributing to the emergence of KS, but working group members mentioned several times that one or more other viruses might eventually be important as well.

In the approach to this problem, Dr. Henle reported, of primary importance is the collection of well-certified specimens, ideally in a coordinated, centralized manner. Among the specimens needed, biopsies are critical and some will have to be available in a fresh state, or perhaps frozen under conditions in which the cells remain viable. Determinations should be made of how often CMV or perhaps other viruses emerge in cell cultures and whether these cultures show evidence of viral antigens. Also important are touch preparations, which have been very useful in the study of nasopharyngeal carcinoma. When touch preparations are properly made and fixed in acetone methanol, they keep for a long time and can be shipped to distant laboratories under dry refrigeration. These preparations can be stained by the anticomplement immunofluorescence technique. For example, the EBV-associated nuclear antigen can be readily detected in anaplastic nasopharyngeal carcinoma cells and thereby aid in the diagnosis of particular cases, especially those involving lymph node metastases in a patient where the primary site of the carcinoma is unknown.

Live preparations also should be used for inoculation of nude mice, in which presumably only tumor cells will propagate. One could then isolate the tumor cells for study of viral content, viral antigens, and viral nucleic acid. Other biopsies should be frozen and frozen preparations used for nucleic acid studies, either by DNA-DNA hybridization or other recent techniques, ultimately to search for a virus-specific RNA. Perhaps *in situ* hybridization will be necessary to identify the cells in which the virus is harbored.

In addition to biopsies from the tumor, normal tissue is required for comparison--perhaps from normal areas adjacent to the tumor. Dr. Henle noted that CMV has been isolated not only from colon, cervical, and prostate carcinoma, but also from tissue of these anatomical areas affected by nonmalignant disease, or even healthy tissue. An area might be selected where a given virus has its natural habitat for its persistent infectious activity and where activation might occur under immunosuppressed conditions, so that the presence of the virus is accidental and not causal in such cases.

The second type of specimens needed are sera from all patients, before diagnosis and then serially at 2- or 3-month intervals, or at times of recurrence. Control sera from other homosexuals without KS and from healthy individuals, categorized by age, sex, race, and socioeconomic status, are required. The working group also stated that sera should be collected from patients with various CMV-associated diseases because, depending on patient backgrounds, one might find different spectra of antibodies to the virus.

The selection of test procedures is also important; Dr. Henle recommended immunofluorescence procedures because particular antigens can be identified by their location within or on the cell. In other tests such as radioimmunoassays, where one works with extracts, antigens would not be identifiable. These techniques must await high purification of the antigens, which has yet to be achieved with EBV and probably will take a similarly long time with CMV.

Concerning the preparation of cell smears for these various antigen procedures, Dr. Henle reported that a number of different CMV-specific antigens already have been identified that appear to correspond to the early antigens of EBV and the EBV-associated nuclear antigen. At present, testing of sera by immunofluorescence depends on infecting cells growing on glass cover slips and then using them for the test. This introduces difficulty because not every cover slip will have an equal number of infected cells; some slips may even be noninfected. It would be preferable to produce these antigens by infection of cells in suspension; after the antigens have been synthesized, smears from these cells should be fairly uniform. Moreover, a much larger production would be possible. The antibodies' spectra would be determined by indirect immunofluorescence, differentiating between IgA, IgG, and IgM antibodies, as well as antibodies for different antigens. If patients with KS would have a spectrum quite different from normal carriers of the virus, and even from patients with other CMV-associated diseases, a diagnostic aid would be provided. Patients should be followed serially to determine whether, following treatment, antibodies' spectra narrow and titers decline, as has been observed in nasopharyngeal carcinoma. If this occurs, the treatment

may be considered successful and the patient becomes a long-term survivor and is probably cured. However, also as has been seen in nasopharyngeal carcinoma, antibody titers may stay high or increase, even months before a clinical recognition of recurrent tumors.

The working group also discussed the need for information on the cause of the severe immunosuppression seen in KS patients. Obvious suspects are some of the recreational drugs used, such as amyl nitrite, the production (and hence use) of which apparently has increased substantially since 1976. Such drugs should be tested in animals for their immunosuppressive and possible oncogenic effects. In addition, the aggressive therapy of KS might contribute to the immunosuppressive effects of any preceding factors. Also discussed was the possibility that perhaps a combination of the numerous infections that KS patients sustain (e.g., hepatitis B, CMV, amoeba, etc.) could overwhelm the immune system and be responsible for these immune deficiencies. Patients should be followed closely as to their immune status, before and after treatment. Determination of the helper-suppessor T-cell ratio, response to skin tests, and all other usual methods of assaying immune responsiveness have become working procedures in the management of patients. A reversal of immune suppression during the course of treatment would be an encouraging signal.

Finally, the working group discussed HLA relationships in KS patients. In light of the various conflicting observations presented, Dr. Henle concluded only that additional studies are required.

During questions, Dr. Henle said the search for other viruses associated with KS is an implicit activity in the types of studies recommended. For example, various examinations of touch preparations and establishment of various cell lines might lead to the discovery of a non-CMV virus. Following discussion, it was recommended that hepatitis virus be added to the list of candidate viruses to be studied in association with KS.

Treatment

Dr. Gerhard Johnson, of the VA medical center in Minneapolis, reported that the working group on treatment recommended a prospective study that would include all patients who could be identified with Kaposi's sarcoma--those with both homosexual and bisexual preferences, and spanning the age ranges involved with the disease. The group devised a classification system to facilitate entry into a treatment-oriented protocol outlined below; a number of the details in this protocol remain to be defined by several people assigned that task. To ensure firm diagnoses, a central pathology review mechanism will be built into the study.

Also discussed by the working group was staging of the patient and of the disease. In regard to staging of the patient, in addition to a variety of studies familiar to oncologists in evaluating the extent of tumor, group members drew specific attention to the need for computer tomography of the abdomen and for careful endoscopic evaluation of the gastrointestinal tract in the search for occult lesions. Specifically, colonoscopy and upper gastrointestinal tract endoscopy would be required.

In regard to staging of the disease, skin test reactivity, hepatitis virus antigen and antibody studies, and other to-be-defined immunologic evaluations of KS patients will be required. Dr. Stanley Balcerzak, of the Ohio State University Hospital, in consultation with the Southwest Oncology Group's immunology committee, will be making recommendations regarding the studies to be performed. Prior to treatment on this protocol, at least for patients treated with chemotherapy and perhaps with radiotherapy, the patient would be treated with trimethoprim and sulfamethoxazole prophylaxis, and possibly a prophylactic regimen for candidiasis.

The working group's therapeutic proposals were as follows:

	Extent of Tissue Destruction	
Anatomic Specification	Indolent	Aggressive
Local and regionalized disease	Radiation therapy*	Radiation therapy*
Generalized disease	Randomized study of ICRF vs. VP-16	Combination chemotherapy regimen

*Details to be further defined by Dr. Arvin Glicksman of CALGB.

Dr. Johnson reported that the proposed chemotherapy regimens included actinomycin D, DTIC, and vincristine for 3 weeks (regimen 1), or Adriamycin, vinblastine, and bleomycin for 3 weeks (regimen 2).

Associated problems discussed by the treatment working group included the serious immunosuppression in KS patients and its risk for life-threatening and perhaps fatal infection after initiation of chemotherapy. Members offered no ready solution to this problem--that chemotherapy may in fact accentuate immunosuppression--except the hope that adequate treatment of the disease will be followed by some improvement in the immunologic deficit.

Finally, the group decided that incorporating tumor markers (e.g., estrogen and progesterone receptors) into the prospective evaluation of the studies is among matters that need to be defined.

During questions, Dr. Johnson said part of the rationale for selection of the specific chemotherapeutic agents was that they be lesser in immunosuppressive properties than other potential drugs. For example, corticosteroids were purposely avoided because of their high immunosuppressive effects. Dr. DeWys also noted that pretreatment prophylaxis or other regimens remained an open question in the proposed protocol, and said consultation will be made with investigators in infectious diseases.

General Discussion

It was pointed out that experience in conducting collaborative multi-institutional clinical trials has shown that, generally, existing patterns of referral will continue, and patients must have the protocol brought to them. Several institutions are forming multidisciplinary clinics to see KS patients, in which the dermatologist, medical oncologist, infectious diseases specialist, and others can aid the patient concurrently. It was suggested that this model might be the best way of not only covering the multiplicity of the problems affecting these patients, but also addressing the requirements of prospective studies.

Discussion ensued about incorporating anti-viral agents into the treatment protocol for KS patients, particularly those with generalized non-aggressive disease. Little success has been achieved at identifying such an agent, although limited clinical data suggest possible activity for a new recombinant interferon, and *in vitro* data show promise for an analogue of Ara-C.

Also mentioned was the need to consider continued lifestyle factors, such as use of nitrite inhalants and degree of sexual activity, in analyzing the results of any study. Finally, concern was expressed about the uncomfortableness of some of the procedures recommended, and the expense of others. Dr. DeWys noted that these and other issues will receive further discussion, and NCI will advance proposals for addressing them.