KAPOSI'S SARCOMA: AN OPPORTUNISTIC NEOPLASM?

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INTRODUCTION

Kaposi's sarcoma (KS) was first described in 1872 by Moricz Kaposi, a Hungarian dermatologist, as multiple idiopathic pigmented hemangiosarcoma. He reported the disease to be a rare, chronic, cutaneous disorder of adult men which manifested itself in the skin as multiple blueish-brown vascular nodules and plaques on the distal extremities. In spite of this clinical presentation he was aware of the frequent concomitant involvement of the mucous membranes and of the gastrointestinal tract with similar nodules; he was, therefore, aware of the multifocal nature of the disease and the occurence of visceral involvement. He was also aware of the potential fatal outcome of the disease; all three men described in his initial report died within three years of diagnosis.

In recent years, a considerable amount of evidence has accumulated indicating that immunological deficiencies may play an important role in the pathogenesis and progress of KS. The purposes of this presentation are to summarize current knowledge about KS in the general population, to examine the increased frequency of this disease in several categories of immunosuppressed individuals (with particular attention to the recently described epidemic form of the disease in AIDS patients), and to consider possible etiological factors. It is clear that the present epidemic of KS has provided a renewed and perhaps unique opportunity to study the nature of this neoplasm and the possible roles of endogenous host factors such as the immune system, genetic influences, and hormonal influences on the predisposition toward and development of this disease. Similarly, the role of other epidemiologic factors, such as exposure to infectious viruses such as cytomegalovirus (CMV), which also seem to influence suceptibility to the development of this neoplasm, will also be considered.

CLASSICAL KAPOSI'S SARCOMA

In North America and Europe, prior to 1979, KS usually occured in elderly males of Eastern European and Mediterranean ancestry, especially Italians and Ashkenazic Jews of Polish and Russian decent. Typically, lesions begin as small violaceous papules and nodules on the lower extremities. Tables 1 and 2, taken from a study of 70 cases of KS seen at the Mayo Clinic in the 38-year period terminating in 1962 (98) indicates the striking frequency with which lesions present on or are confined to the lower extremities. These papules and nodules may enlarge and coalesce to form larger nodules, plaques, and tumors. On the lower extremities, the lesions are generally red or purple in hue in light-skinned individuals, and purplish-brownish in dark-skinned individuals. As the lesions become older, they frequently darken in color, progressing from red to dark purple to brown. While generally beginning on the lower extremities, it can be noted from Tables 1 and 2 that lesions can also be seen on the upper extremities, and scattered lesions can occur on the trunk, head, neck and genitalia. Nodules and tumors may cluster along veins, especially on the lower extremities. In general, the earliest lesions are not palpable, but rather are colored, flat macules (105). As the lesions age, enlarge, and become palpable papules or nodules, they frequently become somewhat doughy and compressible. Though usually asymptomatic, lesions can burn, itch, or cause some pain. Chronic venous stasis and lymphedema of the involved extremity

frequently complicates the clinical course and management of the disease. In contrast to more locally aggressive forms of KS sometimes seen in Africa (see below), local invasion of surrounding subcutaneous tissue and bone rarely occurs in classic KS. Although it may occur at any age, the peak incidence of classical KS observed in several African series has been in the sixth or seventh decade (59, 98, 102). Classical KS has an annual incidence in the United States between 0.02 to 0.06 per 100,000 population (103); therefore, approximately 100 new cases might be expected per year. In a series of 92 patients from the Sloan-Kettering Cancer Institute, 75% of cases were males (103). However, the male:female ratio has been higher in other series, ranging from 10:1 to 15:1 (87, 98).

TABLE 1

Site of Initial Lesion

Site	Cases
Foot	57
Ankle	10
Leg	6
Knee	3
Hand	2
Arm	2
Penis	2
Thigh	1
Groin	1
Spleen	1
Larynx	1
Indeterminate	4

TABLE 2

Distribution of External Lesions

Site	Cases
Lower extremity	70
Upper extremity	31
Trunk	12
Penis	8
Ear	6
Face	4
Scrotum	3
Nose	3
Scalp	2
Neck	1

The natural course of classical KS in the United States ranges widely from one which is slow and indolent and occasionally characterized by spontaneous regression of individual lesions to one which is quite rapid and fulminant with widespread cutaneous and extracutaneous lesions. Average survival time in various American series has been reported to be from 10-15 years; however, survivals up to 50 years have been reported and in such chronic cases death has almost invariably been due to an apparently unrelated cause (75, 87, 98, 103, 106). As noted by Kaposi himself it is not unusual for systemic lesions to appear, especially in the gastrointestinal tract. KS lesions have been observed in almost all organs of the body including tonsils, lungs, adrenals, spleen, liver, kidney, pericardium, lymph nodes and bone. Such multifocal discrete visceral lesions in the classical form of KS are generally asymptomatic and may be discovered only at autopsy (98, 121). Uncommonly, otherwise typical classical KS may behave in an aggressive manner early after onset with development of multifocal mucocutaneous and visceral involvement.

In the Mayo Clinic series of 70 patients, 29 patients died (41%), with an average duration of their disease of 10 years (98). However, KS was thought to be directly related to the cause of death in only 8 of these patients. Three of these 8 patients survived 13, 20, and 32 years, respectively, from the time of onset of their lesions. The remaining 5 patients died within 3 years of onset.

Of the eight patients presumed or proven to have died from KS, death was accounted for by progressive pulmonary involvement in two cases, massive intestinal bleeding in one, and extensive disease of the extremities and visceral lesions in the remainder. While only 7% of the patients (5 of 70) in this series had aggressive, rapidly progressive disease, this rapidly progressive course was observed in one-third (2 of 6) of the women in this series. Thus, while the classical form of KS has a striking male predominance, affected women seem to have a higher chance of having progressive generalized disease; this same tendency has been observed in series of African KS (see below).

HISTOPATHOLOGY AND CELL OF ORIGIN

The cell of origin of KS has been a subject of disagreement among those who have studied this neoplasm, leading Templeton to note as late as 1981, "The list of potential cells of origin for Kaposi's sarcoma reads like a mesodermal hall of fame" (121). Templeton's further analysis of the light and electron microscopic studies as well as histochemical analysis which implicated a variety of different cell types in the histogenesis of KS further led him to quote the bone pathologist L.C. Johnson, "Cell of origin, like paternity, is often a matter of faith" (121). Although the endothelial nature of the cells that line the vascular slits which form a significant component of the histopathology of KS has been acknowledged by almost all investigators, the real debate centered around the nature of the intertwining spindle cells adjacent to the blood-filled clefts. Such spindle cells are rather characteristic of all stages of KS other than the earliest (patch) stage in which lesions are clinically macular or barely palpable, and histopathologically are characterized by dilated, thin-walled vascular spaces. Thus, the usual histologic pattern of classical KS is a mixed cell pattern consisting of roughly equal porportions of spindle cells, vascular slits and well-formed vascular channels. A second histopathologic pattern has been characterized as a mononuclear pattern in which proliferation by one cell type, usually the spindle-shaped cells, predominates. In both the mixed cellularity and mononuclear patterns, anaplasia and mitotic figures are rarely observed. A third histopathologic pattern, the anaplastic pattern, which features marked cellular pleomorphism and frequent mitotic figures, is the most rare and has been observed only in the fungating type of tumor lesions observed in African KS (see below).

The controversy as to the cell of origin of KS recently has, to most investigators' satisfaction, been laid to rest. Several publications utilizing immunoperoxidase techniques all have shown the presence of Factor VIII-related antigen not only in the obvious endothelial cells lining the vascular channels and those around blood-filled clefts, but also in the cytoplasm of the spindle-shaped cells (25, 38, 42, 74, 81). Since Factor VIII antigen has been shown to be elaborated only by cells of endothelial or megakaryocytic origin, positive immunological reactions for this factor in the cells of KS very strongly supports an endothelial derivation.

MULTICENTRIC VERSUS METASTATIC BEHAVIOR OF KS

The typically multifocal and frequently wide distribution of individual lesions of KS (particularly in the non-classical forms to be described below) is unlike the distribution pattern typical of true metastatic lesions seen in malignancies such as melanomas, carcinomas, and sarcomas. Most sarcomas, even the rare angiosarcomas, which originate from vascular tissue, arise as a single localized tumor mass which eventually metastasizes through the blood stream or lymphatic system to visceral organs, especially the lungs or liver (28). In contrast, each of the lesions of KS appear to arise as de novo multifocal tumors either simultaneously or at asynchronous intervals, from the endothelium of pre-existing blood vessels. Histologically, KS-involved lymph nodes contain multiple small foci of tumors located in the capsular and sinusoid regions of the nodes associated with generalized lymphoid hyperplasia (12, 24, 28, 117, 119, 120); again, this is not the typical picture of metastatic invasion of lymph nodes observed in other malignant neoplasms. Similarly, the disseminated KS lesions seen in mucous membranes or visceral organs such as the bowel, liver, kidney or lung also appear to originate from existing organ vessels (12, 28). Thus the current consensus of opinion is that KS represents multicentric, widely disseminated tumors which arrive de novo from different polyclonal proliferations of vascular endothelial cells in susceptible endothelial cells (28, 100). It appears that this tumor rarely, if ever, spreads by metastasis. The one exception to this statement is in the case of the locally aggressive-behaving (e.g. infiltrating or fungating) lesions which are occasionally observed among African KS patients (see below).

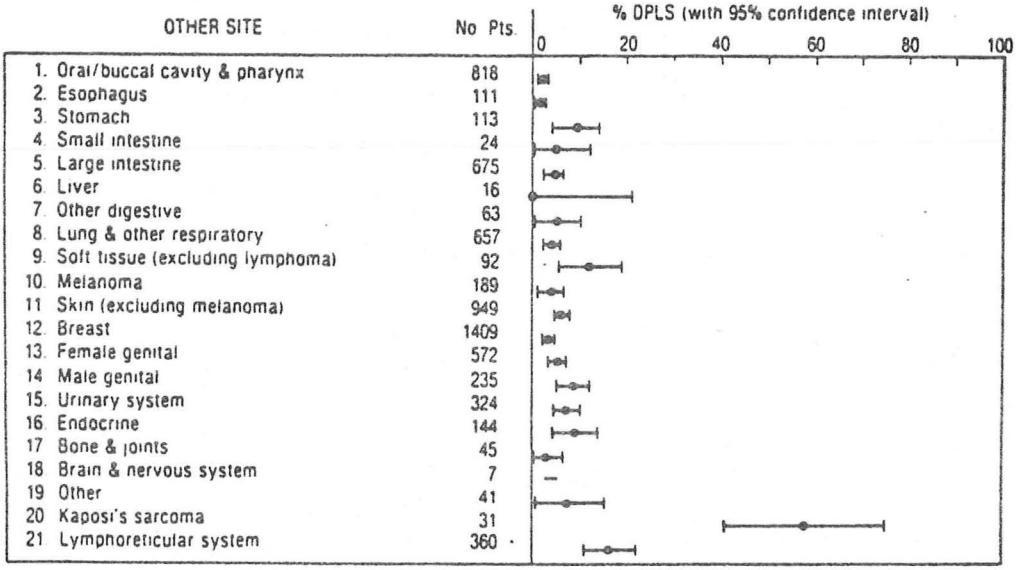
ASSOCIATION OF CLASSICAL KS WITH SECOND PRIMARY MALIGNANCIES

The development of multiple primary neoplasms in the same individual has been the subject of considerable interest, often stimulated by the hope of discovering factors that may play a major role in inducing the neoplastic process. The co-existence of classical KS with other primary malignancies, especially those of lymphoreticular origin, has been noted on numerous occasions (76, 87, 102, 118, 122). While the occurence of more than one neoplasm in an individual is not rare, the extremely high incidence of other primaries in patients with KS is striking. Safai has reported that the prevalence of multiple primary cancers in autopsy studies of patients with at least one known malignant tumor has varied from 2% to 11% (102). The most extensive study has been done on classical KS patients by Safai and colleagues from the Sloan-Kettering Cancer Center (102). Data was collected on their series of 92 patients with KS seen and treated between 1949 and 1975. Thirty-four of the 92 patients, or 37%, had at least one other primary malignancy during the period of study. Twelve patients had another primary before, 8 simultaneously with (diagnosed within 3 months of each other) and 14 after the diagnosis of KS. Three patients had more than one other primary; therefore these were omitted from the analysis of double primaries, leaving 31 cases.

When this data was compared with 4,517 double primary malignancies (including all possible sites) diagnosed at Sloan-Kettering between 1949 and 1974, striking results were obtained. Of the 31 KS patients who had another primary malignancy

at some time, 18 (58%) had a primary involving the lymphoreticular system. Diagnoses in these cases included leukemia, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphoma. A summary of the percentage of double primary malignancies involving the lymphoreticular system, grouped by site of the other primary, is shown graphically in Figure 1. A strikingly consistent pattern is seen across these diagnostic categories. The upper limit of the confidence intervals for all sites other than KS does not extend beyond 21% whereas the lower limit of the confidence intervals for KS is 41%.

Fig. 1. Percent of double primaries involving the lymphoreticular system; grouped by site of other primary neoplasm.



As indicated in Table 3, of the 72 KS patients at risk for developing another primary malignancy after the diagnosis of KS, such double primaries were observed in 14 of these individuals. Of these 14 cases, 9 involved the lymphoreticular system. In order to investigate whether this represented an increase over the expected incidence of such primaries in a general age- and sex-mediated population, an analysis was carried out using two sets of population incidence rates reported by the tumor registries of Connecticut and New York. For all patients at risk, the total length of follow-up (to death, end of study, or diagnosis of second primary) was tabulated by sex and 5-year age groups. To establish the expected number of new lymphoreticular malignancies of each of 5 types, the person-years of observation of each subgroup were multiplied by the corresponding sex- and age-specific incidence rates obtained from the two tumor registries. The results were then summed over sex, age, and the five different lymphoreticular malignancy types, to yield the expected number of lymphoreticular malignancies. Confidence limits for the observed:expected ratios were given under the standard assumption that the incidence of new cancers followed a Poisson distribution. The observed rate per 100,000 of lymphoreticular malignancies in the KS patients was 1,549. This represents a 20-fold greater than expected increase in the incidence of lymphoreticular malignancies after the diagnosis of KS. To summarize, when compared to the age-matched general population, patients with classical KS

appear to have between a 3- to 15-fold increased risk of developing a second primary malignancy and at least a twenty-fold increased risk of developing a second lymphoreticular malignancy. The potential implications of these observations will be addressed later in this presentation.

TABLE 3

LYMPHORETICULAR MALIGNANCIES
AFTER DIAGNOSIS OF KS

Data summary

Number of KS patients at risk		72
Other primary after diagnosis of KS	14	
No other primary malignancy	58	
Number of KS patients with subsequent lymphoreticular malignancy		9
Total number of person-years observed		581
Average length of observation (years)		8
Observed rate per 100.000		1549

Incidence of lymphoreticular malignancies relative to age- and sex-adjusted expected rates per 100.000

Tumor registry	Obs	Exp	Obs/exp	95% confidence interval
Connecticut	1549	75.8	20.4	9.4–38.8
New York State	1549	71.8	21.6	9.9–40.9

AFRICAN KAPOSI'S SARCOMA

In the 1950's new interest developed in KS with the recognition that this tumor occured with striking frequency in Africans, especially those of the Bantu tribe of South Africa and those native Africans living in what is now considered to be an endemic belt located in Central Equatorial Africa where it is now considered one of the most common malignancies. The highest proportional rates (relative frequencies) of KS are found in Northeast and Eastern Zaire, Rwanda, Burundi, French Equatorial Africa, Uganda, Malawi, Tanzania, Zambia, Zimbabwe, and Kenya. The rates fall off towards West and South Africa, although they are still significantly higher than the rest of the world. In this endemic area, approximately 3-9% of all tumors reported are Kaposi's sarcoma (88, 110, 117, 118, 121).

This distribution of African KS does not seem to correlate with any physical map, although in West Africa it is thought to correspond to the heavy rainfall belt. In Nigeria, for instance, KS is found mainly in the delta region of the country, which is wet and humid. However, other wet and humid areas such as South America or New Guinea have a low incidence of KS. The high rate of KS in equatorial Africa is apparently restricted to native Africans, since it has been observed that Asians and Europeans residing these areas do not have an increased incidence (121). It is intriguing that the distribution of African KS is rather similar to that for Burkitt's lymphoma, another malignancy seen with striking frequency in this sub-Saharan portion of Africa.

TABLE 4

CLINICAL CLASSIFICATION OF
KAPOSI'S SARCOMA

I.	Indolent KS
	Cutaneous nodular lesions
	Plaque forms
II.	Aggressive KS
	Local
	Florid
	Infiltrative
	Systemic
	Visceral
	Lymphadenopathic

In tropical Africa, KS may present as either indolent or aggressive disease (Table 4). The indolent varieties are made up the nodular and plaque forms of the disease which clinically are indistinguishable from those seen in classical KS in the United States. Africans with this form of KS may not seek medical attention for many years, and when they do so it is mainly for cosmetic reasons. Aggressive forms of African KS include those which are locally aggressive and those which behave in a systemically aggressive manner. Locally aggressive lesions include the florid variety and the infiltrative variety. Florid lesions differ from typical nodules and plaques in that they grow the deep fascia, grow as fungating tumor masses, and are highly vascular and bleed easily. The infiltrative variety infiltrates the dermis and underlying structures including bone, producing woody thickening and induration of the involved skin. Of the systemically aggressive varieties of African KS, diffuse visceral involvement (with substantial involvement of the gastrointestinal tract and other organs such as liver and lungs) is rather similar to the disseminated aggressive form of the disease occasionally seen in classical KS in the United States. A systemic form of KS, not previously recognized in classical KS cases in the United States, is one which presents with minimal skin disease, but striking and massive involvement of lymph nodes. The lymphadenopathic form occurs most commonly in children and young adults, is frequently and rapidly progressive, and is easily confused with lymphoma. The frequency of these various clinical varieties of Kaposi's sarcoma in Uganda are shown in Table 5 (from ref. 88).

TABLE 5
FREQUENCY OF CLINICAL VARIETIES OF
KAPOSI'S SARCOMA IN UGANDA

Clinical variety	Percent
Nodular and plaques	54
Florid	29
Infiltrative	11
Lymphadenopathic	3
Visceral	3
Total	100

In contrast to classical KS seen in Europe and North America, African KS is most frequently observed in young adults between the ages of 25 and 45 (118, 121). Thus, African KS is much more frequently observed in a younger population than is affected by classical KS. The overall male:female ratio in African KS is between 15:1 and 30:1 (118, 121). However, these overall figures are somewhat misleading. As can be seen in Figure 2 (118) and Table 6 (88) the male:female ratio is much lower for the younger age groups.

Fig. 2: Annual incidence of KS in Uganda, 1964-1968

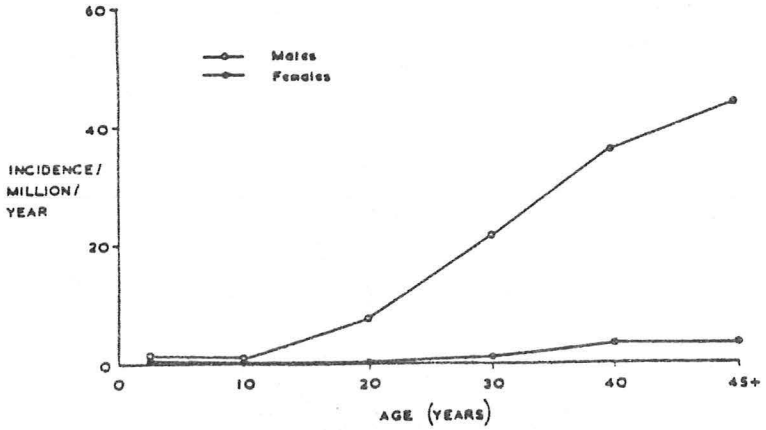


TABLE 6
AGE AND SEX DISTRIBUTION
OF KAPOSI'S SARCOMA

Age group (years)	Male/female ratio
0-9	1.7:1
10-19	2.7:1
20-29	3.6:1
30-39	6.4:1
40-49	7.5:1
50-59	8.1:1
60-69	14.0:1

Templeton's study of 112 Ugandan patients with a histologically proved diagnosis of KS has provided much useful prognostic data (119). As can be seen in Table 7, nodular disease was by far the most common, accounting for nearly 75% of the total cases. Only one of these 76 cases was in a female (1.3%). On the other hand, of the 14 patients with generalized disease (i.e. visceral or lymphadenopathic) 2 patients (14%) were females. Of the 108 cases in males, 12 were of the generalized variety (11%). On the other hand, half the affected females in this series, had generalized disease. This data is consistent with the data previously presented from the Mayo Clinic which suggested that females, while much less likely to contract this malignancy than males, have a significantly greater chance of having their disease be of a more rapidly progressive or aggressive form.

TABLE 7

AFRICAN KS -- CLINICAL PATTERNS OF DISEASE

Clinical Pattern	Males	Females	Total
Nodular	75	1	76
Locally aggressive	21	1	22
Generalized	12	2	14
Total	108	4	112

TABLE 8
AFRICAN KS -- PATIENT STATUS AT FOLLOW-UP COMPARED WITH CLASSIFICATION AT PRESENTATION

Clinical	Number of patients	Deaths (%)	Alive with disease (%)	Alive and disease-free (%)
Nodular	76	5 (7)	31 (41)	40 (52)
Aggressive	22	8 (36)	11 (50)	3 (14)
Generalized	14	14 (100)	----	----
Total	112	27 (22)	42 (38)	43 (40)

That the clinical classification scheme of segregating patients into nodular, locally aggressive, and generalized forms of disease at presentation has prognostic significance is reflected in Tables 8 and 9. While there was an overall 22% mortality rate during the period of this study among the patients with KS (since autopsies were not done on all of these patients, the cause of death could not in all cases be definitivly be determined), it can be seen that the number of deaths in each clinical group was strikingly different. It ranged from 7% in those with nodular disease to 36% in those with locally aggressive disease, to 100% in those with generalized disease. Conversely, of the 112 total patients, 43 (40%) were disease free at the conclusion of this study. However, while there were no survivors in the group with generalized disease and while only 14% of patients were disease free in the locally aggressive group, 52% of the patients with localized indolent disease were clinically free of disease at the end of the study. Similar conclusions are reached by examination of the mean duration of disease of patients known to have died (Table 9).

TABLE 9

AFRICAN KS -- DURATION OF DISEASE IN 27 PATIENTS KNOWN TO HAVE DIED

Clinical pattern	Number of patients	Duration of symptoms	Mean duration (yr)
Nodular	5	1-17 yr	11.5
Aggressive	8	8 mo-17 yr	7.5
Generalized	14	8 mo-3 yr	1.6

Table 10 indicates clearly that survival in African KS is clearly related to age of onset of disease; the highest percentage of deaths were seen in the younger-aged patients. This effect is most likely a result of the different disease patterns seen in the various age groups. Thus, African children and young adults most commonly present with the generalized lymphadenopathic form of the disease which is almost invariably rapidly fatal. It should be pointed out however, that the small numbers of young adults with nodular disease have been shown to follow the same generally favorable course exhibited by older people with nodular disease (110). Similarly, locally aggressive or generalized lesions showed the same progression and relatively poor response to therapy in both young and older patients (119). In other words, the age of the patient influences the type of disease likely to be found; however, disease of similar clinical type behaves the same, regardless of the patient's age.

TABLE 10

AFRICAN KS -- SURVIVAL OF PATIENTS COMPARED WITH AGE AT ONSET OF DISEASE

Age (yr)	Number of patients	Deaths (%)	Alive and disease-free	Alive with disease
0-4	2	2 (100)	----	----
15-29	19	9 (47)	6	4
30-44	41	7 (17)	19	15
45-59	32	6 (19)	13	13
60+	18	4 (22)	7	7

Lymph nodes were involved in all patients with generalized disease, but only a small proportion of those with either nodular or locally aggressive disease (Table 11). Most commonly the lymph node involvement in both the nodular and locally aggressive forms of disease was confined to a single group of nodes. Generalized nodal involvement was associated with a dismal prognosis. Similarly, the local nodal involvement in patients with locally aggressive disease was associated with a significantly poor prognosis (i.e., 3 of the 4 patients succumbed to their disease and the fourth had clinical disease present at the end of the study). On the other hand, of the 6 patients with nodular cutaneous disease and local lymph node involvement only one died; thus, isolated involvement in this clinical group does not appear to be an adverse prognostic indicator.

TABLE 11

AFRICAN KS -- FOLLOW-UP DATA ON PATIENTS WITH LYMPH NODE INVOLVEMENT IN EACH CLINICAL PATTERN OF DISEASE

Clinical pattern	Number of patients	Proportion (%)	Deaths	Mean follow-up of survivors
Nodular	6	8	1	4 yr (all disease-free)
Aggressive	4	18	3	4 yr (disease present)
Generalized	14	100	14	-----

KS IN IATROGENICALLY IMMUNOSUPPRESSED PATIENTS

The first case of KS in association with a renal transplant was described in 1969; since that time, there have been a number of publications documenting an increased incidence of KS in iatrogenically immunosuppressed patients relative to age-matched controls, particularly in renal transplant patients (32, 43-45, 91, 92). Other underlying disorders treated with immunosuppressive therapy in which KS has developed include systemic lupus erythematosus, lymphoma, myeloma, asthma, cirrhosis, nephrotic syndrome, rheumatoid arthritis, hemolytic anemia, ITP, bullous pemphigoid, and pemphigus vulgaris (106). Since 1969 there have been at least 23 cases of KS associated with renal transplants reported in detail in the English Literature. The largest number of such patients (four) from a single center have been seen in Toronto (44, 45). These four cases developed from the approximately 1,400 renal transplants done to date

in that center. During the time period that the four patient with KS developed in the 1400 renal transplants in Toronto, 70 cases of uncomplicated KS were observed in that population of approximately 4,000,000 people. Thus, the incidence of KS in renal transplants in this particular series was between 150 and 200 times the expected incidence of this tumor in the general population. Similar conclusions can be derived from the data collected by the Cincinnati Transplant Tumor Registry which has collected data on 1,600 organ transplant recipients (92). Registry statistics indicate that 1,702 different malignancies arose after transplantation. Of these neoplasms 58, or 3.4%, were Kaposi's sarcoma. If non-melanoma skin cancers and in situ carcinomas of the cervix are excluded (as they are from most compilations of cancer statistics) then KS made up 5% of all malignancies in this highly selected patient population. Again, this figure represents at least a 100-fold increased incidence of KS in transplant patients over that seen in the general population. Furthermore, even when the control population was derived from the same ethnic origin as the renal transplant patients with renal transplant patients, the observed incidence of KS is still strikingly increased (44). Table 12 lists several other striking similarities and differences between renal transplant KS and classical KS. The 2:1 ratio of males:females observed in renal transplant KS patients is much less than that seen in the general population with KS (the 3.5:1 ratio used in Table 12 is the lowest estimate of such ratios derived from analysis of studies of classical KS). In contrast to classical KS, with its peak incidence in the 6th or 7th decade, the average age of diagnosis of KS in renal transplant patients was 42 years, not significantly different from the mean age of all renal transplant patients (32, 92). All the patients with renal transplant KS in Toronto and the majority in the literture developed in patients of an ethnic ancestry (Jewish, Mediterranean, African) previously been reported to be predisposed to the classic form of the disease. In contrast to classical KS with its low mortality rate and rarity of disseminated disease, renal transplant KS is associated with a much higher mortality rate. This increased mortality is attributable to the disease and not to a complication of the transplant. The most common cause of death has been bleeding from extensive gastrointestinal sarcoma; i.e., disseminated disease is fairly common in this group of patients. Finally, the Toronto group has noted that higher doses of irradiation appeared to be necessary to control KS in renal transplant patients as compared to uncomplicated KS.

TABLE 12

COMPARISON OF RENAL TRANSPLANT KAPOSI'S SARCOMA AND UNCOMPLICATED KAPOSI'S SARCOMA

	Renal transplant Kaposi's	North American uncomplicated Kaposi's
Sex	1.6 males:1 female	3.5 males:1 female
Age	42 years	67 years
Ethnic origin	Jewish and Mediterranean ancestry; extremely rare among Anglo-Saxons	Jewish and Mediterranean ancestry; extremely rare among Anglo-Saxons
Pattern of disease	Local disease may ulcerate Disseminated disease common 30% mortality rate	Local disease very indolent Disseminated disease rare 3% mortality rate
Response to radiotherapy	Higher doses of irradiation required for control	Excellent with low doses (800 rads)

Three other striking features of renal transplant KS deserve comment. First, there are numerous examples of complete clinical remissions of both solitary and multiple cutaneous, as well as extracutaneous lesions when immunosuppressive therapy was drastically curtailed (44, 45, 91, 92). Similar clinical complete remissions of KS following discontinuation of immunosuppressive therapy have been reported in patients with other primary diseases which were being treated with immunosuppression (32). The frequency with which this occurence has been reported obviously further fuels the fire of those who would argue for a primary role for immunosuppression in the development of this disease. Secondly, the mean latent period for appearance of KS in renal transplant patients, an average of 16 months (range 2-101 months) is a remarkably short time after transplantation when contrasted with the other malignancies which occured in transplant patients; other malignancies appeared in average of 54 (range 1-206) months after transplantation (92). Finally, it is important to reiterate that the increased incidence of KS in renal transplant patients occurs in a setting of a similarly marked increase in the incidence of lymphoreticular malignancies, particularly B-cell non-Hodgkin's lymphomas (43, 92).

EPIDEMIC KAPOSI'S SARCOMA IN PATIENTS WITH AIDS

Between the late fall of 1979 and the spring of 1981 the CDC reported cases of widely disseminated and unusually aggressive and fulminant KS from New York, and a variety of opportunistic infections from Southern California. Both these highly unusual outbreaks were combined into a single report because of the shared epidemiologic feature of occurence in young, sexually promiscusous, homosexual men. This was the first notification of the epidemic that came to be called the aquired immune deficiency syndrome (AIDS). The nature of the KS seen in these patients was strikingly distinct from that previously observed in classic KS in the United States. It was associated with a 50% mortality rate and a mean survival of less than months, rather than the 10-15 years reported for elderly caucasians. Most of the patients had histologically proved skin and lymph node involvement, and over 75% had documented visceral involvement. The skin lesions, rather than being predominantly on the lower limbs, were generalized. The mean age of affected men was 38, substantially younger than the age group affected with classic KS. The early involvement of lymph nodes and visceral organs in epidemic KS had striking similarities both to the lymphadenopathic, rapidly fatal form of KS observed in African children, and to the generalized aggressive form of the disease very occasionally seen in otherwise typical classic KS patients, occasionally observed in slightly older African KS patients, and relatively commonly seen in iatrogenically immunosuppressed KS patients.

The mucocutaneous manifestations of epidemic KS are much more varied than that seen in other types of this neoplasm. While patients may present with solitary or multiple patches, nodules or plaques on the lower extremities, more frequently they will have multiple lesions which will appear in localized clusters or in widely disseminated, discrete lesions. It is important to point out once again that the early lesions in epidemic KS are frequently flat macules ranging in color from a faint pink to red or purple. These macules may turn brownish due to secondary hyperpigmentation. The lesions are often oval or slightly irregular in their shape, and can range in size from 1-2 mm to several

cm in diameter. Not all lesions are associated with obvious color changes on the skin; some lesions may instead present as deep, dermal or even subcutaneous nodules which vary in consistency from being slightly compressible to fairly firm. As noted above, the lesions may appear any place on the lower or upper extremities, the trunk, the genitals, and the face. The occipital region of skin behind the ears and on the earlobes themselves are particularly common sites for lesions above the neck. Oropharyngeal lesions on the mucosa are most frequently seen on the hard or soft palate. These lesions are usually flat, but may be plaque-like and even nodular. Nodular, deep purple lesions are often seen on the gingiva (68).

Epidemic KS lesions are also commonly found to be dispersed throughout the esophagus and gastrointestinal tract. At NYU Medical Center between 1979 and 1982, 86 men with biopsy proven KS were evaluated by double-contrast radiography of the stomach and colon, upper endoscopy and colonoscopy (113). GI tract KS lesions were found in 36 of the 86 patients (42%). The lesions were characteristically deep red to a crimson with a unique "raspberry"-like appearance. They appeared either as macules, ranging from a few mm to several cm in size in the mucosal plane, as raised plaques, or as confluent polypoid nodules. All parts of the GI tract were involved, the esophagus in 1, the stomach in 20, the duodenal bulb and sweep in 4, the colon in 19 and the rectum in 11. Because many of the KS lesions were not elevated above the mucosal plane, a double-contrast barium studies frequently failed to demonstrate lesions which were easily seen endoscopically. Small bowel X-ray studies were not particularly revealing, although autopsy studies did reveal numerous silent KS lesions to be present.

EPIDEMIOLOGY OF EPIDEMIC KS

It quickly became clear that the epidemic of Kaposi's sarcoma and opportunistic infections was not limited to young male homosexuals, but rather extended to the other now familiar high-risk groups; i.e., intravenous drug users, Haitians residing both in the United States and in Haiti, hemophiliacs receiving lyophilized Factor VIII concentrate, as well as sporadic cases among individuals with no immediately obvious risk factor. With increased epidemiologic investigation, it has become clear that the "Other" category includes children from families in which one or both parents were members of known risk groups, heterosexual partners of high-risk individuals (including an increasing number of female prostitutes), and recipients of blood products from high-risk donors. As the number of newly reported cases of AIDS continues to escalate the CDC report as of 2/11/85 indicates over 8,300 cases diagnosed to date), one perhaps minimally reassuring statistic, indicating that there has been little, if any, change in the percentage of AIDS patients in any one of the known risk groups, is shown in Table 13. The percent composition by risk group of the 6,251 cases reported as of October, 1984, is not significantly different from that reported in the first year or two of the epidemic (see also Lipsky P.E., "Aquired Immunodeficiency Syndrome", Internal Medicine Grand Rounds, 9/6/84). This includes the fact that the percentage of total cases in females has remained at approximately 7%.

The primary disease manifestations of the 6,251 AIDS cases reported to the CDC as of October, 1984, are shown in Table 14. Again, analysis of this data reveals that as the epidemic has evolved there has been no substantial change in

the nature of the morbidity or in the overall or group-specific mortality rates. Thus, at the present time, the overall mortality rate remains at slightly less than 50%. Approximately 24% of AIDS cases present with KS only; the cummulative mortality rate among these patients is 29%. Another 6% of AIDS cases have both KS and Pneumocystis carinii pneumonia; the cummulative mortality among this group of patients continues to be the highest of all the major groupings at 67%. Approximately 70% of AIDS patients do not have or develop KS, but rather present with Pneumocystis pneumonia or other opportunistic infections; the cummulative mortality rate in both of these groups continues to hover around the 50% mark.

TABLE 13

AIDS RISK GROUPS - OCTOBER, 1984
(6,251 Reported Cases)

Homosexual/bisexual men	73%
Intravenous drug users	17%
Haitians	4%
Hemophiliacs	1%
Others	5%
% Total Cases in Females -- 6.8%	

TABLE 14

AIDS CASES REPORTED TO CDC AS OF OCTOBER, 1984

Primary disease	Cases	% of Total	Deaths	% Dead
KS only	1,479	24%	436	29%
KS and PCP	379	6%	254	67%
PCP only	3,358	54%	1,695	50%
Other OI	1,035	16%	565	54%
	6,251	100%	2,950	47%

While KS is seen in approximately 30% of all cases of AIDS, it continues to be very clear that different AIDS risk groups have strikingly different frequencies of KS. The data illustrated in Table 15 (H. Jaffe, personal communication reported in ref. 11) illustrates this point fairly convincingly. Nearly half of the male homosexual cases in this series of 1,000 had KS; these cases accounted for 93% of the total cases of KS in this series. On the other hand, the frequency of KS in the other major risk groups, most notably IV drug users, Haitians, and hemophiliacs, is significantly less (see also 69, 90, 94). Among the "Other" category, KS has been described in infants with AIDS (6). Both patients had the disseminated lymphadenopathic form of KS (with no skin lesions) similar to the form of KS usually observed in children in Africa.

TABLE 15

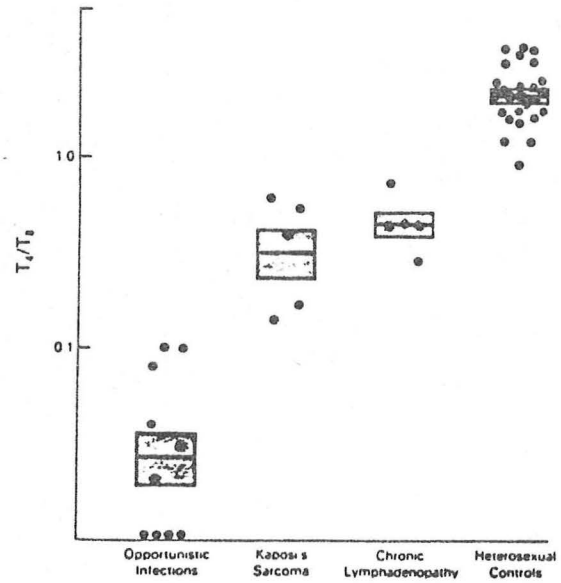
DISTRIBUTION OF KS BY AIDS RISK GROUP

	No. cases	No. cases of KS	%	% Total KS
Homosexuals	727	342	47%	93%
IV Drug Users	155	6	4%	2%
Haitians	50	2	4%	1%
Hemophiliacs	7	0	---	---
Other	61	16	26%	4%
	1000	366	36.6%	100%

The evidence linking HTLV-III infection to the pathogenesis of the immunosuppression so characteristic of AIDS has continued to accumulate rapidly since Dr. Lipsky's Grand Rounds presentation here last fall (for a recent summary of this data see ref. 5). A detailed (or even superficial) discussion of the linkage of HTLV-III with AIDS is beyond the intended scope of this presentation. However, the above-noted non-random distrubution of KS within AIDS risk groups stands in marked contrast to the essentially universal presence of evidence for infection with HTLV-III among all these patients. This data strongly suggests that the developement of KS in an individual immunosuppressed as a result of an aquired infection with HTLV-III is dependent upon other significant risk factors. Furthermore, the obvious risk group on which to focus one's search for such potentially relevant etiologic factors would appear to be the male homosexual.

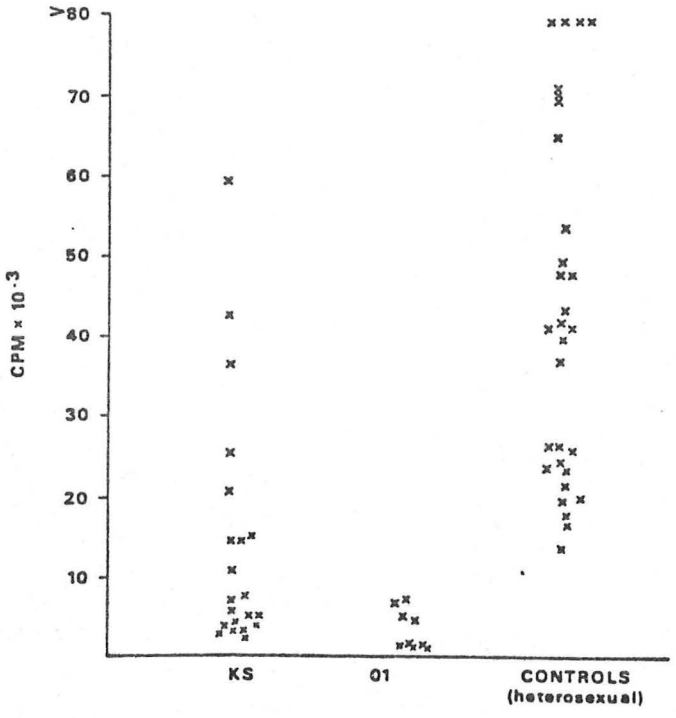
One of the most prominent features of the immune system of patients with AIDS is a depletion of helper/inducer T lymphocytes which results in a lowering of the ratio of T-helper cells/T-suppressor cells, also known as the T4/T8 ratio. Figure 3 (from ref. 57) illustrates the T4/T8 ratios for AIDS patients with opportunistic infections alone, AIDS patients with KS alone, homosexual men with the chronic lymphadenopathy syndrome, and normal heterosexual controls. It is relevant to point out that a similar-appearing figure was obtained if the data were expressed as the absolute number of T4-positive cells. As can be seen, those patients who presented initially only with Kaposi's sarcoma had higher T4/T8 ratios and higher absolute numbers of T4 lymphocytes than did those who initially presented with opportunistic infections. This is the immunologic correlate of the observation noted previously (see Table 14) which indicates that patients with KS only have a significantly lower mortality (i.e., a longer life expectancy) than other clinical presentations. The most straightforward interpretation of this data is that AIDS represents a disease of the immune system which may manifest itself clinically in a variety of ways dependent upon a variety of host factors such as genetic background and environment; those patients who initially present with KS alone may be doing so earlier in the course of a progressive immune deficiency than those initially presenting with a life-threatening infection such as Pneumocystis carinii pneumonia.

Fig. 3: T4/T8 ratios for AIDS patients and controls



One of the other striking and consistent immunologic abnormalities manifested by AIDS patients is a diminished proliferative response of peripheral blood mononuclear cells to B-cell mitogens, such as pokeweed mitogen (26, 135). This abnormality may be a reflection of the hyperactive state of the B-cells (reflected in the frequently elevated serum immunoglobulin levels in vivo and the increased numbers of spontaneous plaque-forming cells in vitro), which renders them relatively unreactive to further stimulation with mitogens in vitro. The data shown in Figure 4 (135) demonstrating the response of mononuclear cells from normal controls or patients with either KS or opportunistic infections after stimulation with pokeweed mitogen, shows that this phenomenon is more acute in AIDS patients with opportunistic infections than in those with KS alone. Thus, cells from patients with opportunistic infections demonstrate the more profound inability to proliferate in response to pokeweed. Cells from most patients with KS also showed this unresponsiveness; however, over 1/3 of the KS patients exhibit responses clearly within the normal range. Thus, this data also is consistent with the above mentioned observation that patients presenting with KS alone are relatively less immunocompromised than other AIDS patients. The other, not mutually exclusive, possible explanation for the above findings, namely, that KS patients have a more profound B-cell hyperreactivity secondary to some other environmental agent such as CMV-driven polyclonal B-cell activation, will be discussed in a later section.

Fig. 4: Pokeweed mitogen response of mononuclear cells from AIDS patients and controls



STAGING EVALUATION AND PROGNOSTIC FACTORS IN EPIDEMIC KS

Eighty-six patients with biopsy-proven epidemic KS have been evaluated and followed at New York University in an attempt to gain insight into those clinical features which correlate with prognosis (54, 55). Table 16 outlines the staging evaluation that was utilized in these patients; presence or absence of fever (100°F orally) and significant weight loss (10% or more) was also noted.

TABLE 16

STAGING EVALUATION OF PATIENTS WITH KAPOSI'S SARCOMA

Skin	Photographs and biopsy of representative lesions
Lymph nodes	Biopsy of accessible node and CT scan of abdomen/pelvis
G.I. tract	Endoscopy, colonoscopy, and G.I. contrast studies
Lung	Bronchoscopy when chest x-ray abnormal
Liver	Radioisotope or CT scan
Bone	Bone scan when alkaline phosphatase abnormal

Figure 5 (from ref. 55) shows the Kaplan-Meier probability of survival of the entire group of 86 patients. Median survival was reached at 28 months with a continued drop-off of survival with further follow-up; i.e. there is no plateau of the survival curve that would suggest any long-term survivors in this group of patients. However, as is shown in Figure 6, a very different picture appears when the patients with KS are separated into those who have never had an opportunistic infection and those who have had an opportunistic infection (OI). Eighty percent of those patients who remain without an OI will be alive at 28 months (n=49), whereas less than 20% of patients who have had an OI will be alive at 28 months (n=37). The median survival of this latter group is 17 months. Clearly then, those patients who remain without an OI do relatively well and those who develop an OI do poorly.

Fig. 5: Survival of all patients with KS

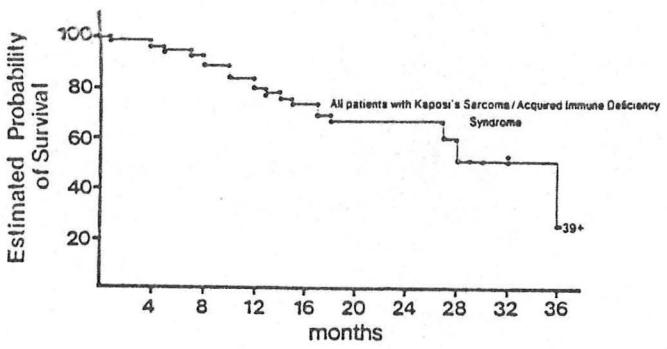


Fig. 6: Survival in KS with and without opportunistic infection

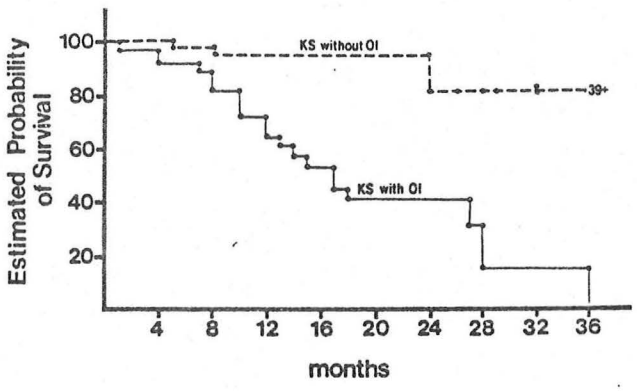


TABLE 17

STAGING SYSTEM OF KAPOSI'S SARCOMA

Stage I:	Cutaneous, locally indolent
Stage II:	Cutaneous, locally aggressive with or without regional lymph nodes
Stage III[a]:	Generalized mucocutaneous and/or lymph node involvement
Stage IV:	Visceral

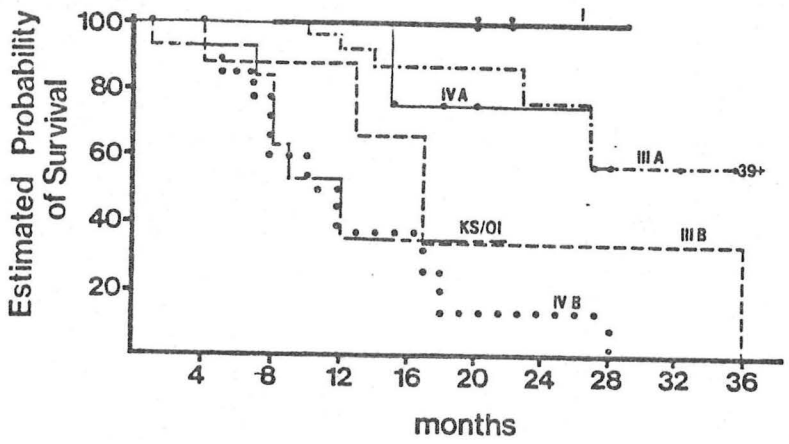
Subtypes
A. No systemic signs or symptoms
B. Systemic signs: 10% weight loss or fever greater than 100°F orally unrelated to an identifiable source of infection lasting more than 2 weeks

[a]Generalized: more than upper or lower extremities alone; includes minimal G.I. disease defined as more than five lesions and greater than 2 cm in combined diameters.

The staging system shown in Table 17 (54, 55) was initially proposed in 1981 and has been used by Krigel and colleagues to attempt to more uniformly define patient groups for a variety of treatment regimens. Stage I represents the typical KS type seen in both classical KS and African KS. Stage II represents the locally invasive (florid or infiltrative) forms of the disease most commonly seen in African KS; recall from the data previously shown in Table 11 that nodular or locally aggressive disease is occasionally associated with regional lymph node involvement. Stages III and IV stratify the disseminated KS seen primarily in the current epidemic but also seen infrequently in patients who are iatrogenically immunosuppressed and in African children. Each stage has been further subdivided as to the presence or absence of fever unrelated to an identifiable source of infection and/or weight loss. Patients with Stage I were treated with local radiotherapy. Patients with Stage IIIA disease were treated primarily with VP-16. Patients with more extensive disease (Stage IVA) or those with consitutional symptoms (Stages IIIB and IVB) were treated primarily with combination chemotherapy (Doxorubicin, Vinblastine and Bleomycin).

Figure 7 depicts the probability of survival of these groups of patients. In general, the proposed staging system correlates relatively well with survival with the exception noted previously; i.e. patients with a co-existent or prior OI do poorly regardless of stage.

Fig. 7: Survival in KS as function of stage of disease



Thus the Stage I patients (n=7) had a 100% survival at 18 months. The Stage IIIA patients (n=38) had a survival of 86% at 18 months, while those in Stage IVA (n=5) had a 75% survival at this time point. At the time of writing this study, none of the above groups had reached a median survival. The Stage IIIB patients (n=9) had a 33% survival at 18 months with a median survival of 15 months, while the Stage IVB patients (n=14) had a 13% survival at 18 months and a median survival of 10 months. The 13 patients in this series with either a prior or co-existent OI regardless of stage had a 35% survival at 18 months and a median survival of 10 months.

Statistically, there was no significant difference in the survivals of patients with Stage IIIA disease and those with Stage IVA disease. Thus, it would appear that the extent of gastrointestinal disease (i.e. whether there are greater than or less than 5 lesions in the GI tract with combined diameters greater than or less than 2 centimeters) is not as important a prognostic indicator as is the presence of constitutional symptoms. This data is shown schematically in Figure 8 and illustrates two points. First there is no difference in survival between patients with minimal and extensive gastrointestinal involvement when the absence or presence of constitutional symptoms is accounted for. Secondly, this figure also illustrates the poor prognostic significance of weight loss and/or fever.

Fig. 8: Survival in KS with and without "B" symptoms

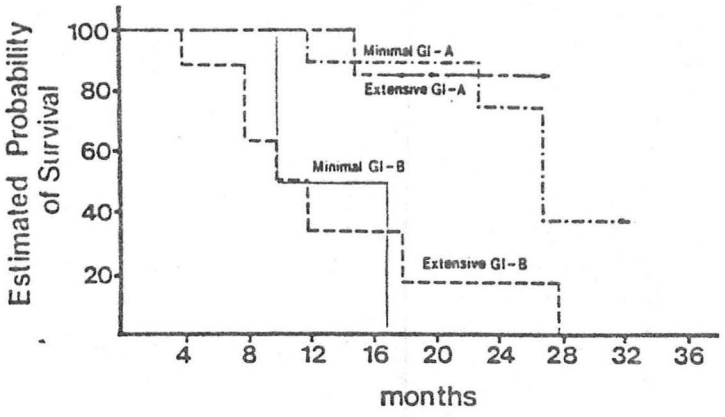
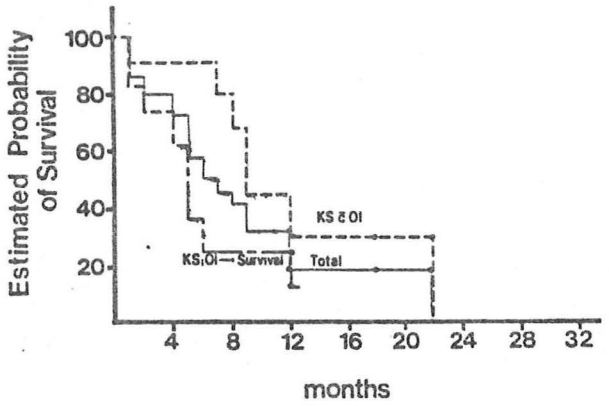


Fig. 9: Survival in KS from initial opportunistic infection



As documented in Figures 6 and 7, the presence of OI is an adverse prognostic sign. The influence of OI on survival in KS patients is further shown in Figure 9. Patients with KS who had either a pre-existent or co-existent opportunistic infection had a median survival of 9 months from the onset of the opportunistic infection. Patients with KS who initially have had no opportunistic infections, but who later developed such an infection, have a median survival of only 5 months from the documentation of the opportunistic infection. For the total group of patients with KS, clinical expression of an opportunistic infection suggests a median survival of only 7 months.

SECOND PRIMARY MALIGNANCIES IN EPIDEMIC KS

Several different types of malignancies have been reported in patients with AIDS in addition to the most prevalent one of Kaposi's sarcoma. The incidence of squamous cell carcinoma of the tongue and cloacogenic carcinoma of the rectum, known to be increased in one of the AIDS high-risk groups, (male homosexuals. According to Ziegler (personal communication in ref. 22) the occurence of these two malignancies in young male homosexuals was recognized in the early 1970's, substantially before the appearance of AIDS in this same group. Thus, it is felt that these two malignancies are not specifically related to AIDS but rather represents the coincidental occurrence in a common risk group; the possibility that these neoplasms may be related to infection with Herpes simplex I and II has been considered (34).

The reported cases of malignant lymphomas in homosexual men have increased dramatically since the AIDS epidemic began in 1980. These lymphomas include both Hodgkin's disease and especially high-grade non-Hodgkin's lymphoma (22, 34, 183, 134). The largest series to date has been the multicenter collaborative study of NHL in 90 male homosexuals (134). All cases were diagnosed between January 1980 and December 1983 in San Francisco, New York, Los Angeles, and Houston. The median age of 37 years was associated with a distribution identical to that for AIDS cases reported to the CDC. Aggressive (high-grade) subtypes of lymphoma were seen in 62% of the patients, intermediate grade subtypes in 29% and low-grade subtypes in just 7%. Although cell marker studies were not performed systematically, the histologic subtypes in the majority of cases were consistent with a B-cell or pre-B-cell origin. Of the 35 lymphomas studied with cell surface marker analysis, 32 displayed monoclonal surface immunoglobulin; 2 lacked surface Ig but were stained with monoclonal antibody reagents which were specific for B-cells; and one lymphoblastic neoplasm had T-cell characteristics.

One striking characteristic of the lymphomas described in these patients was the high frequency of extranodal and primary brain involvement; 88 of the 90 patients had extranodal involvement and 38 patients had central nervous system involvement. Table 18 reveals that in addition to the CNS, other frequent sites of extranodal involvement were the bone marrow, mucocutaneous sites, and the gastrointestinal tract.

TABLE 18

SITES OF EXTRANODAL NHL*

SITE	N	SITE	N
CNS			
Brain Mass	21	Bowel	15
Meninges	14	Lung	8
Nerves	5	Kidney	2
Paraspinal	5	Orbit	2
		Pericardium	1
Bone marrow	30	Bone	1
		Gallbladder	1
Skin/mucosa	14		

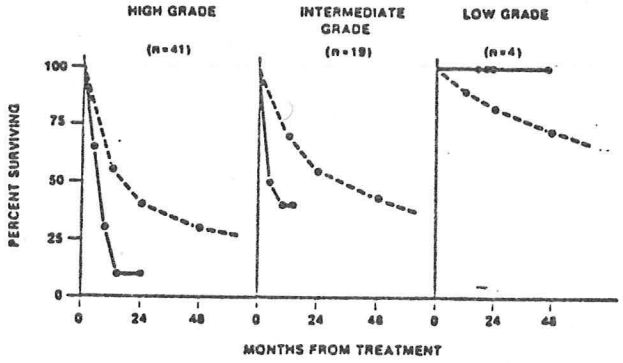
* Some patients had lymphoma >1 site.

This frequency of extranodal lymphoma, particularly in the marrow and CNS, is far greater than what would be expected in de novo non-Hodgkin's lymphoma.

However, the resemblance of this pattern to the lymphomas that develop in patients with iatrogenic or congenital immunodeficiency syndromes is noteworthy (28a, 43, 134).

Another notable characteristic of the lymphomas observed in these patients was the poor response to treatment and poor survival when compared to current treatment results in other patients with similar histologic subtypes of lymphoma. Figure 10 shows the actuarial survival rates for this group of patients. Compared with survival rates reported by the Non-Hodgkin's Lymphoma Pathologic Classification Project, the median survival was 50% shorter in the homosexual men with high-grade, non-Hodgkin's lymphoma (6 vs 12 months) and 88% shorter in men with intermediate-grade lymphoma (5 vs 30 months).

Fig. 10



Actuarial Survival of 64 Treated and Evaluable Men with Non-Hodgkin's Lymphoma (Solid Lines), According to Histologic Grade.

Two patients with unclassified lymphoma are omitted from analysis. Broken lines indicate composite survival of 1175 patients with lymphoma of comparable histologic grade, as reported by the Non-Hodgkin's Lymphoma Pathologic Classification Project.[18] All four evaluable patients with low-grade non-Hodgkin's lymphoma are included.

The prodromal manifestations that preceded the development of NHL in this group of patients is shown in Table 19. The diagnosis of lymphoma was made at autopsy in 13 patients: all 13 met antemortem criteria for a diagnosis of AIDS (all had had either opportunistic infections with or without KS, or KS alone).

TABLE 19

PRODROMAL MANIFESTATIONS IN CASES OF NHL IN MALE HOMOSEXUALS

	Dx of NHL	
	Autopsy	Antemortem
AIDS		
OI	8	15
KS	1	9
KS & OI	4	5
	13	29
Prodrome		
None		15
Lymphadeno-pathy		33
		48

Twenty-nine patients (32%) had a diagnosis of AIDS when the lymphoma was diagnosed; in these 29 patients the frequency of KS of 48% is identical to the incidence of KS in this particular subgroup of total AIDS patients (see also Table 15). Fifteen patients had no prodromal manifestations, and 33 had pre-existing generalized lymphadenopathy which ranged in duration from 3 to 48 months.

The diagnosis of malignant lymphoma in a substantial number of male homosexuals who did not meet CDC criteria for a diagnosis of AIDS, but who did have the features of the chronic lymphadenopathy syndrome (or "pre-AIDS") raises the question of the significance of the histopathologic features seen in lymph nodes of those patients in whom an unequivocal diagnosis of malignant lymphoma cannot be made. This issue was addressed in a recent study from NYU (73) where lymph node biopsies were performed on a large number of patients with the chronic lymphadenopathy syndrome. Histologically, lymph nodes could be divided into three basic patterns: 1) explosive follicular hyperplasia; 2) follicular involution; and 3) mixed (i.e., both follicular hyperplasia and follicular involution). It should be noted that lymph node biopsies which exhibited a clear cut diagnosis of either KS or malignant lymphoma were not included in this analysis. Explosive follicular hyperplasia accounted for the majority (70%) of the biopsies, and was seen to involve not only the follicles but also cortex and the medulla. With increasing size, follicles became confluent and assumed irregular shapes with partial disruption of the mantle zone. The cellular composition of the follicles was rather heterogeneous, consisting of a mixture of small and large cleaved cells, plasma cells, and immunoblasts. Follicular involution (seen in 23% of the specimens) was characterized by small, hypocellular, sometimes hyalinized follicles, with associated hyperplasia of the paracortex. Vascular proliferation was prominent in the areas between the follicles and the medullary cords were often packed with large numbers of plasma cells.

Following lymph node biopsy, these patients were prospectively followed as part of the ongoing study of the outcome in patients with the chronic lymphadenopathy syndrome. Table 20 reveals that a substantial number of these patients subsequently developed either KS or malignant lymphoma.

TABLE 20

LYMPH NODE HISTOLOGY IN PATIENTS
WITH CHRONIC LYMPHADENOPATHY

No. of cases	Histology	Malignant Outcome	%
50	Explosive follicular hyperplasia	Kaposi's sarcoma--1	2%
17	Follicular involution	Kaposi's sarcoma--5 Lymphoma-5	59%
6	Mixed pattern	Kaposi's sarcoma--1 Lymphoma-1	33%

Furthermore, there were rather impressive differences in the frequency of malignant outcome in the histologic subtypes; 59% of the patients whose biopsies showed a predominance of follicular involution ultimately developed malignancies, where as only 2% of patients with biopsies exhibiting follicular hyperplasia developed malignancies by the end of this study. These results suggest that lymph node histopathology may be a relevant prognostic factor in determining the clinical course of patients with generalized lymphadenopathy.

The association between NHL and AIDS raises several interesting issues involving pathogenesis. Malignant B-cell lymphomas appear to arise as a monoclonal outgrowth from a larger pool of polyclonally-activated B-cells (67). In addition to the above-mentioned pathologic studies of lymph nodes from patients with generalized lymphadenopathy, other studies are also consistent with polyclonal B-cell proliferation progressing to lymphoma in some cases (49). This same progression has also been observed in immunosuppressed renal transplant cases (43). Epstein-Barr virus, a B-cell-tropic virus strongly associated with both polyclonal B-cell activation and lymphomas is known to be activated in homosexual men (115, 134). In addition, the potential role of CMV infection and/or reactivation, which is known to involve lymphocytes and induce B-cell proliferation (132), must also kept in mind. Additional discussion of the role CMV in KS and its association with other lymphomas is given in a later section of this review.

The role of HTLV-III in the development of B-cell malignancies in AIDS patients deserves mention. As mentioned previously, the B-cells from AIDS patients are abnormal in that they are polyclonally-activated and are thus unable to respond to de novo signals (109, 135). The most straightforward way to explain this polyclonal activation is the triggering of cells by the secondary virus infections (such as EBV or CMV) that are so commonly seen in patients whose immune system has been suppressed by infection with the T4-cell-tropic retrovirus, HTLV-III. Another possibility is that the massive infection of T4 cells in AIDS results in the elaboration of factors from these T-cells that polyclonally trigger "inocent bystander" B-cells and render them subsequently refractory to other de novo stimuli (57). Finally the possibility that at least some of the polyclonally-activated B-cells are themselves infected with HTLV-III in the same manner as are the T4+ T-cells also must be entertained. Although HTLV-III is well documented to be tropic for T4+ T-cells both in vivo and in vitro, very recent evidence from the laboratories of Robin Weiss (13) and Luc Montagnier (51) have provided not only an elegant explanation for this selective tropism, but for establishing a precedent for HTLV-III infection of B-lymphocytes. In simultaneous publications of their findings in Nature in late December, 1984, these investigators provided evidence that the T4 antigen is an essential part of the receptor that the retrovirus utilizes to infect cells. Furthermore, Dalgleish and co-workers (13) found that an EBV-transformed B-lymphoblastoid line could be infected with HTLV-III; subsequent immunofluorescent analysis clearly revealed that this particular B-cell line expressed low but significant levels of the T4 antigen on its membrane.

IMMUNOGENETIC ASPECTS OF CLASSICAL AND EPIDEMIC KS

The discovery of an association between epidemic KS and the DR5 allele (26, 27) and its independent confirmation (96) strongly suggested a role for major histocompatibility complex-controlled genetic factors in the observed

variability in susceptibility to this disease. The initial study of 19 male homosexuals with KS revealed that 63% of them were HLA-DR5+ compared with a 23% frequency of this antigen in two different control populations, i.e., either a randomly selected population of male homosexuals from New York City or a normal randomly selected heterosexual white population from New York City. Of equal interest was the finding that 62% of non-homosexuals with the classic form of KS also were DR5+. These findings were subsequently confirmed in an independent study by Pollack and co-worker in 1983 (96). However, since it was known that DR5 has its highest frequencies in exactly those groups with the highest prevalence of classic KS (i.e., those of Italian or Jewish extraction) these investigators carried the study one step further by comparing the frequency of DR5 in KS patients and controls when the different ethnic or geographical backgrounds of these individuals were also taken into account. The results of this analysis are shown in Table 21.

TABLE 21

THE FREQUENCY OF DR5 IN KS PATIENTS AND CONTROLS FROM DIFFERENT ETHNIC OR GEOGRAPHICAL BACKGROUND

Ethnic or geographical group	Homosexual Kaposi's	Classical Kaposi's	Healthy controls
Italian	3/3 (100%)	2/3 (67%)	163/455 (36)
Ashkenazi	3/4 (75%)	5/9 (56%)	52/138 (39)
Hispanic	2/2 (100%)	----	8/29 (28)
Other Caucasian or unknown	1/7 (14%)	0/1 (0%)	36/176 (21)
	9/16 (56%)	7/13 (54%)	

One can see that most of the KS patients who were DR5+ were indeed of Italian or Ashkenazi Jewish extraction (16 of 19); however, comparison of the DR5 frequencies in these ethnic subsets with data from appropriate healthy control populations still indicated a higher than expected incidence of DR5 in both patients with epidemic KS and classical KS. It should be noted that this increase in DR5 was not found among KS patients of Northern European extraction; thus the HLA-linked immunogenetic factor that may be involved in the pathogenesis of KS may be in genetic linkage disequilibrium with different HLA antigens in different subpopulations of Caucasians. This would be similar to the situation in multiple sclerosis where different ethnic group, in this case Italians and Ashkenazi populations versus Northern Europeans, show different HLA associations (96).

In order to evaluate the relationship between DR5 and KS -- for example, to determine whether the association is related to susceptibility to immunosuppression in general or perhaps more specifically to increased susceptibility to certain types of malignancy -- HLA-typing data on AIDS patients without KS has been critically needed. Unfortunately, only extremely limited data has thus far been published on this subject. Pollack (96) reported that of a group of 17 male homosexuals with generalized lymphadenopathy ("AIDS-related complex") 13 of them were DR5+, a percentage which, if confirmed, would suggest that DR5 is indeed elevated in patients at risk for developing AIDS. A similar preliminary observation was reported by Nunez et al (personal communication in ref. 100).

Recently published data by Rubinstein and co-workers (100), the same investigators who initially reported the extremely high association of epidemic KS with DR5, has rendered any interpretations as to the significance of this association much more difficult. Table 22 shows the sequential experience of that laboratory in HLA-typing patients with epidemic KS, from their first experience in 1980 through their more recent experience in 1983.

TABLE 22

HLA-DR ANTIGEN FREQUENCIES IN EPIDEMIC KS
ACCORDING TO YEAR OF DIAGNOSIS

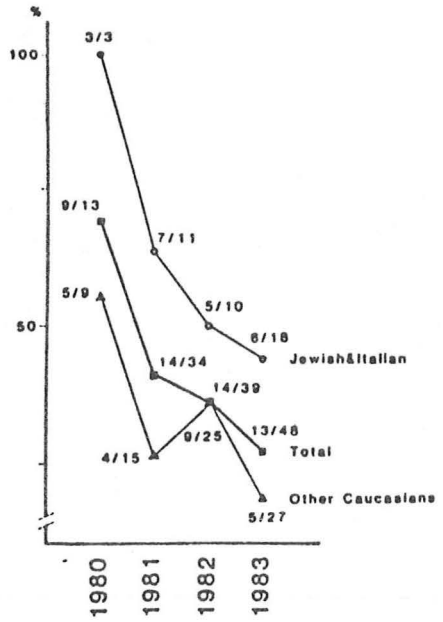
	1980 n=13	1981 n=34	1982 n=39	1983 n=48	New York Controls n=231
DR1	2(15)	8(24)	8(21)	12(25)	42(18)
DR2	1 (8)	8(24)	10(26)	8(17)	58(25)
DR3	3(23)	6(18)	4(10)	8(17)	46(20)
DR4	4(31)	6(18)	7(18)	10(21)	53(23)
DR5	9(69)[1]	14(41)[2]	14(36)	13(27)	53(23)[1,2]
DRw6	2(15)	5(15)	10(26)	9(19)	35(15)
DR7	---	8(24)	10(26)	8(17)	46(20)

1) X^2 = p<0.0008, Fisher's exact p=8 x 10^{-4}
2) X^2 = p<0.025

It can be seen that there has been a progressive reduction in the strength of the DR5 association during the epidemic; this association became statistically non-significant for patients diagnosed in 1982 and after. Because of the known difference in the background frequency of DR5 in different Caucasian populations, the distribution of DR antigens among patients of different racial origins was analyzed. Patients were assigned to a given subset if at least one of their parents belonged to that group; thus, no comparisons to standards for the respective "normal" populations were attempted. Because of the different frequency of DR5 in the different ethnic subsets of New York populations, it might have been postulated that the initially strong DR5 association was caused by a concentration of Jewish and Italian patients early in the development of the epidemic. However, when Rubinstein et al evaluated their data for this possibility, they found that the distribution of patients from the different ratial backgrounds has remained essentially constant throughout the epidemic. This conclusion is depicted graphically in Figure 11 (see next page) which shows the relationship between DR5 frequency within each ethnic subset and the time of diagnosis. It can be seen that an initially elevated frequency is observed for both the major subsets analyzed, with relatively concordant decreases in subsequent years. Thus, patients with epidemic KS regardless of ethnic background have exhibited an unexpected relationship to DR5: i.e., the initially elevated frequency of this antigen has progressively decreased, approaching normal values for patients recently diagnosed.

Several non-exclusive hypotheses to explain these relationships can be considered. One is that DR5 is associated with a shorter "incubation period". Such a model would result in an elevation of the frequency of DR5 in patients with KS, the magnitude above a control population of which will depend on the ratio between the incubation periods for DR5 and non-DR5 individuals. However,

Fig. 11: Ethnic backgrounds, year of diagnosis and DR5 frequency in KS patients



this magnitude should remain relatively constant for as long as both the ratio between the necessary incubation periods and the doubling time for the epidemic remain constant. The possibility that DR5 lowers the threshold of individuals exposed to the environmental agents that generate the susceptible state resulting in KS, also would lead to an increased frequency of DR5 in the affected population when compared to controls; again, however, such a model would not explain a progressive weakening of the association between susceptibility and histocompatibility type. The possibility that DR5 either shortens the "incubation period" or increases the probability of disease by lowering the threshold of individuals exposed to whatever environmental agents generate the susceptible state does find some support in the data published by Marmor et al (70). This data is shown in Table 23 and shows that DR5+ patients with epidemic KS have significantly greater numbers of T4+ cells/mm^3 than do DR5- patients with epidemic KS. This data is consistent with the possibility that a greater degree of immunosuppression is necessary to render a DR5- individual susceptible to the factors that cause KS than is required in DR5+ individuals exposed to the same factors.

TABLE 23

HLA-DR-5+ PATIENTS WITH EKS ARE LESS IMMUNODEFICIENT THAN DR-5- PATIENTS

HLA Type (n)	Number of OKT4+ cells/mm^3
DR-5+ (12)	487 ± 266
DR-5- (7)	289 ± 135
	p = 0.05

A progressive reduction in the strength of such an association could conceivably be caused by changes in the biology of the susceptibility state; such changes have been known to occur during the course of epidemics and maybe caused, for example, by an increased virulence of the causative infectious agent. Finally, if the size of the "at risk" population were limited and relatively small, the preferential removal of DR5+ individuals from the remaining susceptible individuals would necessarily lead to the reduction in the frequency of this antigen. However, there is at this point no data to suggest that essentially all the DR5+ individuals who are potentially susceptible to acquiring epidemic KS have in fact already been exposed to whatever environmental agents are necessary to ultimately result in expression of clinical disease. Viewed in a slightly different way, there is no compelling reason to believe that the pool of "at risk" DR5+ individuals has in fact already been depleted by this current epidemic. In summary, at the present time there is no entirely satisfactory explanation for an apparently very real weakening or loss of association between KS and DR5. Further study of the immunogenetics of KS are clearly indicated: for example, there have been no reported studies on the HLA phenotype of iatrogenically immunosuppressed individuals who develop KS. Since the vast majority of these individuals are renal transplant recipients of HLA-typing data should be available on all of them. Furthermore, no studies have been reported as to the HLA-phenotype of patients with African KS.

THE CMV CONNECTION

Infection with human cytomegalovirus (CMV) a member of the herpesvirus group, is very common, with nearly 80% of the population above the age of 35 showing evidence of prior infection as measured by complement fixation. The virus can be transmitted by blood transfusion, transplacentally and via milk, urine, and respiratory secretions. That the majority of CMV infections do not result in obvious pathologic changes, although infections of newborns and infants may result in failure to thrive and retardation. Furthermore, it is well-known that in immunologically deficient individuals such as transplant recipients and patients with AIDS, infection and/or reactivation of latent CMV is a serious complication, frequently resulting in a fatal interstitial pneumonia. For a more complete and extensive discussion of the epidemiology, immunology, and clinical characteristics of CMV infection, see Luby J.P., "Cytomegalovirus", Medicine Grand Rounds 5/19/83. In 1971, Giraldo and collegues found CMV viral particles in cell lines that were derived from African patients with KS (33). In 1975, this group noted that sera from European patients with classic KS showed elevated anti-CMV titers by indirect hemagglutination when compared with age, sex and race-matched normal controls as well as control patients with melanoma, many of whom were receiving chemotherapy similar to that given to the KS patients (34). These findings were later extended in 1978 to an serologic analysis of American and African KS patients (35). All American KS sera contained CMV antibodies, and their mean titers were significantly higher than those of sera of control patients. While the mean titers to CMV of African KS patients were similar to those of the American KS group, their significance could not be demonstrated because of the equivalent high background titers of CMV antibodies seen in African control populations. These observations suggested that CMV infection, along with reinfection and/or reactivation, occurs very commonly in equatorial African in a manner similar to that known for EBV.

Finally, most recently these same groups of investigators (3, 36, 47) examined classic and epidemic KS tumor biopsies for human CMV DNA sequences as well as viral specific macromolecules by DNA-DNA reassociation kinetics analysis, RNA-DNA in situ hybridization, and anticomplement immunofluorescence tests. In one set of studies, viral DNA and/or RNA could be found in 5 out of 10 tumor biopsies and CMV-specific nuclear antigen could be demonstrated in variable degrees in 80% of the specimens (47).

The ability of a virus to induce host cell macromolecule synthesis has been found to correlate to its transforming potential (47). CMV infection has been shown to greatly stimulate host cell tRNA, ribosomal RNA, cellular mRNA, and mitochondrial DNA synthesis. Further evidence that CMV infection may be a potentially oncogenic event relates to the observation that ornithine decarboxylase activity was dramatically increased shortly after human embryonic cells. Ornithine decarboxylase is an enzyme involved in the first rate-limiting reaction in the biosynthesis of protamine. Its enzyme level is very low in normal stationary phase cells but increases remarkably upon infection of cells with known oncogenic viruses. Plasminogen activator is another biochemical marker that has been related to malignant transformation; transformation of cells by oncogenic viruses frequently leads to high levels of expression of this enzyme. Infection of both hamster and human cells with ultraviolet light-inactivated CMV was also found to lead to the stimulation of plasminogen activator synthesis (47).

The oncogenicity of human CMV is further supported by its known ability to transform a variety of mammalian cell lines in vitro. Albrecht and Rapp (1) first demonstrated that human CMV was able to transform embryonic hamster fibroblasts; these transformed cell lines were found to be tumorogenic in hamsters. The status of CMV genome in such transformed cells has never been totally clarified. After prolonged periods of in vitro subcultivation, the viral genome was undetectable by DNA-DNA reassociation kinetics analysis which supposedly has a sensitivity of 0.1 viral genome equivalent per cell (47).

More recently, investigators have attempted to define the viral genes that are necessary for initiation or maintenance of a transformed phenotype (31). The approach has been to expose NIH 3T3 cells or rat embryo cells to defined fragments of viral DNA and select for cells which can grow in semi-solid media. A transforming 489 bp fragment of CMV has been identified and its position mapped; furthermore, the DNA sequence of the fragment has been determined and the RNAs transcribed from these regions have been characterized. However, the precise mechanisms by which CMV leads to the transformed state in cell lines is still unknown at the present time. The complexity of this question is underscored by the realizaton that the transformed phenotype can persist in the absence of any detectable viral sequences in the transformed cells (31, 47).

The extremely high prevalence of CMV infection among homosexual men was documented by Drew and collaborators prior to the current outbreak of AIDS and epidemic KS (19). In that study, CMV was cultured from the urine of 14 of 190 homosexual but none of 101 heterosexual men attending a VD clinic. In this same study, CMV antibody titers were found in 94% of homosexual men, but in only 54% of heterosexual VD clinic patients and 43% of male volunteer blood donors. This data suggested that sexual transmission was an important mode of spread of CMV of adults, and that homosexual men are at greater risk for CMV infections than are heterosexual men.

More recently, Huang (47) has isolated CMV from the semen of 5 of 17 asymtomatic homosexual men in North Carolina. And in a more recent study of homosexual males with epidemic KS, CMV was isolated from body secretions or peripheral blood in 7 of 9 patients (20). While viral cultures of KS tumor biopsy specimens were negative in all instances, CMV RNA was detected by in situ hybridization in 2 out of 3 cases, and CMV-specific antigens were detected by immunofluorescence in 6 out of 9 cases. While these observations again suggest a significant degree of association of CMV with epidemic KS, other investigators have criticized Drew's experimental design of using whole viral genome as a probe (101, 111). Their criticism was that such technology did not rigorously exclude the possibility that any apparent hybridization of CMV to KS specimens really represented the amplification of cellular DNA or RNA sequences and not the presence of CMV. Both of these investigators therefore utilized as hybridization reagents specific subgenomic fragments of CMV which did not react with the nucleic acids from normal, uninfected human cells. Using Southern block hybridization experiments with the DNA from 7 different epidemic KS lesions, Spector and coworkers (111) found that CMV sequences were present at a level which varied from one copy per two cells to one copy per 20-50 cells for 6 of the specimens while any CMV sequences in the seventh specimen were below the limits of their detection by this particular methodology. However, this latter specimen did show a low level of nucleic acid in the Kaposi's tumor cells by in situ cytohybridization. These results confirm those of others (20) indicating that CMV nucleic acid can be found in association with the tumor cells in KS lesions. However, in contrast to Drew's study, in which normal tissue specimens from 3 KS patients were negative for CMV antigen, Spector did detect CMV DNA in uninvolved skin and lung specimens in one patient with KS (111). Since both active and latent CMV infection is known to be extremely common in male homosexuals, the finding of CMV nucleic acid in tumor tissue in such patients obviously does not prove that CMV plays a crucial role as an oncogenic virus in the development of KS in such patients. Nevertheless, the associations epidemiologic between CMV and all forms of KS are very strong, and when coupled with the known ability to CMV to transform a variety of cell lines which are then highly tumorogenic, as well as the recent work localizing the CMV transforming gene to a defined segment of DNA, it clearly is impossible to dismiss a causal relation between CMV and the KS seen in all of the major risk groups for this tumor.

AIDS IN AFRICA -- A LINK TO AFRICAN KS?

One of the more intriguing aspects of the AIDS story has been the recent detection of a focus of AIDS in Central Africa (9, 93, 124). The initial association between AIDS and Central Africa was first noted by Belgian and French physicians whose patients were non-drug abusing, heterosexual individuals predominantly from Zaire who were living in Europe (9). Subsequently, two one-month surveys taken in 1983 in Kinshasa, Zaire (93), and in Kigali, capital of neighboring Rwanda (124), identified 55 probably cases of AIDS and several additional patients who most likely had an AIDS prodromal syndrome. The calculated attack rates in these cities were as high as those recorded in New York and San Franscisco. Furthermore, the clinical features of the patients seen in these two patients were very similar to those previously observed in the original European report: nearly one half were female and, with one possible exception, all were heterosexual. Several patients were known to be or admitted to being promiscuous, and most came from the relatively small

upper and middle class sections of their communities. A wide variety of opportunistic infections were seen, and low T4/T8 ratios and T4 total lymphocyte counts were seen in virtually all patients. Furthermore, antibodies to HTLV-III have been detected in a high portion of patients with this syndrome (40). The two clinical features in the African AIDS patients which were rather distinctive include the striking increase in proportion of affected females (nearly 50%) and was the relatively low frequency of KS. KS was diagnosed in only 9 of the 64 patients (14%). While this frequency is higher than that seen in several of the high-risk AIDS groups in the United States (i.e. Haitians, hemophiliacs, and IV drug users), it is substantially less than the 47% frequency of KS observed in male homosexuals with AIDS. While this in and of itself is not necessarily noteworthy, it must be kept in mind that the geographic area with the highest prevalence of AIDS, namely equatorial Africa, is precisely the location which has the highest prevalence of Kaposi's sarcoma. Although it is clear that endemic African KS differs from the disseminated KS associated with AIDS in a number of ways (including the fact that the majority of cases of African KS are the typically indolent lower extremity nodules and plaques also characteristic of classic American KS), nevertheless, aggressive and disseminated forms of KS were well recognized in this region of Africa long before there was any awareness of AIDS and HTLV-III, thereby raising the possibility that aggressive KS in Africans has always been associated with HTLV-III infection.

An interesting but unfortunately flawed study of a potential association between African KS and AIDS was recently reported from Zambia (18). Having noted an apparent increase in the numbers of cases of KS in this known endemic area in 1983, these investigators studied 16 patients along with 10 age and sex-matched controls to determine whether or not there was any evidence in the KS patients for immunodeficiency or evidence of infection with opportunistic pathogens. The T4/T8 ratios of the patients were significantly lower (0.77) than those of the controls (1.81, $p<0.002$). All of the patients and all of the controls exhibited evidence of past infection with CMV. Thirteen of the 16 KS patients had antibody to HTLV membrane antigen, whereas only one of ten of the controls had antibodies to this determinant. The 15:1 male:female ratio of the KS patients is consistent with the patients belonging to the typical endemic African KS grouping. Unfortunatley, no description of the clinical lesions in these patients was given. The authors noted that "an unusual number of patients had generalized progressive disease"; however, absolutely no attempt was made to separate these patients from those with more classical indolent disease. Thus, it is not possible to know whether there was any difference in the pattern of disease in those patients who had evidence of HTLV infection compared with those who had no evidence of such infection.

Retrospective analysis of case records of patients seen in Europe suggests that AIDS has been present in Zaire since at least 1976 (40) -- i.e. nearly two years before the first cases apparently occured in the U.S.A. or Haiti. If true, this would suggest that Central Africa may be the original focus of the AIDS agent which then spread from Zaire to Haiti, with which Zaire has close links, and also to the United States. At this point in time there is no direct evidence to support this view, and spread across the Atlantic could equally as likely have taken place in the opposite direction. However, the former possibility is intriquing in light of the additional suggestion that HTLV-I, the human T-cell lymphoma/leukemia virus closely related to the AIDS agent, also originated in Central Africa and spread from there to foci in Japan, the Carribean, and Southeastern United States (5, 30). At this point in time it is unlikely

that the origin of AIDS will ever be definitively determined unless serological analysis of stored specimens in a variety of locations might provide some additional, interpretable information. Clearly, however, further sero-epidemiologic studies and clinical investigations are warranted among the equatorial African population. Among other things, it would be particularly interesting to determine the frequency of HTLV-III seropositivity in patients with all clinical variants of African KS, including the rare but usually aggressive and fatal lymphadenopathic form of the disease seen most commonly in infants and youngs children. Given the recent tremendous flurry of activity in all areas of HTLV-related research, it is unlikely that this particular stone will be left unturned for very long.

KAPOSI'S SARCOMA: AN OPPORTUNISTIC NEOPLASM?

While all of the identified risk groups for developing KS share at least one common potential etiologic factor with each other, and several of the risk groups share other potential etiologic factors, it is clear that no single constellation of etiologic factors umbrellas all of the risk groups. It is furthermore apparent that several observations remain inadequately explained and incompletely understood.

Perhaps the only potential etiologic factor shared by all of the KS risk group is evidence for exposure to CMV. In considering a potential role for this virus in the pathogenesis of KS, Pagano has identified those features of malignancies which suggest causation or initiation by viral infection; these features are listed in Table 24 (89). Most of the malignancies suspected of a viral etiology are not common ones; diseases such as Burkitt's lymphoma, Kaposi's sarcoma, unusual forms of lymphoma/leukemia (such as that associated with HTLV-I), and hepatoma have been prominently linked to various viral infections, where as gastrointestinal and lung tumors have not. Like most viruses, viruses linked to

TABLE 24

CLUES TO VIRAL ETIOLOGY OF MALIGNANCY

Unusual disease phenotype
High incidence infection/low incidence disease
Latent infection
Virus reactivation or persistent infection
Endemicity
Cofactors

malignancies generally produce primary infections which are silent. The viruses are common infectious agents with the oncogenic outcome a relatively rare event. The malignancy is a late manifestation, usually appearing after a period of latency following early infection. The appearance of the malignancy may be tied to either reactivation of the virus infection as in Burkitt's lymphoma and nasopharyngeal carcinoma, or to a persistent active infection as postulated in hepatoma. Although most of the virus-associated malignancies exhibit a sporadic incidence, the hallmark of a possible viral etiology is endemicity of the tumor; virally-associated malignancies therefore usually exhibit both sporadic and endemic patterns of incidence. Finally, in the endemic regions, epidemiologic

considerations invoke a need for a co-factor to explain the high incidence of disease in the endemic area as opposed to areas with a more sporatic incidence. Postulated co-factors cover a broad range of agents and conditions including issues of when the exposure to viral infection initially occurs, genetic predisposition, other environmental co-carcinogens, immunosuppression, etc.

It can be seen that CMV fulfills many of these hypothetical features. It is a common infection with relative foci of endemicity (i.e. immunosuppressed renal transplant patients, male homosexuals, and equatorial Africans). CMV infects early in life, causes silent infections, enters a latent phase, and is readily reactivated by immunosuppression. CMV has striking tissue pleiotropism and tissue-proliferative and transforming capacities in vitro in a variety of cell types including endothelial cells. Finally, the striking multifocal nature of the lesions of KS in the vast majority of affected individuals is also consistent with initial bloodborn dissemination of the virus which subsequently becomes latent in multiple sites.

A genetic predisposition to the development of KS appears to be a potential etiologic feature of at least three of the four major risk groups, i.e., classic KS (appearing predominantly in those of Italian or Ashkenazi Jewish decent and showing an increased incidence in DR5+ individuals), iatrogenically immunosuppressed individuals (again most frequently seen in those of Italian or Jewish decent), and at least in the early portion of the current epidemic, young male homosexual men (increased frequency of DR5+). It is not clear at the present time whether there is an identifiable genetic predisposition in the other AIDS risk groups or in the population at risk in equatorial Africa.

Similarly, nearly all of the KS risk groups share a commmon factor of immunosuppression. The most obvious examples of such immunosuppressed individuals are those whose immune systems have been iatrogenically dampened in order to treat another disease or prevent graft rejection, and the victims of AIDS. Within this latter group, it is important to point out that HTLV-III infection may be the principal but is certainly not the only infection that can lead to a state of immunosuppression. A variety of viral infections, including both EBV and CMV, are associated with profound and frequently long-lasting immunosuppression, due primarily to an absolute increase in the numbers of T8+ lymphocytes, a reversal in the normal T4:T8 ratio, polyclonal activation of B lymphocytes leading to a diminished ability to respond to exogenous signals, and a decreased ability to generate cytotoxic T lymphocytes (7).

The question of whether patients with the usually indolent form of classic KS in the U.S. as well as the large numbers of individuals similarly afflicted with indolent KS in equatorial Africa are also immunosuppressed is more problematic. The vast majority of such patients do not exhibit any obvious evidence that they are immunosuppressed. In fact, immunologic testing of such individuals for their ability to mount a delayed hypersensitivity response to the contact allergen DNCB, has shown that this response is normal in nearly all such individuals (116). On the other hand, the strong epidemiologic association with CMV infection in both classic KS and African KS raises the possibility that these individuals too are immunosuppressed at some critical point in time by virtue of infection or reactivation of CMV.

In the case of African KS, there is an additional reason to suspect that many, if not all, affected individuals are at least transiently immunosuppressed by

other infectious agents. Very recently, Whittle and co-workers produced evidence that during acute attacks of P. falciparum malaria there is a transient loss of the capacity of T cells from such individuals to control the proliferation of polyclonally activated EBV-infected B-cells (129). The significance of these observations must be viewed in light of the known fact that the areas in Africa in which Burkitt's lymphoma is endemic are exactly the same areas in which malaria is hyperendemic. EBV seems to play its part by infecting and thereby "immortalizing" a pool of B-cells. The continuous division of such cells (which has now been shown to be facilitated by a loss of T-cell control) facilitates any one of three characteristic chromosomal translocations that can activate the c-myc oncogene. In view of the fact that the areas most endemic for KS in equatorial Africa are also hyperendemic for malaria, it is very possible that repeated attacks of malaria will, via similar mechanisms, favor the unrestrained growth of CMV-infected cells (perhaps endothelial cells).

Many of the KS risk groups share the feature of fairly continuous exposure to a variety of foreign antigens. Warner and O'Loughlin (128) originally suggested that KS may be the end result of such a chronic immunologic reaction, that in the course of this reaction an angiogenesis factor is released from responding lymphocytes resulting in the proliferation of susceptible endothelial cells. While Warner and O'Loughlin postulated that the immunologic reaction was response to antigenically altered neoplastic lymphoid cells, there does not seem to be any compelling need to postulate that the antigen was neoplastic tissue of any sort. Conceivably, any immune reaction occuring in a milieu of a compromised immune system would suffice; the antigenic stress of a CMV infection itself could be sufficient stimulus for elaboration of postulated lymphocyte-derived endothelial growth factors. Taking this hypothetical situation one step further, there is actually no compelling need to invoke a lymphocyte-derived angiogenesis factor as the initial stimulus for proliferation of susceptible endothelial cells. Indeed, it is possible that any stimulus to an endothelial cell to proliferate might suffice. If this proliferative response by an endothelial cell previously infected by CMV was associated with whatever molecular changes ultimately are responsible for CMV-induced transformation, the end result could be a neoplastic growth of such endothelial cells. It is not inconceivable that such a stimulus to endothelial cells could come from local trauma. In fact, several authors have considered the possibility that the susceptibility of the lower extremities to chronic trauma (and perhaps even the stress of chronic, low-grade venous or lymphatic stasis would be sufficient) may account for the striking tendency for KS lesions to involve the lower extremities (104, 106, 121).

A factor which clearly affects susceptibility to KS but in a way which defies simple explanation relates to sex differences in the frequency and pattern of involvement. Indolent KS is predominantly a disease of men in both Caucasian and Native African populations. On the other hand, both American and African studies have suggested that when females do express the disease, it is more likely to be of an aggressive variety (98, 119). Similarly, aggressive fulminant KS is more likely to occur in Africa in infants and young children, and in this age group the male:female ratio is much lower than it is in other age groups. Finally, it is worth reiterating the observation that the male:female ratio of renal transplant patients or other iatrogenically immunosuppressed individuals who develop KS is substantially lower than the ratios seen in the general population of classic KS patients; furthermore, the

disease in such patients more often pursues an aggressive course. Thus, while it is clear that there must be some hormonal and/or X-linked factor which provides females with some degree of relative protection against some forms of KS, it is equally clear that this protection does not extend to all forms of the disease. Indeed, females appear to be relatively more susceptible to aggressive variants of the disease than are males.

Finally, the striking association of KS and the appearance of other malignancies in such KS patients, particularly lymphoma/leukemia, deserves reiteration. This increased susceptibility extends to classic KS patients, to iatrogenically immunosuppressed patients, and to male homosexuals with KS in the setting of AIDS. The strong association in these risk groups suggests that common etiologic factors are operative in the pathogenesis of these different malignancies. The roles of underlying immunosuppression and of CMV infection have been discussed previously; it may be worth mentioning again that CMV has recently been shown to be capable of polyclonally activating B cells in a manner reminiscent of EBV (132). However, any satisfactory explanation for the association of KS with lymphoma/leukemia in some of the KS risk groups ultimately must also take into consideration the observation that one group of KS patients, namely those in equatorial Africa, do not appear to be at significantly greater risk for developing lymphoma/leukemia than the general population in that region (87, 117, 120, 121). This observation appears more significant when one considers that it is in this same geographic region that both Burkitt's lymphoma and CMV infection are also endemic. It is possible that this apparent lack of association in this population is simply due to insufficient or inadequate data collection; future studies specifically designed to address the question of an associtionin this population clearly are indicated.

It seems fairly clear that Kaposi's sarcoma, like so many other diseases, involves a multifactorial pathogenesis in which the relative importance of any one particular etiologic factor may differ from individual to individual. Those factors which appear to most frequently play a critical role in KS include CMV infection, genetic predisposition, and immunosuppression. The typically multifocal nature of the lesions, the extremely high incidence of KS among male homosexuals with AIDS, the dramatically increased incidence in iatrogenically immunosuppressed individuals, and the numerous reports of spontaneous remissions of clinical disease when the cause for the immunosuppression is removed, all make a strong case for Kaposi's sarcoma behaving as an opportunistic neoplasm subject to some degree of regulation and control by the immune system. The observations that KS lesions frequently appear a relatively short period of time after the onset of immunosuppression contrast with the generally longer latent periods observed for other malignancies seen in such patients. This tendency for lymphoma/leukemia to "shadow" KS is also compatible with KS being relatively more opportunistic than those tumors, i.e., that relatively less compromise of the immune system is necessary for its expression. In fact, there is data to suggest that at least in the male homosexual AIDS risk group, KS is more opportunistic than the so-called "opportunistic infections" which plague these individuals (Fig. 3).

It is very clear that much, if not the overwhelming majority, of the current interest in studying KS has arisen because of the AIDS epidemic. One of the solaces one may be able to cling to, as the number of new cases of KS and AIDS

continues its exponential rise and our minds boggle thinking about the potential magnitude and truly staggering costs of this epidemic, is that out of this calamity has come an almost unparalleled opportunity to gain insight into the complex interrelationship between environmental, genetic, viral and immunologic factors that control the evolution of a neoplasm.

APPENDIX -- TREATMENT OF KS

One of the more commonly ulitized general schemes for approaching treatment of the various clinical forms of KS is illustrated in Table 25. The extreme variability in the natural history of KS has made it difficult to assess to efficacy of therapy, including whether treatment of localized indolent disease is mandatory and whether such treatment significantly alters long-term survival. In the case of the generalized, aggressive form of KS associated with AIDS, the optimal approach to therapy has yet to be determined.

TABLE 25

THERAPEUTIC CONSIDERATIONS IN KS

Form	Indolent	Aggressive
Localized disease	Local radiotherapy Intralesional vinblastine	Local radiotherapy Systemic vinblastine, vincristine, VP-16
Disseminated disease	Systemic vinblastine	Combination chemotherapy and/or immunomodulation therapy

The indolent nodules, plaques, and even small tumors occuring in the classic form of KS seen in elderly patients may not require specific therapy early in the course of the disease if the tempo of progression of the lesions has been determined to be fairly slow. If a lesion progresses, and an individual has only a solitary or localized disease, surgical excision may well be curative (106). Fractionated radiation also produces good therapeutic results with nodular KS (10). While orthovoltage X-ray is the most widely utilized type of radiation therapy, electron beam radiotherapy has also been used successfully for superficial disease (84). Furthermore, high-voltage electron beam therapy can be utilized successfully for deeper lesions (46). There is a suggestion, which has not yet been varified in other studies, that radiotherapy is more effective on newly arisen lesions as opposed to those which have been present for extended periods of time (65).

A variety of chemotherapeutic agents may be effective in Kaposi's sarcoma (22, 106). Chemotherapy has been utilized for localized disease unresponsive to radiotherapy, widespread but indolent disease, localized but aggressive (i.e. florid or infiltrating) disease, and widespread lymphadenopathic or visceral disease. As shown in Table 26 (22) drugs that have been shown to have some efficacy include the Vinca alkaloids vinblastine and vincristine, dacarbazine (DTIC), actinomycin D, and razoxane. Clinical responses have also been reported with alkylating agents such as cyclophosphamide, chlorambucil, bleomycin and doxorubicin, as well as etoposide (VP-16) (22, 106). Disseminated but relatively indolent disease has been treated perhaps most frequently with single agent chemotherapy using intravenous vinblastine; however, vincristine, actinomycin D, and VP-16 have also been reported to have activity as single agents (22, 106).

TABLE 26
TREATMENT OF NONEPIDEMIC KS

Intervention	Patients Tested	Complete Responses	Complete + Partial Responses
	n	*n(%)*	
Stop iatrogenic immunosuppression	8	5 (63)	...
Single agent chemotherapy*			
Vinblastine	26	11 (42)	23 (88)
Dactinomycin	46	14 (30)	40 (87)
Bleomycin	10	0 (0)	6 (60)
ICRF-159	18	1 (5)	11 (61)
BCNU	21	4 (19)	9 (43)
Adriamycin	6	0 (0)	4 (67)
DTIC	10	3 (30)	5 (50)
Cyclophosphamide	10	1 (10)	1 (10)
Combination chemotherapy†			
Dactinomycin + vincristine	52	31 (60)	47 (90)
Dactinomycin + vincristine + DTIC	39	37 (95)	39(100)
Vinblastine + bleomycin	1	1(100)	...

* ICRF-159 = Razoxane (Imperial Cancer Research Fund); BCNU = Bischloronitrosourea (carmustine); DTIC = dacarbazine; 5-(3,3-dimethyl-1-triazeno) imidazole-4-carboxamide.

Combined chemotherapy is probably the most effective choice for generalized aggressive disease. However, it must be pointed out that while studies in small number of patients with such disease have indicated that combination therapy appears to be superior to single agent therapy, no particular combination has yet been established which has shown obvious superiority. The combination of vincristine and actinomycin D has been used successfully for long-term, disease-free control in a significant number of patients in Uganda (106). One recent combination that is being utilized extensively, particularly by the group at New York University is ABV (doxorubicin, bleomycin and vinblastine). Another combination that has been employed with success is ABV + DTIC (16).

Treatment of epidemic KS associated with AIDS has not been as successful as the treatment of classical KS (22). As illustrated in the summary Table 27 (22 from ref. 22, see next page), only two relatively small series of patients treated with either single agent or combination chemotherapy have been reported. It is important to point out that these studies were not randomized, and that patients with more aggressive disease generally were given combination chemotherapy. Thus, at this point, it is difficult to be certain whether the apparent increase in serious opportunistic infections observed in patients receiving combination chemotherapy as opposed to single-agent chemotherapy (in this case VP-16) is attributable to greater immunosuppression secondary to chemotherapy, or rather to the fact that the patients treated with the combination regimen were more immunosuppressed (and thus perhaps exhibited more aggressive clinical disease) to begin with (60). The causes of death in most patients with epidemic KS, have been overwhelming opportunistic infection or irreversable wasting and cachexia; tumor-related deaths have accounted for only approximately 25% of the total (22).

Because of the concern that immunosuppressive therapy might actually accelerate the disease itself, as has clearly been suggested by the fairly aggressive course that KS exhibits in iatrogenically immunosuppressed individuals as well as the observation that such rapidly progressive disease not infrequently regresses when immunosuppression is decreased or discontinued, several clinical trials have been initiated to investigate the efficacy of immunomodulatory

agents such as alpha-interferon. It can be seen from the data in Table 26 that approximately 60 patients have received some type of interferon. However, the complete response rate has been only approximately 10% and an additional 20% of patients had short-lived partial responses. It is obvious that further studies are necessary including controlled trials comparing the response and toxicity of biologic modifiers such as interferon with other forms of standard or investigational chemotherapy.

TABLE 27
TREATMENT OF EPIDEMIC KS

Regimen	Patients Tested	Complete Response	Partial Response	Institution*
	← n →			
Recombinant leukocyte A interferon†				MSK
36-54 × 10^6U im every day × 28 d	31	6	9	
Recombinant alpha 2 interferon‡				UCSF
1 × 10^6U/m^2 every day × 5 d, every other week	9	...	1	
50 × 10^6U/m^2 iv every day × 5 d, every other week	9	...	4	
Human lymphoblastoid interferon§				NCI
7.5 × 10^6U/m^2 im every day × 28 d	10	...	2	
Vinblastine 4 mg iv every week	12	1	8	UCSF
Adriamycin (40 mg/m^2 body surface area · iv day 1) + vinblastine (6 mg/m^2 body surface area · iv day 1) + bleomycin (15 mg/m^2 body surface area · day 1) 15 cycle repeats every 21 days	9	1	6	
VP-16 (Etoposide) 150 mg/m^2 body surface area iv every day × 3 every 28 days	22	10	9	NYU
Adriamycin (40 mg/m^2 body surface area · iv day 1) + vinblastine (6 mg/m^2 body surface area · iv day 1) + bleomycin (15 mg/m^2 body surface area · day 1) 15 cycle repeats every 21 days	22	4	15	

* MSK = Memorial Sloan-Kettering; UCSF = University of California in San Francisco; NCI = National Cancer Institute; NYU = New York Univ
† Hoffman-LaRoche, Inc., Nutley, New Jersey.
‡ Schering-Plough Corp., Kenilworth, New Jersey.
§ Burroughs Wellcome Co., Research Triangle Park, North Carolina.

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