

July 7, 1982

National Cancer Institute

Opportunistic Infection/Kaposi's Sarcoma Syndrome

As the magnitude of the Kaposi's Sarcoma/opportunistic infection/acquired immunodeficiency syndrome problem grows, it is becoming increasingly apparent that the sarcoma is only one manifestation of an overall acquired immunodeficiency syndrome. Other diseases manifested as a result of this epidemic dysfunction of the immune system are under consideration by other governmental agencies and research institutions. The major NCI initiative in response to this epidemic so far is an award of grant funds under the terms of a cooperative agreement.

Proposed Cooperative Agreement

A project to be entitled "Etiologic Studies of Acquired Immunodeficiency Syndrome" is proposed for FY 1983 in the amount of \$1.25 million.

Since June of 1981, investigators have identified an epidemic of acquired immunodeficiency in the United States, with some 430 cases thus far of Kaposi's Sarcoma and/or opportunistic infections. The affected individuals have been predominately homosexual men, but heterosexual men and women are increasingly involved. Some 70% of the cases have been in New York City or California; the fatality rate has been about 70% in the earliest reported cases. The patients have shown profound anergy, quantitative and functional T-lymphocyte abnormalities, and evidence of infection with multiple organisms. In addition, thousands of individuals appear to have a prodrome of chronic fever, weight loss, diarrhea, lymphadenopathy, and/or T-lymphocyte immunologic abnormalities. Other immunodeficiency-related malignancies, particularly non-Hodgkin's lymphomas, are now appearing in this population. There is no evidence that the epidemic is abating, with two to three new cases per day of Kaposi's Sarcoma or opportunistic infections being reported to CDC. Research into this epidemic could yield important new information on the etiology of cancer in man. Study of this emergent health problem provides an opportunity for detecting new risk factors. The purpose of this grant is to encourage such research by providing support to institutions possessing an interest in the problem, as well as a population of affected patients and/or laboratory facilities and personnel appropriate to the conduct of such research. The intent of this grant is to encourage innovative, multidisciplinary studies of this problem.

It is proposed that a number of institutions receive awards to support research into the causes and means of preventing this problem. Awards would be made as Cooperative Agreements with NCI staff serving as a resource for information on the activities of various members of the working group and acting to facilitate collaboration among involved researchers. With the cooperation of the awardees, collaborative areas will be identified and developed at semi-annual meetings with the working group. Studies to be proposed by the applicants should stress innovative approaches and should include any or all of the following three components:

- 1) Epidemiologic studies designed to identify possible etiologic factors in affected patients or in individuals with prodromal conditions.

- 2) Basic research projects on etiology and pathophysiology. These would include studies in such areas as immunology, microbiology, virology, toxicology, etc., and would include studies of acquired immunodeficiency syndromes, Kaposi's Sarcoma, and allied conditions.
- 3) Innovative clinical treatment and prevention research protocols which are linked to hypotheses of etiology.

Applications from institutions or consortia possessing multidisciplinary resources and expertise in all areas will be encouraged.

Other research carried out by the National Cancer Institute on problems related to Kaposi's Sarcoma and other aspects of this epidemic are conducted within larger research projects, both grant and contract.

Contract Efforts

Laboratory and technical support for NCI studies of patients with this syndrome, or at risk of developing it, are being provided by a series of contracts which were originally established to provide program-wide support for a variety of research projects in the Environmental Epidemiology Branch (EEB), Division of Cancer Cause and Prevention. At the time these contracts were awarded, the Kaposi's Sarcoma problem had not yet surfaced. However, these existing contracts are now being employed to provide support for the relevant studies. Current contract efforts directed at this epidemic total \$450,000 in FY 1982, and are estimated at \$520,000 for 1983.

The Environmental Epidemiology Branch (EEB) of the National Cancer Institute conducts studies to define the distribution and determinants of cancer in man. These activities include the formulation of hypotheses using national and other data resources and the testing of these hypotheses in analytic case-control and cohort studies. Descriptive studies are conducted at whatever locales within the United States offer the greatest likelihood of producing meaningful new clues to cancer etiology.

Grant Efforts

A large number of NCI-supported research grants have traditionally included funds for studying the treatment of Kaposi's Sarcoma and other sarcomas. The major therapeutic work is supported with Clinical Cooperative Research awards, which fund research activities utilizing patient volunteers to assess the effect and value of various treatment modalities. Because the clinical resources necessary for the conduct of a major clinical trial are often not available at a single institution, a cooperative study is initiated which involves investigators in a number of institutions following a common protocol. NCI personnel and award recipients are jointly responsible for monitoring and coordinating the federally supported clinical trials, reviewing the treatment protocols, and analyzing the data therefrom.

In addition to clinical cooperative research, other types of grants are supporting studies which may be of direct relevance to this epidemic of cancer and infection.

The two objectives of a large NCI Human Cancer Serology Program Project grant, (total, \$503,030) for example, directly focus on problems which may relate to these patients. They are: (1) serological definition and biochemical characterization of distinctive cell surface antigens of human cancers and, (2) immunovirologic analysis and biochemical characterization of human cancers of suspected viral etiology. These studies relate to two central questions concerning human cancer: Do human tumor-specific antigens exist, and do viruses play a role in the etiology of human cancer? Immunovirological studies are focused on selected human cancers that are suspected from serological, virological, and epidemiological evidence to be related to herpesviruses or papovaviruses. The relation of cytomegalovirus to Kaposi's Sarcoma is being studied as part of this project, as well as other cancers developing in immunodeficient patients. Using a variety of serological assays and reference viral antigens and antibodies to identify the range of herpesvirus and papovavirus antigens, evidence is being sought for the presence of viral antigens, and for the occurrence of corresponding antibody, in patients with Kaposi's Sarcoma as compared with the normal population.

Since the development of Kaposi's Sarcoma is thought to be related to a dysfunction of the immune system, research involving immunodeficiency, or the immune system as a whole, may hold the key to understanding the genesis and etiology of this rare malignancy. For example, one of our comprehensive Program Project grants (total, \$580,392) is investigating the relationship of the development of the lymphoid system and immunodeficiency diseases and cancer of man. This program project will coordinate and focus the efforts of ten interrelated projects working in both clinical and fundamental perspectives. The program will be organized into three major areas of research emphasizing:- (1) T cell differentiation in man and mouse; (2) The effects of T cells and T cell factors on B cell differentiation; and (3) Animal experiments (chicken, mouse, pig) which are closely related to the clinical model of immunodeficiency diseases.

Finally, it should be noted that some NCI grants have been specifically supplemented in the past year to allow an expansion of studies on these patients. For example, the University of California at San Francisco, through our cooperative agreement with the Northern California Oncology Group, will receive funds to hire a Kaposi's Sarcoma ambulatory care nurse and data manager. Moreover, a number of investigators have redirected their existing NCI grant funds to laboratory and clinical problems raised by this epidemic, including those at UCLA, UCSF, NYU, Mt. Sinai, and Memorial Sloan Kettering.

Our estimate of total NCI grant funds which have been supplemented, redirected, or relate closely to this epidemic in fiscal year 1982 is \$291,000. The large number of publications by NCI-supported researchers which have recently appeared confirms that significant NCI funds supported this work in 1981 - 1982.