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The Syndrome of Kaposi's Sarcoma and Opportunistic Infections: An Epidemiologically Restricted Disorder of Immunoregulation

IN JUNE AND JULY of 1981 the Centers for Disease Control (CDC) reported to the medical community the alarming and unprecedented occurrence of Kaposi's sarcoma, *Pneumocystis carinii* pneumonia, and other severe opportunistic infections among apparently previously healthy homosexual men in the United States, with a concentration of cases in New York and California (1, 2). Soon thereafter more detailed reports appeared in the literature clearly documenting this unique pattern of disease (3-6). The number of cases being recognized is increasing, with at least one case per day being reported to the CDC. The current total is 290 recognized cases, making this illness a public health problem of essentially epidemic proportions for a particular segment of our society.

The common denominator in these patients seems to be a profound immunosuppressed state, particularly among the patients with severe opportunistic infections (4-6). Virtually all the patients studied have manifested a severe acquired immunodeficiency that was selective; cell-mediated immune function, as measured by in-vivo (delayed cutaneous hypersensitivity) and in-vitro (T lymphocyte function) testing, was selectively impaired, whereas humoral immune responses appeared to be intact by both in-vitro testing and the presence of normal in-vivo antibody titers. One study (4) found that inducer or helper subset of T cells was selectively impaired with a resulting reversal of the ratio of inducer/helper T cell subset to suppressor/cytotoxic T cell subset in favor of a selective predominance of suppression.

The types of opportunistic infections that these patients developed indicated the selective impairment of cell-mediated immunity; of particular note were infections with *P. carinii*, *Cryptococcus neoformans*, *Candida albicans*, *Mycobacterium tuberculosis*, *Mycobacterium avium*-intracellular, and several others. Cytomegalovirus and herpes simplex virus infections were strikingly predominant, both with regard to documented infections and serum antibody titers indicating recent exposure.

Cytomegalovirus has been thought to be the primary causal agent in the induction of the immunosuppressed state (4), with subsequent infections or Kaposi's sarcoma resulting from the underlying immunosuppression originally caused by cytomegalovirus. This hypothesis is not unreasonable because cytomegalovirus can cause transient immunosuppression in normal hosts (7). The likelihood of frequent re-exposure and reinfections with cytomegalovirus among persons with a high degree of sexual promiscuity within a confined group could conceivably lead to a state of profound and apparently permanent immunosuppression directly related to recurrent viral infection, as opposed to the clinically insignificant degree and duration of immunosuppression usually seen in hosts with a single exposure. However, a counter-argument can be made that patients who are immunosuppressed for other reasons, such as iatrogenesis, also have a high incidence of cytomegalovirus infections (8). Therefore, it is possible that the immunosuppressed state is caused by other factors and cytomegalovirus infec-

tion is merely a consequence of this immunosuppression. Similarly, it is likely that the other opportunistic infections as well as Kaposi's sarcoma are secondary to the immunosuppression. Thus, the primary cause of the immunosuppression in this syndrome is currently unknown.

In this issue, four additional reports (9-12) give insights into the further ramifications of the syndrome. The finding of a selective depletion of the inducer T cell subset is consistent in all four reports. Whatever agent or agents—acting independently, in combination, or synergistically—are responsible for the noted immunosuppression, the remarkable feature of the defect is the apparent selectivity for a specific immunoregulatory T cell subset. Because the inducer T cell subset is responsible for the induction of antibody responses to T-cell-dependent antigens (13), there is an apparent paradox noted in the current reports (9-12) and in previous studies (4-6): Unexpectedly antibody responses are preserved. This finding, however, should not be surprising because even within the inducer subset of T cells, there are likely to be subsubsets of cells that selectively induce cell-mediated versus humoral immunity. Thus, it is quite conceivable that a person can have selective impairment of the ability to induce a cell-mediated immune response with relative sparing of the inductive function for humoral responses. Furthermore, suppressor-effector function of the suppressor T cell subset (OKT8) requires induction by an inducer (OKT4) subset of cells (13). Even certain suppressor cells need an intact inducer T cell subset for normal expression of suppressor function. Although most studies up to this point (4-6, 9, 10, 12) have indicated a predominance of immunosuppression in this syndrome, the report by Morris and colleagues (11) on the occurrence of autoimmune thrombocytopenic purpura among homosexual men in the absence of opportunistic infection or Kaposi's sarcoma raises an interesting alternative possibility. Their patients who have relative increases in numbers of phenotypically identified suppressor cells may have ineffective suppressor cell function related to a deficiency of the OKT4 inducer of the OKT8 suppressor cell, thus leading to or perpetuating an autoimmune state. The authors' suggestion that the syndrome should be termed a defect in immunoregulation rather than strictly an immunosuppressed state is appropriate.

The complexity of the syndrome becomes even more apparent from the study of Friedman-Kien and colleagues (12) who report a significant elevation of the frequency of the HLA-DR5 haplotype in homosexual as well and nonhomosexual men with Kaposi's sarcoma. This finding suggests that the common denominator of the syndrome is indeed a severe disorder of immunoregulation, the underlying cause of which is unclear. Depending on the severity of the immune defect, the precise genetic profile of the host, as well as a number of other unrecognized factors, a given person may develop Kaposi's sarcoma without other associated infections, opportunistic infections in the absence of Kaposi's sarcoma, autoimmune disease, or a combination of all of these. In this regard, it is highly likely as more cases are reported and carefully studied that a wider spectrum of associated diseases will become apparent.

Despite the important new information made available in the four reports in this issue, critical questions remain unanswered. Paramount among these questions are those relating to the epidemiologic aspects of the syndrome: why homosexual men and why occurrence or recognition only as recently as 1979? With regard to the latter point, it now appears that beyond question this syndrome is truly a new disease. Monitoring of cases of *P. carinii* by the CDC (14) as well as careful documentation of cases of Kaposi's sarcoma render it virtually impossible for more than an extremely small number of cases to have gone unrecognized before 1979 (14). Some recent change, therefore, seems to have occurred within the unique epidemiologic confines of the male homosexual population that has been expressing itself only over the past 2 to 3 years. Is there a new virus or other infectious agent that has expressed itself first among the male homosexual community because of the unusual exposure potential within this group? Is this an immunosuppressed state due to chronic exposure to a recognized virus or viruses? Is this illness due to a synergy among various factors such as infectious agents, recreational drugs, therapeutic agents administered for diseases that are peculiar to this population such as the "gay bowel syndrome," or is this illness due to a combination of all of these factors?

Of note is the geographic clustering of cases with almost half of all recognized cases being reported from New York City, and the vast majority of cases reported from New York, Los Angeles, and San Francisco (14). If this clustering represents a real phenomenon, then it is likely that risk factors for the syndrome are not randomly distributed in the nationwide homosexual community (14). In this regard, it is unclear whether the predominance of this syndrome in these three cities relates to the unusual life-style of the homosexual men in these locations or to the presence of common sources of possible primary infectious factors. Still, the questions of why now and why this group remain unanswered. The CDC Task Force on Kaposi's Sarcoma and Opportunistic Infections currently is examining a broad range of epidemiologic, virologic, toxicologic, immunologic, and genetic factors in an attempt to shed light on these questions. Precise delineation of risk factors for the syndrome (such as sexual practices, drug usage, and virus exposure history) may be difficult because individual cases are now being recognized that lack one or all of these features. In fact, not all patients are homosexual and not all of them are even men. The CDC Task Force has been informed of at least 27 heterosexual men and 10 women with the syndrome. However, several of the heterosexual men and most of the women were users of illicit drugs. Determination of the factors or combinations of factors (whether drugs, virus, or others) that link homosexual men with these other groups will obviously be critical to the understanding of the cause of the syndrome.

Furthermore, because the predominant and immutable feature of this syndrome is the striking selective and persistent immune dysfunction in virtually all patients, it is imperative to determine the overall baseline immune status of the population of homosexual men who do not have the syndrome and to identify risk factors for the development of immune dysfunction before the onset of clinical disease.

Aggressive therapeutic approaches to the infections in these patients have in many cases been frustrated by the re-

currence of infections and death in an extraordinarily high proportion of patients (4, 6, 9, 10). Unfortunately, the immune defect in patients with this syndrome seems to be persistent even after they recover from the opportunistic infection that brings them to the attention of a physician. Thus, the question arises concerning therapies for the persistent immune defect. Foremost among these therapies would seem to be immunologic reconstitution with normal immunocompetent cells. However, the difficulties that accompany transplants of nonhistocompatible lymphoid tissue (such as bone marrow) currently render this approach impractical for extensive use.

Clearly, this extremely important public health problem deserves intensive investigation, and the CDC is to be commended in rapidly deploying a task force to investigate this problem. Important information of scientific interest may ultimately result from study of this syndrome, such as a more precise delineation of the relation between immune defects, viral infection, and oncogenesis. However, the immediate goal that must be recognized and vigorously pursued is the designation of resources and energy to the solving of the mystery behind this extraordinary disease, which currently seems to selectively affect a particular segment of our society. The population that currently is affected deserves this effort. Furthermore, because we do not know the cause of this syndrome, any assumption that the syndrome will remain restricted to a particular segment of our society is truly an assumption without a scientific basis. (ANTHONY S. FAUCI, M.D.; National Institutes of Health, Bethesda, Maryland)

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Clinical Utility of Immunologic Tests

A HEIGHTENED AWARENESS of potential immunologic mechanisms in various diseases has led increasingly to extensive and expensive immunologic testing of patients. As a result, most immunologists share a growing concern that many tests of immune function are prematurely applied in practice, and are inappropriate and far too costly for patients. This notion suggests a reversal of the accusation that medicine is very slow to adopt the clinical advances in both science and technology; indeed, this situation may be a case of too much science being clinically applied too soon.

In May 1981, the World Health Organization (WHO) sponsored a meeting of members of the International Union of Immunology Societies' (IUIS) Clinical Immunology Committee and its Immunology Unit staff to consider such concerns (1, 2). The participants' concern was that some immunologic tests have limited usefulness like many laboratory tests, but because of clinicians' apparent lack of familiarity, or possibly an overabundance of faith, clinical immunologic tests are frequently overutilized. Mindful that such tests are usually complex and expensive, the committee approached its task by identifying recommended methods and the failings for each of the commonest immunologic tests. Just as importantly, the committee suggested the clinical situations in which test results would be essential, possibly helpful, or indeed not at all indicated and relevant only for investigative purposes.

The eight tests the committee focused on included: quantitation (both total and specific IgE); complement; immune complexes; autoantibodies by indirect immunofluorescence; B- and T-cell determinations; and mitogen-induced blastogenesis.

The IUIS/WHO report found the essential indications for the eight tests to be quite modest, and in the main limited to defined immunodeficiency states or conditions in which perturbations in immunoglobulins, complement, or an autoantibody would be expected.

The measurement of immunoglobulins in serum and body fluids is the commonest assay in clinical immunology. The report summarizes the uses and limitations of quantitative radial immunodiffusion and nephelometric methods for serum and immunoelectrophoresis for biological fluids. The committee's opinion is that quantitative serum Ig measurements are essential for suspected primary or secondary immunodeficiency diseases, even in the absence of electrophoretic analytical results, as well as for the monitoring of gamma globulin substitution therapy. Similarly, im-