New Disease Baffles Medical Community

"AIDS" is a serious public health hazard, but may also provide insights into the workings of the immune system and the origin of cancer

Within the past 4 years, a new disease of unknown cause and high virulence has afflicted more than 470 people, killing almost half of them. "It is a serious public health problem," says Harry Haverkos of the Centers for Disease Control (CDC), referring to what is known as acquired immunodeficiency syndrome (AIDS). "So far 184 people have died, which is more than the combined total of deaths attributed to toxic shock and the Philadelphia outbreak of Legionnaire's disease." Moreover, the toll continues to mount as 15 to 20 new cases are reported every week.

About one-third of the patients contract a hitherto rare form of cancer called Kaposi's sarcoma, although additional kinds of cancer are also turning up. The other major way in which the disease manifests itself is through infection by any of several pathogens. By far the most common is the protozoan *Pneumocystis carinii*, which causes a severe pneumonia. But the underlying problem is a defective immune system, which leaves the patients unable to resist the infections and, apparently, the cancer.

Not only is the disease a public health threat then, but analysis of the immune defect may have profound implications for research on cancer causation and the workings of the immune system. Michael Gottlieb of the University of California School of Medicine in Los Angeles describes it as "one of the most remarkable medical developments in 50 years. It may lead to important answers about immunoregulation and the origin of cancer."

Although other explanations have not been ruled out, most investigators currently think that the disease is caused by an infectious agent, possibly a new virus or a new variant of an existing virus. The spread of AIDS resembles that of hepatitis B virus.

Most of the patients—some 75 percent—are homosexual or bisexual men who are very active sexually. According to one study by the CDC, homosexuals who came down with AIDS averaged about 1100 sexual partners during their lifetime, whereas a control group of homosexual men averaged about 500.

The next biggest group of AIDS patients, some 12 percent, are users of intravenous drugs, such as heroin. Drug users, like sexually hyperactive homosexual males, have a high incidence of hepatitis B infections, which may be spread through sexual contact or by contaminated needles.

Hepatitis B is also transmitted through transfusion of whole blood or blood products. Recently, three individuals with hemophilia have come down with AIDS, an occurrence which is particularly disturbing because of the possibility that they acquired an infectious agent from the blood product they take to prevent bleeding. So far, however, there is no evidence linking ordinary blood transfusions to the immunodeficiency disease, Haverkos says. Hemophiliacs require two or three injections of clotting factor per week and the material is prepared from the blood of many individual donors, which means that hemophiliacs' total exposure to foreign substances is much greater than that of patients who receive transfusions of whole blood. The CDC has not been able to implicate any particular lot of clotting factor as a possible source of infection for these patients.

A third identifiable group of AIDS patients, who comprise 6 percent of the total, are Haitian immigrants to this country. At this time, no one knows how these individuals might have contracted the disease. They deny homosexual experience and, except for one patient, the use of intravenous drugs.

Finally, about 6 percent of AIDS patients do not fit into any of the three groups and have been classified as "other." Only 27 of the patients are women, and half of these use intravenous drugs.

Unusual cases of Kaposi's sarcoma began to attract notice a little over a year ago. For example, at about that time Alvin Friedman-Kien and Linda Laubenstein of New York University Medical Center acquired three young male homosexual patients with the cancer.

Kaposi's sarcoma had been very rare in this country. When it did occur it primarily affected elderly men—60 years of age or older—of Mediterranean origin or individuals whose immune systems were suppressed, either by cancer itself, cancer chemotherapy, or by drugs to prevent rejection of transplanted organs such as kidneys. But it was almost unheard of in young individuals who did not have these predisposing conditions. "Suddenly to see three cases of Kaposi's sarcoma in young men was most unexpected," Friedman-Kien remarks.

Similar cases soon began turning up, mostly in cities with large homosexual populations, including New York, Los Angeles, and San Francisco. The victims were male homosexuals of young or at most middle age. AIDS also began to be seen in intravenous drug users. "It is probably one of the first human cancers to be occurring in epidemic form," according to Friedman-Kien. (Burkitt's lymphoma in certain parts of Africa may be another.)

Moreover, the course of the sarcoma in these patients was much different from that in the older men. The latter usually have characteristic skin lesions on their legs. Their disease responds well to therapy and they rarely die from the cancer. But in the young patients the skin lesions were often located on the upper body, including the head and face. In addition, their internal organs were affected. Most of the patients respond poorly to therapy and death within 2 years is common.

The infections seen in AIDS patients, which first began to be noticed in about mid-1979, are also typical of those occurring in immunosuppressed individuals, but not in people who are generally healthy. The most common of these infections, which are called "opportunistic" because of their predilection for immunocompromised hosts, is *Pneumocystis* pneumonia. Roughly 60 percent of the AIDS patients, including some who also have the sarcoma, have *Pneumocystis* infections. Other infections, caused by viruses such as cytomegalovirus (CMV) and herpes simplex virus (HSV), by fungi such as *Candida* and *Cryptococcus*, by protozoans such as *Toxoplasma*, and by bacteria such as the tuberculosis bacillus, also occur.

The infections often have a relentlessly progressive course. Frederick Siegal of Mount Sinai School of Medicine says, "Infections that can be controlled with antimicrobials can be treated or suppressed, but eventually they recur or another infection overwhelms the patient." He estimates the long-term mortality of AIDS patients to be 65 percent.

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The high incidence of Kaposi's sarcoma and the nature of the opportunistic infections in the patients suggested that their cellular immunity might be defective. As Siegal points out, "The organisms involved [in the infections] are mostly resisted by cellular immunity."

That the underlying defect affects cellular immunity has been borne out by several investigators. The patients' humoral immunity does not appear to be impaired; they have normal or elevated concentrations of antibodies in their blood.

The patients have low lymphocyte counts, often half or less than half of the normal lower limit of about 1500 lymphocytes per cubic millimeter of blood. In general, the antibody-secreting B lymphocytes are not much affected, but the T cells, the ones needed for cellular immunity, are both low in number and abnormal in composition. Gottlieb says, "In addition to the depletion of the total number of lymphocytes, certain subpopulations are more depleted than others."

In particular, the helper T cell subpopulation is greatly depleted or even missing, whereas the killer-suppressor T cell subpopulation is much less reduced. As might be expected from the names, helper T cells aid other immune cells to perform their functions and suppressor T cells inhibit them. Loss of the helpers, while the suppressor subpopulation remains more or less intact, could produce a profound suppression of cellular immunity, thus allowing the opportunistic infections to take hold.

The results also provide support for the controversial immune surveillance theory, which holds that immune cells help to protect against cancer by seeking out and destroying abnormal, cancerous cells before they can grow into a life-threatening tumor. In immunosuppressed patients, according to the theory, the cancer cells grow in the absence of the normal restraints. Precisely which immune cells might be important here is uncertain. In addition to the T cell abnormality, AIDS patients may have a reduced population of another type of immune cell, the natural killer, which has also been implicated in cancer cell surveillance.

According to Siegal, a shift in T cell subpopulations similar to that seen in AIDS patients, although less severe, occurs in many homosexual men. At this time, it is not known whether this is a subclinical manifestation of AIDS or is unrelated.

In addition, the CDC has received reports from physicians around the country of lymphadenopathy (enlarged lymph nodes) in homosexual men. By May of this year 57 patients had been reported. These individuals have enlarged lymph nodes in various locations throughout the body, and often experience fever, weight loss, fatigue, night sweats, diarrhea, and other symptoms of general malaise. Many of the patients with full-blown AIDS had similar symptoms in the months before they developed Kaposi's sarcoma or opportunistic infections. Moreover, profiles of the characteristics of the two groups—those with AIDS and those with the lymphadenopathy—are very similar. Thomas Spira of the CDC says, "The age distribution and other factors are virtually indistinguishable. . . . We don't know if the lymphadenopathy is a prodrome [premonitory symptom] or milder manifestation of the more severe disease, but our concern is that it is related." At least one of the lymphadenopathy patients has developed Kaposi's sarcoma.

The big question is what causes the immune defects of AIDS. For a time, health officials thought amyl nitrite and related vasodilator drugs might be involved. The drugs were used by practically all of the homosexual patients to intensify their sexual experiences. However, other patients among the intravenous drug users, Haitians, and hemophiliacs were not exposed to them. At most, the nitrites might have contributed to the homosexuals' immune deficiency without being its primary cause.

Most interest right now is focused on the possibility that an infectious agent causes AIDS. The resemblance of the population at risk to that at risk for hepatitis B suggests a viral pathogen, as does the discovery of the disease in hemophiliacs. In addition, David Auerbach and William Darrow of the CDC identified a cluster of nine AIDS cases in Los Angeles and Orange counties for whom they could establish sexual connections. This was out of a total of 19 cases at the time, although pertinent information could be obtained for only 13 of them. Auerbach says, "We estimate that it would be highly unlikely that these connections would occur at random. The finding speaks a little more strongly for some kind of infectious agent rather than some kind of toxic agent." One of the patients also had sexual contacts with AIDS patients in several other cities.

Gottlieb, for one, favors the idea that CMV plays an important role in AIDS. He suggests that it may be a major contributor to the development of Kaposi's sarcoma and may also help to produce the underlying immune defect. As he notes, the virus has been linked with Kaposi's sarcoma in other studies. It may be transmitted sexually, and homosexuals may have high rates of infection by CMV, up to 95 percent in some studies. Moreover, CMV is immunosuppressive, although the milder immunosuppression it causes has not been associated with Kaposi's sarcoma or opportunistic infections.

Nevetheless, there is a major problem with the idea that CMV, or any other known virus for that matter, causes AIDS. Neither homosexuality nor CMV is new, but the disease apparently is.

According to Haverkos, the earliest cases with the peculiar characteristics of the current disease that the CDC could identify began appearing in late 1978 and early 1979. The CDC came to this conclusion by examining tumor registries in several cities and their own records of requests for one of two major drugs used to treat *Pneumocystis* pneumonia. The CDC is the only source for this particular drug.

"It is probably one of the first human cancers to be occurring in epidemic form."

A new variant of CMV may have appeared a few years ago, but if it did, it has so far eluded detection. Many strains of CMV have been isolated from AIDS patients; the condition does not appear to be associated with any strain.

Another possibility is that the homosexual population at risk for AIDS experiences a more profound immunosuppression than members of the general population who might contract a viral infection, because they are exposed to many variants of CMV and other viruses. Spira favors the view that a new pathogen causes AIDS, but remarks, "As an alternate hypothesis, recurrent antigenic stimulation may cause a paralysis of the immune system." A similar explanation might apply to the hemophiliacs, who are exposed to many foreign antigens in the clotting factor preparations. The hypothesis also suffers from the problem of failing to explain how a

CO_2-Climate Models Defended

A National Research Council panel has concluded* that the best estimate of the long-term, global warming due to a doubling of atmospheric carbon dioxide is still 3° ± 1.5°C, despite recent claims that global climate models of the greenhouse effect have exaggerated the warming. The panel enters the fray on the side of the overwhelming majority of specialists in the field, but the dissenters are not likely to withdraw soon.

The center of the controversy is the work of Sherwood Idso, a physicist at the U.S. Water Conservation Laboratory in Phoenix. In 1980, Idso (*1*) calculated the warming due to a doubling of carbon dioxide to be 0.26°C, about one-tenth of that produced by most mathematical models of the climate system. Rather than constructing a mathematical model whose workings would mimic the physical world, Idso based his calculations on measurements of the temperature effects of naturally induced changes in radiation. Carbon dioxide affects temperature by altering radiation fluxes, but no carbon dioxide–induced temperature change is detectable yet. So Idso determined the relation between temperature changes and changes in radiation induced by carbon dioxide surrogates—in two cases dust or water vapor over Phoenix, and in a third case the seasonal changes in incident radiation over the United States.

Idso claims that a given change in radiation at the ground produced the same change in temperature in each case, with the exception of the seasonal changes along the Pacific Coast. This being so, he reasons, the response over Phoenix and the inland United States can be taken as that of all of the continents, and the response of the U.S. Pacific Coast is equivalent to the maximum response of the world ocean. In support of his calculations, Idso cites an equally small carbon dioxide response by tropical ocean temperatures in a model by Reginald Newell of the Massachusetts Institute of Technology and T. G. Dopplick of Scott Air Force Base, Illinois (*2*).

In public at least, climate model specialists have, without exception, criticized these conclusions. Attempting to verify numerical models by comparison with observations is commendable, the panel and other critics emphasize, but observations from a single site, a single country, or one part of the ocean cannot suffice to verify what is a global process. A major failing, they say, is the omission of the ocean from Idso's natural experiments, as he calls them. Those experiments extend over only a few months, while the surface layer of the ocean requires 6 to 8 years to respond significantly to a change in radiation. A part of that response is to send more water vapor into the atmosphere, which traps even more radiant energy, just as carbon dioxide does. Without this and other feedback mechanisms to amplify the carbon dioxide warming, an apparently small response is inevitable, critics say. Researchers make similar complaints about Newell and Dopplick's model, pointing out that the allowed increase in humidity is unrealistically small.

Critics point out that their sophisticated, global climate models can produce a similarly small effect, given unrealistic conditions for a global study. In independent model experiments, Stephen Schneider of the National Center for Atmospheric Research (NCAR) and James Hansen of the Goddard Institute for Space Studies limited their models geographically and temporally in order to duplicate Idso's observations. Their models' responses were comparable to that calculated by Idso. V. Ramanathan of NCAR has in the same manner duplicated the results of Newell and Dopplick for the tropical ocean. Climate researchers believe that their evidence against these challenges is undeniable. The dissenting minority, as small as it is, has yet to concede.—RICHARD A. KERR

References

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2. R. E. Newell and T. G. Dopplick, *J. Appl. Meteorol.* **18**, 822 (1979).

**Carbon Dioxide and Climate: A Second Assesment* (National Academy Press, Washington, D.C., 1982). Available for $7.25 (prepaid) at 2101 Constitution Avenue, NW, Washington, D.C. 20418. Panel members: J. Smagorinsky (chairman), K. Bryan, S. Manabe, L. Armi, F. P. Bretherton, R. D. Cess, W. L. Gates, J. Hansen, and J. E. Kutzbach.

new disease might have arisen, however.

Exposure to sperm from many sources may contribute to the immunodeficiency of homosexual men. Sperm are immunosuppressive if they enter the blood stream. Friedman-Kien, Laubenstein, and Pablo Rubinstein of the New York Blood Center and Bijan Safai's group at Memorial Sloan-Kettering Cancer Center have detected antibodies against sperm in the homosexual patients. These antibodies cross-react with T cells and could thus result in their depletion.

Neither Friedman-Kien nor Safai attributes AIDS solely to immunosuppression by sperm, however. Friedman-Kien says, "I don't think it is just the sperm; it may be a multiplicity of factors." A new virus, possibly carried by sperm, is a good possibility for one of the factors.

How the Haitians acquire AIDS, if they are not homosexuals or drug users, is one of the many puzzles of the disease. Nonetheless, their disease appears to be the same as that in the other groups. According to Spira and Margaret Fischl of Jackson Memorial Hospital in Miami, the Haitians with AIDS have a severe immune deficiency that closely resembles that of the other patients. "The syndrome we see in the Haitian group was strikingly similar to that in the gay community," Fischl explains.

Moreover, AIDS may be occurring in Haiti, too. B. Liautaud, a dermatologist in Port-au-Prince, recently reported 11 cases of Kaposi's sarcoma, a high number for such a small country. Fischl and Spira have begun immunological studies of some of these individuals to see if they have the same immunodeficiency as patients in this country.

Friedman-Kien and Safai point out that Haiti is a favorite vacation spot for many homosexual males. They might have carried the disease to or from that country. At present, no one knows if the syndrome being seen there began before or after AIDS in this country.

Although Kaposi's sarcoma is the most common cancer to be found in AIDS patients, it is not the only malignancy. This was not a surprise. Gottlieb remarks, "I would expect that we are going to see other cancers since these individuals are so profoundly immune deficient."

This expectation is rapidly being fulfilled. Friedman-Kien has now seen nine AIDS patients who have a cancer of the lymph system. In addition, three of the patients with Kaposi's sarcoma have also developed lymphomas.

According to John Ziegler of the Veterans Administration Hospital in San Francisco, Kaposi's sarcoma may be

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just one of a number of opportunistic tumors that may affect these immunosuppressed individuals. He and his colleagues have now found three individuals, young gay males with characteristics similar to those of the AIDS patients, who have a squamous carcinoma of the tongue. This cancer is rarely seen in young nonsmokers like these patients. One of the men was a lover of a patient with Kaposi's sarcoma. In addition, the San Francisco group has identified four AIDS patients who have a Burkitt's-like lymphoma.

Ziegler says, "The question arises—are these individuals susceptible to the cancers because of the activation of DNA viruses that are passed between the individuals?" All three of the cancers have been linked with members of the DNA-containing herpes virus family. Oral cancers, such as the squamous cell carcinoma, have been associated with HSV, Burkitt's lymphoma with Epstein-Barr virus (EBV), and, as already noted, Kaposi's sarcoma with CMV.

In fact, the Ziegler group has identified CMV DNA and proteins in sarcoma cells from AIDS patients, but not in normal cells from adjacent tissue. And they have found EBV in tumor cells from two of the lymphoma patients. Ziegler suggests that the immunosuppression of the patients may have allowed activation of the viruses, thus leading to the cancers. If his hypothesis is borne out, there would be another link for the chain of evidence supporting a causative role for the herpes viruses in cancer.

In addition to a possible role of the viruses in the etiologies of these cancers, there appears to be a genetic element influencing who gets the cancer, at least for Kaposi's sarcoma. According to Friedman-Kien, Laubenstein, and Rubinstein, there is an association between the sarcoma and a particular HLA antigen, the one designated DR5. The DR antigens, which are encoded by genes in the major histocompatibility complex, are thought to be involved in the regulation of immune responses. "Between 50 and 60 percent of the patients have HLA-DR5 in the classic as well as the homosexual variety of Kaposi's," says Friedman-Kien. "This indicates a genetic predisposition." Exactly how the DR5 antigen predisposes to Kaposi's sarcoma is not understood. Safai and Marilyn Pollack of Memorial Sloan-Kettering Cancer Center have similar findings.

In general, AIDS is providing researchers with a wealth of clues for investigating how the immune system works normally and how its malfunction can result in disease, including cancer. Meanwhile, a major effort is under way at CDC and elsewhere to pinpoint the agent or agents that cause the disease. "Identification of the cause and then prevention are the major goals," Gottlieb says.—JEAN L. MARX

Repeated DNA Still in Search of a Function

As new families of DNA sequences are discovered the picture becomes more complicated, more fascinating, and more mysterious

A large and varied zoo of repetitive DNA sequences from eukaryotic organisms was on view at a workshop* held in mid-July at the National Institutes of Health (NIH), Bethesda. "It is truly astonishing that even in 1982 people can still report the discovery of a family of 100,000 members of a repeated sequence that makes up 3 percent of a mammalian genome." Thus comments Giorgio Bernadi, of the University of Paris, who organized the meeting jointly with Maxine Singer of the National Cancer Institute. "It's clear there are many more families to be found," adds Singer, "and the discovery process is moving at a tremendous pace."

Interest in repetitive DNA sequences goes back many years but, as with many aspects of molecular biology, the advent of recombinant DNA technology and DNA sequencing now permits previously unmatched scrutiny of the structures of interest. It was therefore not surprising that the NIH meeting showed a heavy emphasis on new structural, rather than functional, information. For example, new repeat families were described, sequences of known ones were clarified, relationships between families were explored, and so on. Singer expressed a common frustration when she said, "We all go on grinding out the data on structure without thinking enough about what it means."

The truth is, however, that the functions of the large and motley collection of repeated DNA families are proving particularly resistant to elucidation. Putative functions are many, including, variously, involvement in chromosome pairing, control of gene expression, processing of messenger RNA precursors, and participation in DNA replication. So far none has been established, save for the single exception of a small family that gives rise to 7*S* RNA, a molecule that recently was serendipitously discovered to be an essential component of a particle that mediates the secretion of proteins from cells.

For Eric Davidson, of the California Institute of Technology, a key message of the NIH workshop was the inference that many families of repeated sequences dispersed throughout the genome have been mobile through evolutionary time. "The evidence for mobility is indirect, but compelling," he suggests. If mobility is a reality, and most agree that it probably is, then it seems likely that at least some members of repeat families will have important effects in the genome, even if they have no formal function. Enhancing recombination and altering rates of gene expression are obvious possibilities, while the initiation of new species is a more recondite proposal.

Some repetitive DNA will undoubtedly be shown to have a function, in the formal sense; some will likely be shown to exert important effects; and the remainder may well have no function or effect at all and can therefore be called selfish DNA. Repetitive DNA constitutes a substantial proportion of the genome (up to 90 percent in some cases), and there is considerable speculation on how it will eventually be divided between these three groups. Current bets would put a small fraction in the function category, with distribution of the rest rising steeply through the effect and selfish categories.

Eukaryotic DNA can conveniently be divided into three classes. First is single copy sequence DNA, which contains but is not exclusively composed of, protein coding sequences. Second is moderately

*International Workshop on Highly Repeated DNA Sequences in Eukaryotes, sponsored by the National Cancer Institute and the Fogerty International Center, 12 to 14 July.

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