Biomedicine

Hemophiliacs and AIDS: Really at risk

Of all the population groups deemed at high risk of contracting AIDS, hemophiliacs — who frequently receive blood-clotting factors derived from pooled human plasma — have remained most uncertain about their fate. Until 1984, these blood products did not receive effective heat or chemical treatments to kill viruses, leaving them in many cases contaminated with HIV, the AIDS-causing virus.

A substantial majority of the approximately 15,000 hemophiliacs in the United States who received non-heat-treated clotting factor concentrates now have HIV antibodies. But researchers have debated whether this indicates true HIV infection — especially since some unconfirmed studies have suggested a relatively low incidence of clinical AIDS developing in antibody-positive hemophiliacs. Perhaps, some have suggested, AIDS viruses sometimes become noninfectious during normal preparation and storage of clotting factors, even without heat treatment. If so, the antibodies seen in hemophiliacs might in many cases be simply a response to a few noninfectious fragments of HIV proteins.

Not so, says J. Brooks Jackson of the University of Minnesota in Minneapolis, reporting with his colleagues in the Oct. 21 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION. In a study of 56 HIV-antibody-positive hemophiliacs who received non-heat-treated clotting factors, all but one had HIV DNA in their blood when tested with the extremely sensitive polymerase chain reaction test — indicating they are indeed infected with the virus and at high risk of contracting AIDS.

Cancer sleuths find clues to Kaposi's

For the first time, scientists have successfully maintained long-term laboratory cultures of Kaposi's sarcoma (KS) cells taken from AIDS patients. In analyzing these cells, they have found that AIDS-associated Kaposi's sarcoma is initiated by one or more as-yet-unidentified growth factors secreted by HIV-infected white blood cells.

The work, led by National Cancer Institute researcher and HIV co-discoverer Robert C. Gallo, provides the strongest evidence yet that Kaposi's sarcoma is not a true cancer but a "polyclonal proliferation" of cells. In other words, its tumors are not the result of a single cell gone reproductively awry, as in a true cancer, but instead represent a *population* of cells that grow abnormally under the influence of an unusual growth factor.

Kaposi's sarcoma is characterized by skin lesions associated with abnormal blood vessel formation and a proliferation of so-called spindle cells that scientists believe originate in the body's circulatory system. Traditionally afflicting men in Mediterranean and African countries, it has more recently become common in HIV-infected men and in other immunosuppressed individuals.

Gallo and his co-workers found that KS cells would not survive in culture even when fed a variety of traditional cell growth factors. But they grew well for more than one year in a culture medium containing the secretions of cells infected with human retroviruses such as HIV and HTLV-II (a cancer-causing virus closely related to HIV).

These findings suggest retrovirus-infected cells may become genetically "reprogrammed" to secrete a product that is necessary for KS cell growth. They are consistent with the fact that KS cells themselves do not show evidence of retroviral infection (SN: 10/15/88, p.244).

The scientists say their newfound ability to culture KS cells will facilitate identification of the growth factor or factors supporting KS cell growth. The work may further lead to the engineering of antibody-like molecules or other drugs capable of specifically blocking these growth factors' action.

Mathematics

Tying up a knotty loose end

One way to picture a mathematical knot is to think of a tangled string with its two ends spliced together. In more abstract terms, it can be thought of as a one-dimensional curve twisting through three-dimensional space to form a closed loop. Knottedness, however, is not a property of the curve itself. An imaginary ant crawling along a narrow tunnel within the one-dimensional confines of such a curve, even after completing its circuit, would never be able to tell whether the curve is knotted. Instead, knottedness resides in the way the curve sits in three-dimensional space. That relationship between a knot and the space in which it sits has long intrigued mathematicians and has suggested several important questions that play a central role in knot theory.

One problem, first considered in 1908 by topologist Heinrich Tietze, concerns determining whether two knots that look different are really the same knot when untangled. One knot could be merely a twisted, stretched version of the other. Tietze conjectured that if the space around two knots is the same, then the two knots themselves are tied in the same way. Eighty years later, Cameron M. Gordon of the University of Texas at Austin and John E. Luecke of New York University's Courant Institute finally proved Tietze right: No essential information about a knot is lost by throwing away the knot and, instead, studying and manipulating the space around it.

The theorem justifies a commonly used strategy for distinguishing knots. Whereas a knot can be thought of as a twisted loop of string, the space around a knot — the knot's complement — can be pictured as a slab of jelly from which a thin tube has been extracted. Instead of working with knots themselves, mathematicians often manipulate and deform the corresponding complements to derive mathematical expressions useful for characterizing and sometimes distinguishing knots. Mathematicians already could prove that two knots are not the same simply by proving that their complements are not the same. Now they know that if two complements are the same, the corresponding knots are also the same.

The idea that knots with identical complements would also be the same sounds obvious. But, in the case of two or more knots linked together, mathematicians have already proved that links having identical complements are not necessarily equivalent. That curious behavior provided one clue that the problem of single knots and their complements was mathematically quite subtle.

Indeed, Gordon and Luecke's proof takes up most of a 59-page manuscript. "It's a simply stated problem, but it turned out to be tricky to prove," Gordon says. "One approaches the problem in a somewhat roundabout way, and you end up proving something that seems to be a little bit stronger." Their proof involves the consequences of a mathematical process known as Dehn surgery, in which a knot is fattened into a tube, removed from its complement and then stitched back in again.

To arrive at the proof, Gordon and Luecke developed techniques that reduced the problem to studying sets of labeled diagrams. In recent years, that kind of approach, in which problems are reformulated in terms of questions about appropriate diagrams, has turned out to be useful for a variety of mathematical proofs. "We would hope that what we have done already, with a little bit more work, will give some information on other problems," Gordon says. "We're trying to refine the techniques now."

Gordon and Luecke would like to use such techniques to explore the mysterious behavior of linked knots. "It would be nice to explore where these arguments lead, but that's still rather speculative," Gordon says. "You never know in mathematics until you really get down to it whether a method will work for a given problem."