Is a New Virus the Cause of KS?

Kaposi's sarcoma, a once-rare skin tumor, is a scourge of gay men with AIDS. Several theories have attempted to explain it. The latest: a novel herpesvirus

More than a decade ago, clinicians in American cities began seeing an unusual kind of cancer in their gay male patients. The tumor was Kaposi's sarcoma (KS), a rare malignancy that causes purple blotches on the skin and was then mostly seen in elderly men of Mediterranean origin. In that population, KS was rarely fatal—but some of the gay men were dying from it. That was one of the first signs of the disease now known as AIDS, and as the AIDS epidemic has expanded, the mystery of KS has deepened with it.

Much of the mystery lies in the fact that although the subgroups afflicted by AIDS have broadened to include transfusion recipients, injecting drug users, and hemophiliacs, KS is almost exclusively confined to homosexual men. Further confusing the story was the finding in 1984 that HIV causes AIDS, which led some researchers to investigate whether it directly causes KS, rather than simply providing the opening for some other opportunistic agent or disease process. Since then, attempts to explain what is known as AIDS-KS have hatched at least a half-dozen theories implicating everything from other viruses to the nitrite inhalants popular among gay men. But none of these theories has been widely accepted, and investigators have kept searching.

Now, a group headed by researchers at Columbia University has accrued some tantalizing evidence that a new agent may be to blame. In KS lesions of AIDS patients, Columbia's Yuan Chang, Patrick Moore, and their co-workers report on page 1865, they found DNA sequences that appear to be from a new herpesvirus. The authors are careful to stress that their work is preliminary: It remains to be proven whether a new virus even exists, let alone causes KS, they say. Nevertheless, the work is turning heads. "I think it's a tremendously exciting result," says epidemiologist Harold Jaffe, head of the HIV/AIDS division at the Centers for Disease Control and Prevention and an authority on AIDS-KS. "At this point, we can't say it's the etiologic agent, but I think it's a very good candidate." Herpesvirus researchers like Bernard Roizman from the University of Chicago are equally impressed. "I think it's real," says Roizman.

Other researchers are impressed with the data but cautious about its import. "It's provocative and interesting and important," says Harvard University virologist Elliott Kieff, director of infectious disease at Boston's Brigham & Women's Hospital. But, Kieff adds, "this is not going to explain everything, and it may turn out to be just a passenger in KS lesions." Robert Gallo of the National Cancer Institute (NCI), whose lab focuses on KS pathogenesis, has similar reservations. "What singles out this paper is that it's exceptionally careful," says Gallo. "It's really good work, and it could be a substantial advance. But I have major questions."

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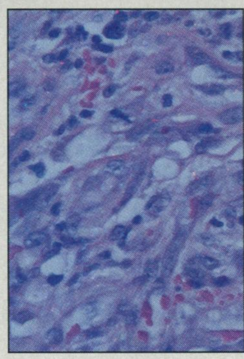


YUAN CHANG

Virus hunters. Patrick Moore and Yuan Chang report that they may have found a new virus that causes Kaposi's sarcoma (KS); a section of an AIDS-KS lesion is shown at right.

Those questions center on Chang and Moore's claim that the new herpesvirus is found only rarely—if at all—outside gay men. That would make it unique among the herpesviruses, because all the rest are found in a large proportion of the population. But that kind of unique behavior is just what Chang and Moore, a wife-and-husband team, say their data suggest. The Columbia group (with help from researchers at California's DNAX Research Institute) biopsied KS tissue from 27 patients who died of AIDS and found that 25 had unique DNA sequences that appear to be from the herpesvirus family. In comparison, those sequences turned up in only six of 39 non-KS tissues from AIDS patients and none of 85 non-KS tissues from people without AIDS. "It does look like a nonubiquitous virus," says Moore, an epidemiologist.

Yet Moore's conclusion presupposes that the Columbia team has indeed found a new virus. Moore, Chang, and their colleagues only plucked out short DNA sequences from KS tissues, and these sequences represent a fraction of the DNA a herpesvirus would contain. These data are thus too preliminary to prove the existence of a new virus.

To find those short DNA sequences, the researchers used a new method called "representational difference analysis," or RDA, which was first described in *Science* last year by Cold Spring Harbor Laboratory's Nikolai and Natalya Lisitsyn and Michael Wigler (12 February 1993, p. 946). In essence, RDA is a technique for purifying unique DNA sequences—such as those that belong to viruses—from among all the sequences in an organism's genome.

After identifying unique DNA sequences in AIDS-KS tissue, the researchers compared those to the DNA of known viruses and found similarities to two herpesviruses: saimiri and Epstein-Barr virus. They then made chemical probes from these short sequences and hunted for similar gene fragments among the tissues of AIDS and non-AIDS patients.

From here, the researchers must solve several problems before they can demonstrate that they have indeed found the cause of KS. First, they must isolate the putative virus, not just pieces of its DNA—a quest in which Moore says his group has some "hot leads." They must also present stronger evidence that the putative virus truly is unique to KS, says Steven Miles, a KS researcher at the University of California, Los Angeles (UCLA). "I think this is really terrific work, but I'm not satisfied with the controls," Miles says.

Specifically, Miles would like to see tests for the virus in classic KS patients, the elderly Mediterranean men not infected with HIV. If this virus does cause KS, he reasons, it should be found in those patients, too. Moore and Chang says they now have such analyses under way. They are also attempting to develop a serological test for the virus that would allow them to screen many people rapidly and more rigorously test their findings in AIDS-KS patients.

NCI's Gallo says that if a herpesvirus does turn out to play a role in causing KS, "it will go a long way to further understanding a major issue in KS that has been gnawing us for a long time." But he adds that he believes such a finding will complement rather than supplant the work by his lab and others, including Miles' lab at UCLA, on the role of chemical messengers called cytokines—in particular, various interleukins, tumor necrosis factor, and basic fibroblast growth factor (bFGF)—in the formation of KS lesions. Gallo, Barbara Ensoli, and co-workers think HIV's Tat protein may work synergistically with the excess levels of bFGF found in HIV-infected people to induce KS lesions—and they have done experiments in mice that support this thesis, detailed in the 20 October issue of *Nature*.

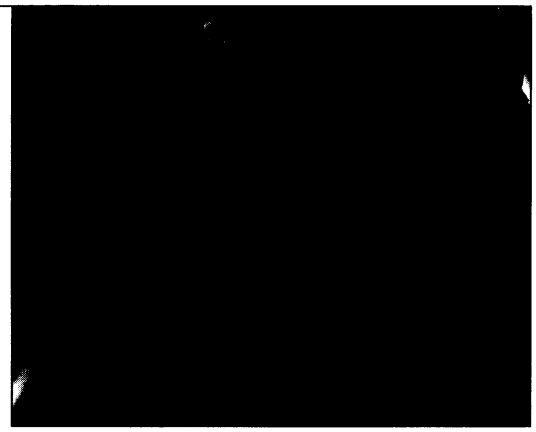
Moore agrees that even if he and his colleagues do isolate a new herpesvirus, it may fit in well with hypotheses about cytokines. "It could be that this agent doesn't transform cells but works through a secondary mechanism like cytokines," says Moore. Alternatively, Miles suggests that a herpesvirus could transform cells, making them susceptible to wayward growth from secondary factors like cytokines.

Whatever the actual mechanism of tumor formation is, says Moore, "this virus is probably playing a central role." That thesis will be intensely scrutinized over the coming months. But if it stands up, solid headway will have been made toward solving a vexing riddle that arose more than a decade ago when an old tumor began popping up in new places, with deadly results.

–Jon Cohen

PHYSICS

Can Sound Drive Fusion in a Bubble?



JOSEPH T. CARLSON / U.S. NAVY

Point of light. A bubble flashes, driven by sound waves from transducers around the flask.

At Lawrence Livermore National Laboratory, the hundred-million-dollar machine known as Nova fills a room the size of a gymnasium. Built to study nuclear fusion, Nova is the most powerful laser in the world. Its 10 beams zap a tiny hydrogen-filled pellet from all sides and cause the pellet to implode, creating temperatures and pressures approaching those in a hydrogen bomb.

Meanwhile, on a benchtop in a nearby building sits a second machine, this one nameless. It cost about $2000 and consists of little more than a flask of water surrounded by several sound-generating transducers. Yet according to recent calculations, this simple device can produce temperatures and pressures just two or three orders of magnitude short of those in Nova. And if things work out as Livermore's William Moss hopes, the device or one like it may someday rival Nova's temperature-pressure combinations. If so, such a tabletop tool could someday be used to trigger fusion—at least on a very small scale in the laboratory. "We don't expect to power the Energizer bunny," Moss says.

He and others, who discussed these calculations last month at a meeting of the Acoustical Society of America in Austin, Texas, are quick to point out that this scheme has nothing to do with an earlier "fusion in a flask" notion. Five years ago, cold-fusion advocates claimed they could fuse atoms of deuterium, or heavy hydrogen, without the bother of high temperatures and pressures. There are no such shortcuts here—only a clever idea for doing some of the same physics Nova does, but on a smaller scale and with finesse instead of brute force. Even so, the idea faces skepticism from laser fusion experts. It's not impossible, says John Nuckolls, a former director of Livermore, but he thinks it's "highly improbable" that Moss and his colleagues can achieve the necessary temperatures and pressures.

The scheme stems from a research area far removed from fusion: sonoluminescence. For several decades, scientists have known that passing sound waves through water can cause myriad tiny air bubbles to form and then collapse with a flash of light, but only recently have researchers begun to get a good idea of what is happening in the bubbles (*Science*, 14 October, p. 233). Six years ago, Felipe Gaitan at the University of Mississippi found that by carefully tuning the frequency of the sound waves, he could create a single, stable bubble that stayed in one place and expanded and contracted, emitting light, in sync with the applied sound. That gave researchers a simple system to analyze in detail—what Seth Putterman of the University of California, Los Angeles, calls "the hydrogen atom of sonoluminescence."

Following up on the discovery, Putterman and his student Bradley Barber found that each light flash lasts less than 50 picoseconds (10^{-12} seconds). Another student of Putterman's, Robert Hiller, studied the spectrum of the flashes to learn that temperatures inside the bubbles must climb to tens of thousands of degrees or more. The most likely explanation for these observations seemed to be that the walls of the collapsing bubble generate an imploding shock wave that squeezes the gas and briefly pushes the temperature and pressure sky-high.

In the last 2 years, Putterman's co-workers C. C. Wu and Paul Roberts did calculations supporting this picture, leading Putterman to speculate about producing low-level fusion in the bubbles. More recently, Moss attacked the problem with a Cray supercomputer and complex computer codes that had been designed to simulate implosions in bombs. According to his calculations, for about 10 picoseconds the temperature at the center of the imploding bubbles peaks at between 100,000 and 1 million degrees and the pressure at 100 million or more times normal atmospheric pressure.

No one has directly measured conditions inside the tiny, pulsating bubbles to confirm the predictions, but researchers think they're in the right ballpark, says Larry Crum of the University of Washington. "When Moss got involved," he adds, "I thought he would shoot down the idealized calculations." Not only did Moss confirm the calculations, Crum says, but "he became excited too."

The excitement stems from both the scientific fascination of a simple system that can create such extreme conditions and the realization that the temperature and pressure in the bubbles need to be increased by a few—perhaps just one or two—orders of magnitude to fuse deuterium. That may still be a tall order, but Moss has been studying how to increase the force of the imploding shock wave by shaping the sound waves. He believes it should be possible to give the shock front an extra push by adding a "spike" to the acoustic wave. And Mike Moran, an experimentalist working with Moss, thinks he has produced sonoluminescence with bubbles containing deuterium instead of normal air.

The next step, which Moss and co-workers are already preparing to take, will be to run the experiments and watch for neutrons—the signature of a fusion reaction. That will be the real test, Putterman notes. No matter what the simulations say about what's going on inside the bubbles, he says, the only way to be sure is to see for yourself.

–Robert Pool