AIDS RESEARCH

Controversy: Is KS Really Caused By New Herpesvirus?

AIDS researchers have had few victories so far. But over the past few months, many became excited at what appeared to be a major success: the discovery of the cause of Kaposi's sarcoma (KS), a virulent, sometimes fatal tumor that afflicts as many as 20% of AIDS patients. The culprit was, it seemed, a newly discovered member of the herpesvirus family.

Three weeks ago, however, at the first-ever conference devoted to KS in AIDS,* the putative culprit took a beating from researchers who are far from convinced that the excitement is warranted. And, in an echo of the past that historians will relish, one of the most vocal critics at the meeting was the National Cancer Institute's (NCI's) Robert Gallo, whose lab has played a key role in discovering several viruses, including HIV—and who is also famous for assailing scientific theories with which he disagrees.

The finding of what has been dubbed KS-associated herpesvirus (KSHV) was but one reason the NCI finally sponsored a meeting on this riddling disease. "There's a tremendous breadth of new knowledge that has emerged over the last 12 to 18 months" in relation to KS and AIDS, said Judith Karp, a leukemia researcher at the NCI who organized the conference. NCI's Robert Yarchoan, who tests experimental KS treatments, said research in what is known as AIDS-KS "is a lot like AIDS research was in 1983–1984, when a lot of things were coming together."

One striking parallel to 1983–1984 (the period when HIV was isolated and shown to be the cause of AIDS) was the discovery late last year of evidence for KSHV by Columbia University molecular biologist Yuan Chang and epidemiologist Patrick Moore (*Science*, 16 December 1994, p. 1865). The researchers did not isolate the virus itself, but they identified DNA sequences from the novel agent in KS lesions of AIDS patients—but not in tissue from patients who did not have AIDS. Many KS researchers have long suspected that a virus other than HIV caused the disease, and they jumped on the finding, with several labs around the world since reporting similar data in several different populations (*Science*, 17 February, p. 959).

Yet just as some researchers were highly skeptical of the first reports of the discovery of the AIDS virus—NCI's Robert Gallo harshly challenged the Pasteur Institute's Luc Montagnier in a famous 1983 incident at Cold Spring Harbor Laboratory—some researchers had deep reservations about KSHV's role in KS from the start. But those misgivings had been muted—until the AIDS-KS meeting. And in a reprise of history, Gallo was at the center of the debate.

The NCI researcher, who is often referred to as "co-discoverer" of HIV along with Montagnier, has developed a leading KS lab. The Gallo lab has also become an important contributor to research involving human herpesviruses (HHVs), having discovered HHV-6, which causes roseola in infants, and made important findings about the more mysterious HHV-7. So Gallo's withering critique of KSHV packed a punch. And he alone referred to the virus as HHV-8, adding another historical echo: When HIV was discovered, Gallo called it HTLV-III because he initially argued that it was a member of the same family as HTLV-I and HTLV-II, both of which his lab had discovered.

If HHV-8 is the cause of KS, said Gallo, "this would be the most unorthodox virus in nature." Gallo noted AIDS-KS is found almost exclusively in gay men and only rarely in women or injection drug users who are infected with HIV. Yet herpesviruses are famous for spreading freely throughout populations. Gallo is also concerned because his coworkers cannot find evidence of the virus in a cell line derived from an AIDS-KS tumor they have shown can cause KS-like lesions in mice. "The problem for us is very serious," said Gallo, who argues that HIV itself might play a central role in causing KS.

Others echoed Gallo's concerns. Oncologist Parkash Gill of the University of Southern California said he has failed to find DNA sequences from KSHV in 11 KS cell lines. "At the moment, there's no proof that it's linked," said Gill. "I think the interpretation has gone beyond the data."

Other researchers, such as NCI epidemiologist Robert Biggar, were enthusiastic about the early evidence but now have doubts about the virus. "In January, I thought they had nailed it," explained Biggar. "I'm beginning to draw back." Biggar's doubt stems largely from a 27 May *Lancet* paper that describes how researchers at the University of Texas Medical Branch in Galveston found evidence of KSHV in various skin lesions—including basal and squamous cell carcinomas; premalignant actinic keratoses; and the common wart, verruca vulgaris—biopsied from four HIV-negative transplant recipients receiving immunosuppressive therapy. This evidence runs counter to the notion that KSHV is unique to KS. "Suddenly we've found the cause of all cancers," Biggar scoffed.

Yet Columbia University's Chang stuck by the data she and others have amassed that supports KSHV's role in KS. In contrast to Gallo and Gill, Chang described KS cell lines in which KSHV has been found. And she stressed that a bevy of independent labs has confirmed her work. "It's clear that there is a new herpesvirus and that it's associated with KS," said Chang.

Steven Miles of the University of California, Los Angeles, went further: He is convinced KSHV causes the disease. He maintains that the inability to find the viral DNA in some cell lines might be due to the fact that the lines have been regrown too many times, which may lead to the viral DNA sequences being cleaved out. Miles says the *Lancet* paper did not sway him because it involved few patients and could have been riddled with lab contamination. Veteran KS researcher Alvin Friedman-Kien of New York University Medical Center adds that although he also found evidence of KSHV in squamous cell carcinomas, he does "not at all" rule out the virus as somehow triggering KS.

NCI's Yarchoan and other researchers are already acting on the notion that KSHV causes the disease and have trials of the anti-herpes drug foscarnet on the drawing board (an idea Gallo lambasted as "ridiculous"). But no one at the meeting argued that attacking KSHV was the only way to go; indeed, even if the virus causes the tumor, it might simply be the first step in a cascade of events that transforms cells and causes KS lesions, so whether or not KSHV proves to be the cause of KS, there are other potential

EXPERIMENTAL AND PALLIATIVE TREATMENTS FOR KAPOSI'S SARCOMA

Systemic	Local
Interferon-α	Liquid nitrogen cryotherapy
Taxol	Excision
Human chorionic gonadotropin	Electrocauterization/laser surgery
Vinca alkyloids	Photodynamic therapy
Liposomal-encapsulated anthracyclines	Radiation therapy
Andriamycin-bleomycin-vincristine	Topical retinoids
Thalidomide	Intralesional chemotherapy
Anti-angiogenesis agents	

ALVIN FRIEDMAN-KIEN/NYU

* "Conference on AIDS-Related Kaposi's Sarcoma," sponsored by the National Cancer Institute, 5 and 6 June, Bethesda, MD.

anti-KS approaches.

One therapeutic strategy discussed at the meeting that some researchers believe is marginally effective is to attack the transformed cells with conventional cancer treatments. Another is to inhibit KS cell proliferation with inhibitors that block the action of the cytokines, immune system messengers that are believed to cause KS cells to proliferate; among the possibilities are inhibitory cytokines and the banned sleeping pill thalidomide. Gallo's lab has also promoted the use of human chorionic gonadotropin, a hormone that plays a key role in pregnancy and cures KS lesions in mouse experiments. Other potential KS drugs inhibit angiogenesis, the process by which new blood vessels are formed—blood vessels that cancer cells must have available to spread widely.

Susan Krown of the Memorial Sloan Kettering Cancer Center closed the conference by urging her colleagues "to look ahead to combining agents," even ones that don't appear promising by themselves. "I think we all need to be treatment artists to move the field forward," said Krown. And the hope is that if enough researchers make small steps forward, that might soon translate into a giant leap for people infected with HIV.

–Jon Cohen

PHYSICS

A Gentle Scheme for Unleashing Chaos

Chaotic systems behave unpredictably. So does the science of chaos, whose theories describe everything from planetary orbits to the irregular dripping of a faucet. Who could have predicted that just 5 years after learning how to summon the reliable Dr. Jekyll of periodicity from that unruly Mr. Hyde of chaos, researchers would want to reverse the process? "People have spent years trying to make chaos regular," says chaos researcher William Ditto of the Georgia Institute of Technology. "Now we are starting to see that irregularity is something good."

For certain biological behaviors, such as the electrical activity in the brain and heart, some researchers are beginning to think that chaos may be the norm. Pathological effects, they argue, including abnormal heart rhythms and epileptic seizures, could actually result from an excess of regularity. Now Ditto and his graduate student Visarath In, along with physicist Mark Spano of the Naval Surface Warfare Center in Silver Spring, Maryland, have come up with a way to restore complexity: a practical scheme for chaos "anti-control," in which precisely timed jolts make a system with a penchant for periodicity stay chaotic.

Although chaos control and anti-control have opposite goals, they are based on a common principle, spelled out in 1990 by Edward Ott, Celso Grebogi, and James Yorke of the University of Maryland. The key to mastering chaos, they determined, lies in the same quality that makes chaotic systems so hard to predict—their sensitivity to small perturbations. This sensitivity is called the "butterfly effect," after the classic example of a small perturbation that leads to big effects on the overall system: a hypothetical butterfly's wingbeat that ultimately changes a weather pattern. "If you can control the butterfly," says Ditto, "you can control the system."

That same year, Ditto and his colleagues at the Naval Surface Warfare Center first demonstrated such control in the laboratory, coaxing the chaotic vibrations of a flexible metal ribbon in a changing magnetic field into periodic states with small magnetic nudges. Chaos control has since been applied to electronic circuits, lasers, chemical reactions, and more. Then last year, Ditto and Steven Schiff, a neurologist at George Washington University, announced that they had achieved the converse: maintaining chaos in brain tissue (*Science*, 26 August 1994, p. 1174). Using precisely timed electrical shocks, they manipulated the chaotic firing of neurons in slices of rat brains—a system where Ditto thinks the loss of complexity may cause "spiking" akin to epileptic seizures—to keep it aperiodic.

Some skeptics weren't convinced Ditto and Schiff had really demonstrated anti-control, arguing that the brain tissue's behavior may not have been truly chaotic in the first place. After all, says Tim Sauer, a physicist at George Mason University in Fairfax, Virginia, the electrical shocks weren't the tiny "butterfly" nudges that should be enough to influence a chaotic system. "You can control anything if you bang it around enough," says Sauer.

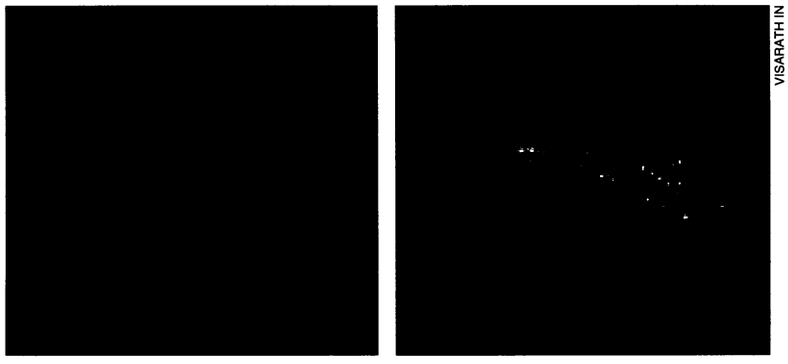
But now the blunt force of this first attempt has given way to calculation. Ditto and colleagues have returned with a general algorithm for anti-control, which they report in the 29 May issue of *Physical Review Letters*. It allows a computer to learn how to recognize signs that a system is approaching areas in its phase space called "loss regions," where it slips into periodic behavior. Researchers can then make small, precisely timed perturbations to the system, causing it to avoid the periodic traps.

Sauer, impressed by the technique, likens it to controlling a ball bouncing around a billiard table with irregular sides and a hole in the middle. The ball will follow a chaotic trajectory, but once in a while it will get stuck in the hole, which represents a loss region. By observing the table and learning to identify events that send the ball into the hole—say, a collision with a particular side at a particular angle—one can gain enough predictive power to "anti-control" the ball and keep it on its chaotic course. In this case that might entail tilting the table slightly when an encounter with the hole is imminent.

The group successfully tested their scheme on an oscillating metal ribbon that intermittently becomes trapped in periodicities. But Frank Moss, a physicist studying chaos in crayfish ganglia at the University of Missouri, says the method should also be well suited to detecting and maintaining chaos in biological systems, which are often plagued by noise and changing conditions. It doesn't demand complete knowledge of a chaotic system—its initial conditions or the differential equations describing it—just a relatively brief period of observation for finding the loss regions. And the scheme's reliance on subtle perturbations is well suited to sensitive living tissue.

All of which has researchers thinking about the therapeutic potential of chaos anti-control. "There is a large prize at the end of the tunnel," says Moss. Ditto, for one, already has his eye on that prize; he has formed a company to develop an epilepsy "pacemaker" based on anti-control techniques. "Our goal," he says, "is to take it straight to the brain."

–Antonio Regalado



VISARATH IN

Chaos resurrected. A chaotic attractor—a structure mapping chaotic behavior—shows how a system trapped in periodicity *(left)* is made chaotic again *(right)* when nudged at specific points *(circles)*. Peak height represents probability.