# Lymphoma Enigma

## AIDS-linked tumors may defy traditional views of cancer genesis

By KATHY A. FACKELMANN

For people with AIDS, survival means fighting one illness after another, as normally meek microbes slip past crippled immune defenses. And despite recent advances in treating these opportunistic infections, an increasing number of AIDS patients now find themselves battling a cancerous time bomb of mysterious origins and deadly force.

The cancer, a type of lymphoma, targets antibody-producing white cells residing in the lymph nodes and called B-lymphocytes. It can also strike people with lowered immunity who do not carry the AIDS virus (HIV), such as organ-transplant recipients taking immunosuppressive drugs. But physicians have observed that the B-cell lymphomas afflicting people with AIDS seem more aggressive than those of transplant patients, who often recover fully when taken off the drugs. In AIDS patients — who suffer chronic immunosuppression — these tumors often spread beyond the lymph nodes to the brain, bone marrow, liver and lungs.

Research described in June at the Sixth International Conference on AIDS suggests a recent surge of B-cell lymphoma cases among people with long-standing symptoms of AIDS or its precursor, AIDS-related complex (ARC). At the same conference, another team of investigators proposed that some AIDS patients may have a new form of B-cell lymphoma, which the researchers call "polyclonal." Like their "monoclonal" counterparts, these malignancies invade distant body parts and can kill the patient, but they seem to spring from many genetically distinct B-cells rather than from a single "parent" cell. The mechanisms underlying both tumor types remain unclear, but research from the same group hints that HIV itself may play an indirect role in the development of B-cell lymphoma.

Some scientists voice skepticism about claims of a polyclonal lymphoma. However, they acknowledge that the existence of such tumors, if confirmed, would force oncologists to reexamine current concepts of how cancer develops. At the same time, research into the cause of polyclonal tumors might lead to more effective treatment of B-cell lymphomas in general.

Nobody really understands why AIDS-associated cases of B-cell lymphoma have popped up with increasing frequency. Some researchers suggest the rise may reflect the lengthening life expectancies of people with AIDS or ARC as patients gain access to the antiviral drug zidovudine (AZT) and experimental drugs that block HIV replication, as well as new treatments for opportunistic infections. Many of these people are living longer than earlier AIDS patients who lacked such treatment, but each passing year boosts their risk of developing B-cell lymphoma, notes Michael McGrath of the University of California, San Francisco (UCSF).

B-cell lymphomas strike about five people per million in the general U.S. population each year, McGrath says. But at San Francisco General Hospital, nearly 2 out of 100 people with AIDS or ARC develop B-cell lymphoma annually, a rate that is about 3,000 times that seen in the general population, he says.

"There is clearly an increase in [B-cell] lymphoma that is caused by the AIDS epidemic," says Robert Yarchoan at the National Cancer Institute. In a study of 55 people with AIDS or severe ARC who were taking zidovudine, he and his colleagues found that those who lived for three years after treatment began ran a 46 percent risk of developing B-cell lymphoma. Yarchoan discussed these preliminary results at the AIDS meeting in San Francisco. A full report appeared in the Aug. 15 Annals of Internal Medicine.

Yarchoan believes the damage HIV inflicts on immune-system cells called T-lymphocytes may allow B-cell lymphomas to flourish in some people. The eight people who developed B-cell lymphoma in his study had shown fewer than 50 CD4 T-lymphocytes per cubic millimeter of blood for at least a year. In healthy people, the same amount of blood generally holds 800 to 1,200 of these white cells, which play a crucial role both in killing various cancer cells and in regulating normal B-cell activity.

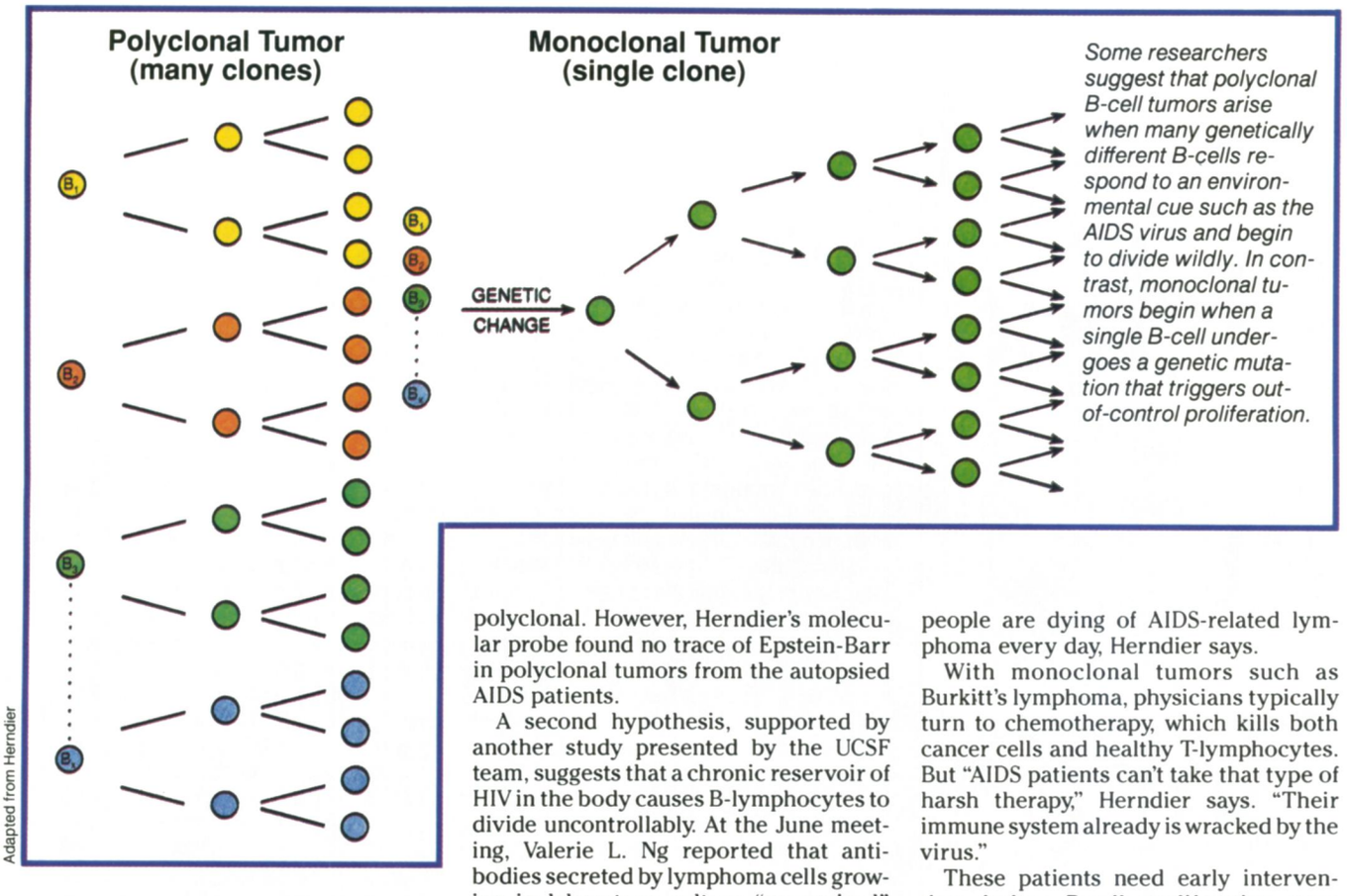
The immune system consists of a tightly orchestrated assortment of white cells, ensemble players in the body's reaction to infection. In healthy people, B-lymphocytes divide and secrete antibodies to combat microbial enemies. Responding to a cue from the T-lymphocytes, that B-cell proliferation generally subsides when the threat is over. But in HIV-infected people, the threat doesn't end. Some researchers speculate that people with AIDS may develop B-cell lymphoma because the virus persists and the regulating T-cells dwindle, leading to out-of-control B-cell division.

Evidence supporting that theory comes from data presented at the June conference by McGrath and UCSF colleague Brian Herndier, a pathologist who studied tumor tissue removed during autopsies of three people with AIDS and B-cell lymphoma. The examination showed aggressive B-cell tumors spreading to the liver, kidneys, lungs and other body sites.

Some of these were standard, monoclonal tumors, originating from one mutant B-lymphocyte that spawned progeny identical to itself. However, Herndier's molecular analysis indicated that other tumors were polyclonal, arising from multiple B-cells without any identifiable genetic flaw. Even without the mutation typical of aggressive monoclonal lymphoma, these B-cells proliferated wildly.

"The rate of growth of these tumors is spectacular," Herndier says. "You can literally see the thing grow in a day."

Elaine S. Jaffe, a pathologist at the National Cancer Institute, is among those who question whether polyclonal lymphomas exist at all. Many people with




Adapted from Herndier

AIDS show B-cell proliferation, she says, but the process is relatively benign and the cells do not invade distant tissue.

Jaffe says the very notion of a polyclonal lymphoma contradicts one of the central tenets of tumor biology. "Lymphoma or cancer is almost by definition a clonal process. It results from a genetic defect or abnormality in a single cell, which then expands, and all the progeny of that cell are identical," she says.

But the UCSF scientists think their findings may force revisions in that theory.

"You get strict definitionalists who say, 'Well, that's not really cancer,' but my argument would be that [the polyclonal tumor] behaves biologically almost identically to a monoclonal tumor," McGrath says. The polyclonal B-cell tumors identified by his team invade many body parts just as monoclonal cancers do, he says.

Calling the tumor benign won't make it go away, Herndier adds. "It's still just as likely to go on and kill the patient."

Whether or not the proposed lymphoma represents a true cancer, its underlying mechanism remains mysterious. McGrath's team offers several theories, including the idea that an as-yet-unidentified virus infects many different B-cells, causing them to divide uncontrollably. In patients taking immunosuppressive drugs during organ transplantation, scientists have linked the Epstein-Barr virus with B-cell lymphomas suspected as polyclonal. However, Herndier's molecular probe found no trace of Epstein-Barr in polyclonal tumors from the autopsied AIDS patients.

A second hypothesis, supported by another study presented by the UCSF team, suggests that a chronic reservoir of HIV in the body causes B-lymphocytes to divide uncontrollably. At the June meeting, Valerie L. Ng reported that antibodies secreted by lymphoma cells growing in laboratory culture "recognized" part of HIV's outer protein coat. The tumor cells came from an AIDS patient with Burkitt's lymphoma, an especially deadly monoclonal cancer arising from a specific B-cell mutation.

The finding hints that this patient's tumor began when many B-lymphocytes started dividing and secreting an HIV-specific antibody, Ng says. As B-cells divide over and over again, individual cells are at great risk of a genetic mutation such as the one causing Burkitt's lymphoma, she adds. Thus the army of proliferating B-cells may spawn a mutant cell that represents the genesis of a monoclonal tumor, Ng says.

Ordinarily, the proliferating B-lymphocytes form a chorus line of cells that rapidly divide to HIV's tune, Herndier explains. But when a single B-lymphocyte undergoes a genetic mutation, it may no longer need HIV to trigger its division, he speculates. In that case, uncontrollable multiplication may become an intrinsic drive, forming the genesis of a monoclonal tumor, he says.

Indeed, polyclonal tumors may represent an early stage in the process leading toward a monoclonal variety of tumor, Herndier believes. His research suggests polyclonal tumors take longer to kill patients—about eight months as opposed to three or four months for people with monoclonal tumors.

Such findings call for new treatment approaches in a high-stakes arena where people are dying of AIDS-related lymphoma every day, Herndier says.

With monoclonal tumors such as Burkitt's lymphoma, physicians typically turn to chemotherapy, which kills both cancer cells and healthy T-lymphocytes. But "AIDS patients can't take that type of harsh therapy," Herndier says. "Their immune system already is wracked by the virus."

These patients need early intervention, before B-cell proliferation runs amok and well before the unyielding monoclonal tumors can form, McGrath says. For example, if HIV itself drives B-cell proliferation, scientists might prevent tumor formation with drugs that slow or stop HIV replication, McGrath says. Another possible approach is to treat AIDS-associated lymphoma with laboratory-grown T-lymphocytes that turn off B-cell proliferation, Herndier adds.

Skeptics point out that the UCSF reports, so far based on limited data, remain very preliminary. "A true lymphoma that's polyclonal is somewhat of an unprecedented finding," Jaffe says. "I think there needs to be more documentation."

Cancer specialist Carl E. Freter at the Georgetown University Medical Center in Washington, D.C., agrees that researchers need more extensive studies to back the finding of polyclonal tumors. Still, he says, "whether polyclonal lymphomas exist is something that people have wondered and argued about for a long time. I think they probably do [exist]."

And even if the polyclonal concept withers under further scrutiny, Freter says, such basic research may have a useful side effect: helping scientists unravel the inner workings of AIDS-associated B-cell lymphomas. In turn, those inner workings may yield important clues to all B-cell lymphomas, and perhaps even to other forms of cancer. □