CANCER VIRUS REDUX

Viruses were once a hot subject of cancer research; after a decade out of the limelight, they're back again

By JOANNE SILBERNER

When the U.S. government declared its "war on cancer" in 1971, viruses were considered to be among the most likely cancer-causing agents. The National Cancer Institute (NCI) in Bethesda, Md., had a special program to screen tumor cells for the presence of virus particles, but, says current NCI head Vincent T. DeVita, "it wasn't to be that simple."

Despite expense and effort, no one was able to isolate a cancer virus from human tumor cells during that initial push; there arose "a lot of skepticism about viruses as a cause of cancer," DeVita says today. Some researchers dropped out of the field; others shifted their emphasis to basic virology research.

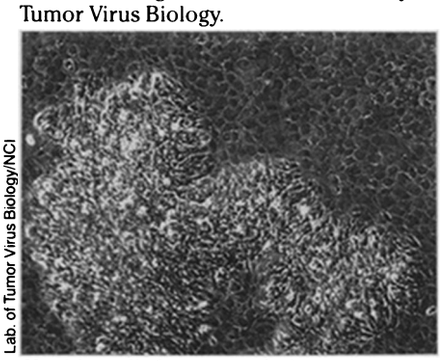
"Out of that [shift] emerged the basic ability to isolate viruses that we didn't have in the beginning," says DeVita. "We're now back in the business of finding viruses [as a] cause of cancer," he said at the recent American Cancer Society's science writers' seminar in San Diego. Researchers there described virus-cancer connections ranging from epidemiological links — coincident occurrences of a virus and a type of cancer in a given population — to direct laboratory observations of a virus transforming normal cells into cancerous ones.

Viruses have been fingered in liver cancer, the most common cancer in the world; cervical cancer; Burkitt's lymphoma; nasopharyngeal carcinoma; and an adult T cell leukemia. But researchers are quick to caution that though these cancers are believed to be caused by viruses, they don't spread as easily as common viruses spread — for example, with a sneeze. "We have not found that kind of transmission of cancer viruses," says DeVita. "You need very intimate contact to spread the viruses that we know can be spread. None of it seems to be easy, thank God."

Virus-associated cancers are more common in less developed nations, DeVita notes. Differences in hygiene may be one reason, he suggests, with individuals exposed at an earlier age, giving cancer viruses a longer time to act. The virus-associated cancers, which tend to occur earlier in life, also wind up representing a greater proportion of total cancers in these countries, possibly because people in less developed countries are more likely to die before getting the "old age" cancers like cancer of the urinary tract, bladder and gut wall.

Cervical cancer was an early candidate for a virus-caused cancer because it seems to be transmitted venereally. The most popular culprit was herpes simplex virus. But after years of failed attempts at isolating herpesviruses from cervical cancer cells, researchers discarded the herpes option in favor of the papillomavirus.

Papillomaviruses cause warts, from common skin warts to cervical and penile warts. But while warts on the hands and feet have never been known to progress to cancer, cervical warts can go on after many years to become cancerous, says Richard Schlegel of the NCI's Laboratory of Tumor Virus Biology.



Lab. of Tumor Virus Biology/NCI

Healthy cells from a cow's throat (upper right) become cancerous (lower left) when infected with a bovine papillomavirus.

The cervical warts are venereally transmitted, as the cancer appears to be — cervical cancer is associated with other venereal diseases, multiple sex partners and the early onset of sexual activity.

Schlegel and his colleagues tested cells from eight patients with cervical cancer and found that two particular members of the papillomavirus family predominated in six. The viruses were in an active state — the researchers found viral mRNA, indicating the viruses were directing protein production. When they screened cells from other types of cancer, they were unable to find the virus. One of the two viruses apparently disturbs normal cell division and in this way may lead to cancer, says Schlegel.

But the case isn't closed for the papillomaviruses. Many women with no tissue abnormalities harbor the virus in cervical cells; it could be that the virus is present in the tumor cells as an innocent passenger. "It's difficult to tell if it's a cause or latent infection," says Schlegel. In addition, human papillomaviruses have been unable to initiate cancer in either cell cultures or animal models. This may be because the right culturing techniques haven't been found, or because another agent is needed.

Cervical warts don't necessarily lead to cancer, and the virus may not prove to be the only cause of cervical cancer. "I don't think it's the sole actor," says Schlegel. "You may need either another virus or another carcinogen."

In cows, for instance, where a papillomavirus is linked to esophageal cancer, the cancer occurs only when a papilloma-infected cow eats a particular type of fern.

Since the virus seems to be venereally transmitted, are public health recommendations in order? They would be hard to formulate right now, says Schlegel. "We just don't know [the virus's] etiologic role.

"No one is willing to jump out and say if we eliminate papillomaviruses we'll eliminate cervical cancer," Schlegel says.

Another cancer linked to a virus has a clear preventive — vaccination. Hepatitis B, believed to be the villain in liver cancer, can be avoided with a currently available vaccine. Developed to stop the spread of the hepatitis-causing virus, this is the first true vaccine against cancer, say researchers.

The evidence implicating the virus in liver cancer is epidemiological — the cancer is rampant where the virus is rampant, and it occurs predominantly among people carrying the virus.

The virus, says William A. Haseltine of Harvard University, plays "from a mechanistic viewpoint, a rather obscure [role], but from an epidemiological viewpoint, an unambiguous role in the etiology of this disease."

Says DeVita, "There's very little doubt the hepatitis vaccine could wipe out hepatitis B and liver cancer." But, he notes, because people who have already been infected will remain at risk, the process will take 30 years to show an effect.

Another common cancer in less developed nations is nasopharyngeal carcinoma, believed to be caused by Epstein-Barr virus, a herpesvirus that causes mononucleosis (see sidebar). In addition, many cases of Burkitt's lymphoma, a cancer of white blood cells called B cells, have been linked to

Epstein-Barr virus. The virus is believed to act by "turning on" a cancer gene. "My personal feeling," says DeVita, "is that the Epstein-Barr virus is not a cancer virus per se but it's a motor. You put it in a B cell and it cranks away. The more you drive that motor, the greater the chance of an accident occurring."

The "accident" is a translocation — a bunch of genes moving from one chromosome to another. In the process, the lymphoma-related oncogene is "switched over [to] the control of another gene and bang—you get a cancer," says DeVita.

The list of cancers associated with Epstein-Barr virus is ever growing; in the May 16 NEW ENGLAND JOURNAL OF MEDICINE, researchers from Mt. Sinai Hospital in New York report finding the virus in cells from a cancer of the thymus gland.

Viruses have also been implicated in a seemingly new cancer — adult T cell leukemia. The virus, called human T cell lymphotropic virus-I (HTLV-I), is now endemic in southwestern Japan, the Caribbean, South and Central America, the southeastern United States and Africa. "It is estimated," says Haseltine, "that as many as 1 million Americans are infected with this virus and that this number is growing." About one of every 100 people infected with the virus will develop leukemia, he says.

As a retrovirus, HTVL-I enters the cell as RNA and is transcribed into the cell's DNA, where it takes up residence for the life of the cell. The viral link here is strong, supported by animal models, coincident occurrence of the disease and HTLV-I, the consistent ability to isolate the virus from leukemic cells and the ability to transform T cells (a type of white blood cell) in culture into leukemic cells.

HTLV-I has a peculiar way of working. Other retroviruses that cause cancer in animals either insert themselves next to a specific cellular gene and turn it on, or carry their own cancer-causing gene, says Flossie Wong-Staal of NCI. But HTLVs carry a gene that "bears no similarity to known cellular genes," she says.

What the gene apparently does is produce a protein; the protein then binds to a control portion of the normal cellular gene that encodes the growth factor receptor. Creating more growth factor receptors, notes DeVita, makes the cell very easy to stimulate.

As researchers begin to figure out how each of the viruses linked to cancer exerts its effect, it appears that there may be as many ways for viruses to initiate cancer as there are virally caused cancers — each requiring its own treatment. While this diversity complicates the picture, studying viruses' role in cancer is enabling scientists to look farther back in time, to the actual onset of the cancer process. □

Establishing a link

About 13 years ago, a baby in Texas was born without a functioning immune system. Faced with what was, back then, a fatal situation, doctors placed the boy in a completely sterile environment. They were buying time until they could figure out what to do, and beginning a unique scientific experiment.

That experiment ended last year when David, the "bubble boy," died after a gallant fight and despite the heroic efforts of his team of doctors (SN: 3/3/84, p. 133). In his death, though, he provided a clear link between Epstein-Barr virus and cancer.

It is likely that more was known about David's health history than that of anyone else who has ever lived. With no "compatible" relatives to provide him with immune-cell-producing bone marrow, David had to wait for the technology to rid donated marrow of the cells that would attack his own. After David spent 12 years in a bubble, doctors hoped the technology was ready, and the boy received treated marrow from his sister.

Eighty days after the transplant and still in a germ-free environment, David developed some of the clinical signs of mononucleosis, a condition caused by Epstein-Barr virus. As his health slipped away, doctors brought him out of isolation for easier treatment, hoping his sister's marrow cells had taken hold and would protect him from the microbes the rest of us encounter every day. Her cells hadn't established themselves, and David died about four months after the transplant.

What killed him was not the immediate failure of the transplant but cancer. His own B cells had run amok—a proliferation induced by Epstein-Barr virus. The autopsy revealed small, whitish-pink cancer nodules throughout his body, and closer study showed that these cells all contained Epstein-Barr virus—a virus he could only have gotten through his sister's bone marrow.

"We're certain [the cancer] came from the transplant itself," says William T. Shearer of Baylor College of Medicine in Houston, who was the lead physician on David's case. David had a B cell cancer of a type similar to Burkitt's lymphoma, and while Shearer can't absolutely say the two types of cancer are kicked off in the same way, "it seems likely that some of these same processes occur."

David's case has also shed light on what was until recently a serious problem for transplant recipients. People who receive hearts, kidneys or other organs are given drugs to bring them closer to the immune-suppressed state that David was born into, so they won't reject their new organs. Many of them have then been beset by cancer, most commonly lymphoma.

Baylor College of Medicine

Shearer and David in 1983.

At one time, says Jeffrey Sklar of Stanford University, who with Shearer and others authored a paper in the May 2 NEW ENGLAND JOURNAL OF MEDICINE detailing David's death, 13 percent of heart transplant patients died of lymphomas 100 to 200 days after the transplant. (With the refinement of immunosuppressive therapy, he notes, cancer following transplantation is no longer a problem.) Epstein-Barr virus had been suspected in such cases; David's case, says Sklar, "confirms our suspicions about Epstein-Barr virus being an inducer of cancer in immunosuppressed individuals."

Because of the peculiarities of David's situation, the time sequence — how quickly Epstein-Barr virus can induce cell transformation—is now known. "We can now without any doubt describe the very clear progression from infection to the development of cancer," says Shearer.

"This is a very clear demonstration of a virus causing a cancer," says Sklar. "It's also clear as to how the tumors evolved." First, David's B cells were activated by the Epstein-Barr virus, and began dividing. Then a handful of cells took hold, with some of the cancer nodules arising from single cells and others apparently arising from several different cells.

One of the requisites for proving viral transmission of a disease is to infect a test subject with the virus and see if the disease occurs. "Inadvertently this is what happened," says Sklar.

David had been germ free—there's no way he could have come into contact with Epstein-Barr virus before the transplant. "In a way you have a documented transmission of virus followed by development of tumor," says Sklar.

Says Shearer, "I think this study documents that this common virus produced this cancer." While there's a tragic human story behind the finding, it resulted in an important advance in knowledge, he says. "This will be the beginning of many studies to come."

—J. Silberner