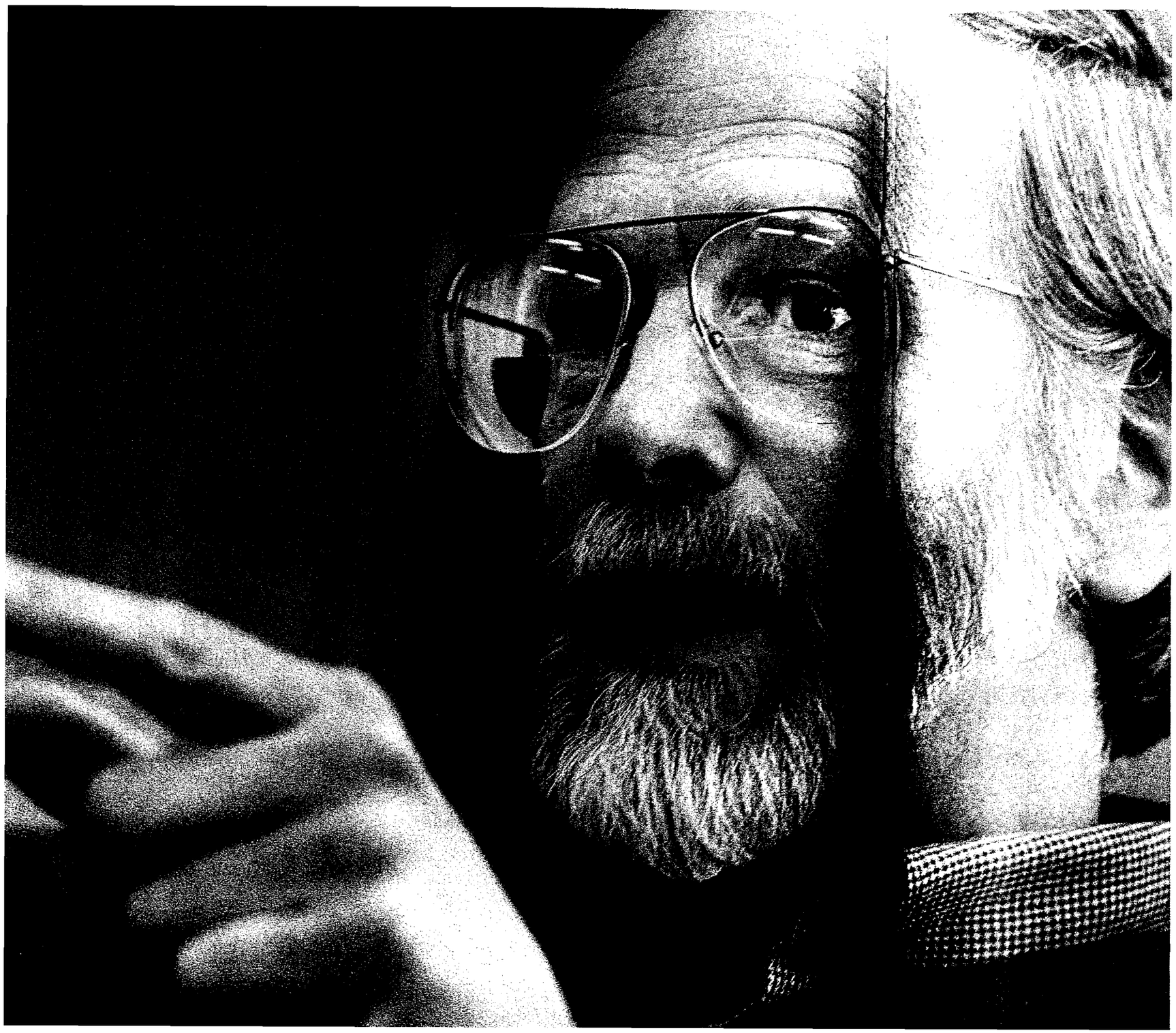
Is cancer part of our genetic dowry?



Virologist J. Michael Bishop

The most important development in cancer research within the past decade has been the concept of oncogenes, and it came from an unexpected direction—the study of viruses.

The first virus found to cause cancer was the Rous sarcoma virus, discovered by pathologist Peyton Rous in 1911 in a cancer of chickens. Few believed the finding, however, until confirmation in the 1960s set off a widespread search for viruses that could cause cancer in humans.

The search has been partially successful. Hepatitis B virus has been strongly linked with liver cancer, and scientists have shown a connection between cervical cancer and the human papilloma virus. These cancers are major world problems. Liver cancer, for example, is the most prevalent cancer in the Third World.

Thanks to the pioneering work of Hormone Research Institute director William Rutter, who was first to clone the gene for the viral coat of the hepatitis B virus, a genetically engineered human vaccine now has been developed. Unlike conventional vaccines, which can cause the disease they are trying to prevent, the synthetic vaccine mimics the shape of the virus so the body prepares to fight the real thing when it appears.

Nevertheless, researchers have been unable to establish links between viruses and most other cancers, and the general view is that most cancers are not caused by viruses.

The search, in both humans and animals, had major consequences, however. Researchers found many viruses that cause animal cancers, and one class of these—so-called retroviruses—pointed to genes in our own chromosomes that might be involved in cancer.

Retroviruses, like many other medically important viruses, carry their genetic information in the form of RNA. Unlike these other viruses, however, retroviruses also have the ability, upon infecting a cell, to transcribe their RNA to DNA and stick the DNA into the chromosomes of the invaded cell. The retroviral genes are then treated like the cell's own genes.

These retroviral genes often disrupt the host cell, either by disturbing the regulation of the cell's own genes or by bringing in a gene that runs amok. When this happens in animals, the cell sometimes turns cancerous. Usually only one of the retroviral genes, the so-called oncogene, is responsible for the damage, however.

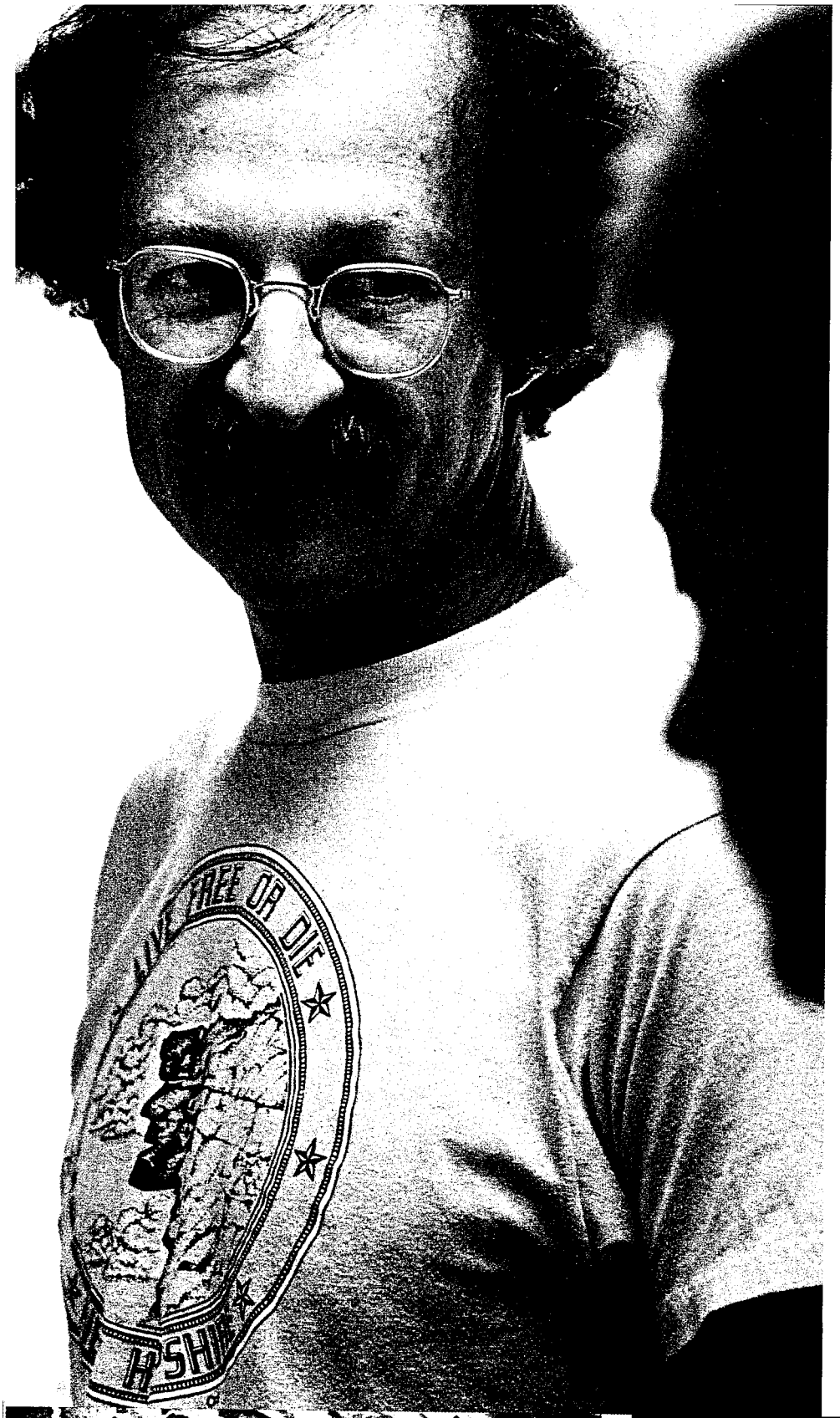
The surprise came in 1976, when UCSF virologists J. Michael Bishop and Harold Varmus searched the chromosomes of normal animals and found a gene very similar to the oncogene in the Rous sarcoma retrovirus. Because even humans had this gene, the question arose as to whether we carry the potential for cancer in our own genetic dowry.

The first human oncogene they found to have a counterpart—a "proto-oncogene"—was called *src*. Other researchers soon found genes similar to a host of other retroviral oncogenes. Today there are more than 40 known proto-oncogenes in humans, more than one-half of which were first found in retroviruses. But if retroviral oncogenes can cause cancer in animals, what do proto-oncogenes do in us? Are these the switches?

The answer appears to be yes. Studies in cell culture show that many different carcinogens can flip these switches on and turn a normal cell into a cancer cell. At least nine proto-oncogenes have been implicated in human cancers so far, and presumably damage to them sets cells on the path to malignancy.

And there are many ways proto-

Proto



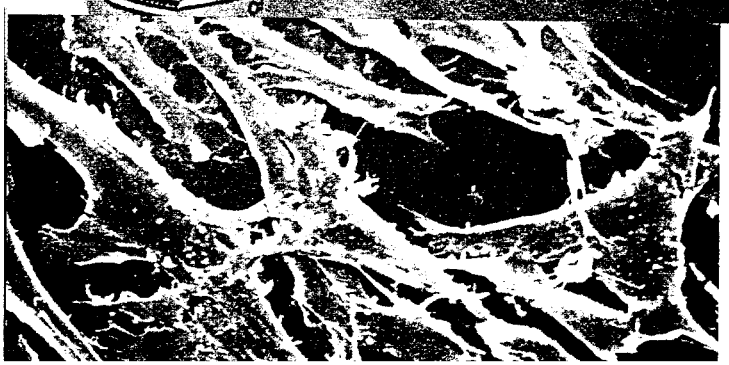
oncogenes can be damaged. A change in only one of the hundreds of nucleic acids in the gene could make it go awry. Occasionally, chromosomes break and exchange pieces, disrupting a proto-oncogene. A jumping gene can land in the middle of a proto-oncogene, or a gene that controls it, and send it out of control. And sometimes a cell will generate hundreds of copies of a proto-oncogene, presumably causing havoc by flooding the cell with the protein product of the gene.

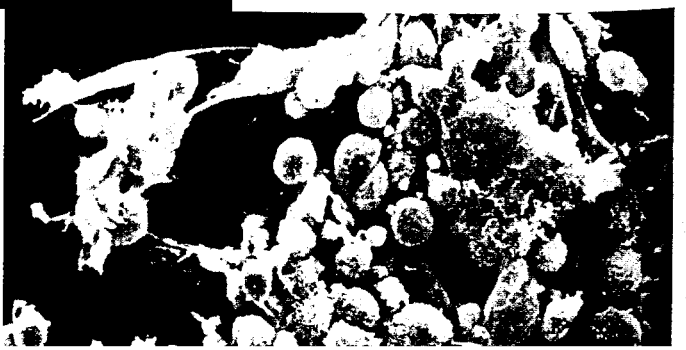
"So far the scientific community has been able to identify a mutated proto-oncogene in only 20 percent of human tumors, though I suspect nearly all will be found to have at least one," Varmus says." No one argues that this single mutation is the sole cause, but it probably has some role in the origin of each cancer.

"One of the main questions now is, 'What is the role of the proto-oncogene in the normal cell?' "

In the 11 years since Bishop and Varmus' discovery the role oncogenes play in normal—and cancerous and leukemic—cells gradually has been clarified. Research also has led to the discovery of genes called *int* that may play a role in the evolution of breast cancer.

Basic research to identify the protein progeny of specific oncogenes continues, of course. Once they have that information, scientists will be able to see more clearly how best to interrupt the cancer-causing message at its source.





Virologist Harold Varmus; normal connective-tissue cells (lower left) become round and cluster together in piles after infection by Rous sarcoma virus (lower right)

Oncogenes may be cancer switches

Since cancer is a disorder of growth, it is no surprise that researchers have found a link with growth factors. These usually small proteins which stimulate cells to divide and multiply and, in embryonic cells, to make them mature have been known since the 1950s. Since then, more than a dozen growth factors have been found, each secreted by a variety of tissues and each affecting a broad range of cells.

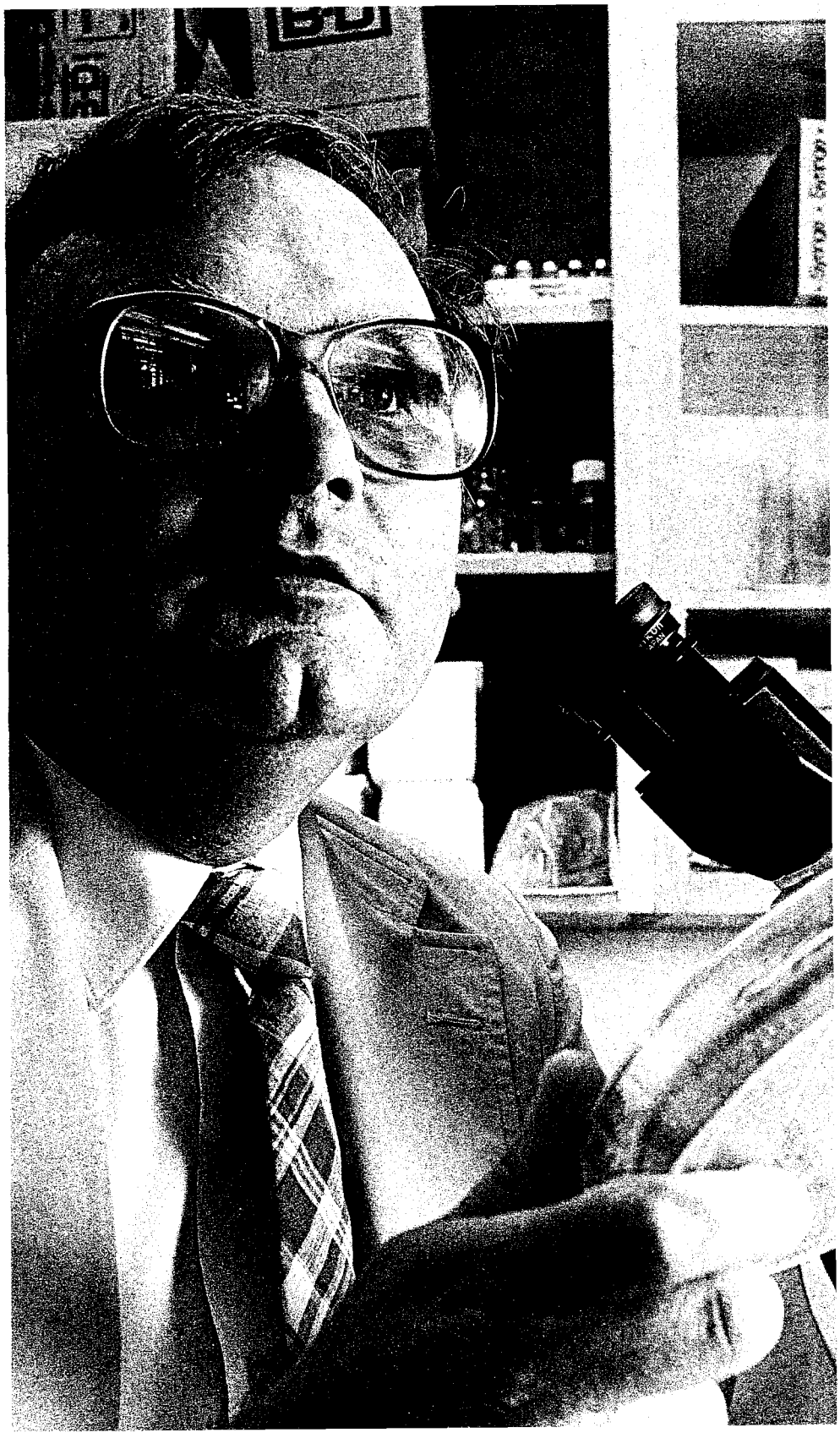
Several oncogenes already have been identified with growth factors, one of which is similar to platelet-derived growth factor, which stimulates the proliferation of cells in the walls of blood vessels. Another oncogene, which causes a tumor in chickens, is derived from a proto-oncogene that codes for the receptor for epidermal growth factor. Epidermal growth factor causes cells like skin and the lining of the lung and gut to grow and proliferate.

According to UCSF cell biologist Denis Gospodarowicz, a pioneer in the study of growth factors and the discoverer of fibroblast growth factor in 1974, there is little doubt that this also will be found to be the product of a so-far unidentified oncogene.

Given these discoveries, it is no wonder that cancer researchers are homing in on growth factors—even to the point of reversing their strategy of searching for oncogenes in viruses and, instead, testing growth factors to see whether they induce cancer when inserted into a cell.

Gospodarowicz, who was studying fibroblast growth factor long before oncogenes were recognized as being important in cancer, already has shown that it is critical not only to the growth of connective tissue cells, but also to cell growth in everything from the brain to bone.

But the substance also has been found in high levels in several fast-growing and deadly cancers, such as



Cell biologist Denis Gospodarowicz