The Biology of Cancer

Cancer is now the second leading cause of death in America; in 1972 about 345,000 Americans will die of it. Yet, it is surprising that cancer is not more widespread than it is.

Cancer is a group of complex, frequently occurring diseases that now touch every household in the nation. To bring the latest information about cancer to the various communities it serves, Caltech, in cooperation with Pasadena's Huntington Memorial Hospital, is devoting its 1971-1972 series of eight seminars in biology and medicine to the topic: The Biology of Cancer. The seminar series is sponsored by Eli Lilly and Company with assistance from the Damon Foundation.

At the first seminar held on December 7, 1971, Dr. Karl Erik Hellström, professor of pathology of the University of Washington School of Medicine in Seattle, discussed "Blocking Antibodies in Cancer."

Cancer is now the second leading cause of death in America; heart disease ranks first. In 1972, it is estimated that 345,000 Americans will die of cancer; about 32,000 of these deaths will be in California. One of every six American deaths now is due to cancer.

Yet, it is surprising that cancer is not more widespread than it is. Although cancer can occur in the most diverse types of tissue—lung, kidney, skin—all malignant growths share one characteristic: They represent tissues growing out of control. Since an adult human is made up of trillions of incredibly complex cells, and there are numerous things that could go wrong in the control of the growth of each individual cell, one would expect cancer to be even more prevalent than it is.

The prevalence of cancer is not higher, apparently, because the body has a specific anticancer surveillance and defense system—called the *immune system*—that recognizes cancer cells when they arise and destroys them. Much evidence indicates that cancers and the immune system are intimately related. Thus, when the immune systems of either experimental animals or of humans are destroyed or suppressed—by the administration of drugs or by radiation—these animals or humans then show a greater tendency to develop cancer than do animals or humans whose immune systems have not been suppressed. If the administration of immunosuppressive drugs or radiation is stopped, then the immune system recovers, returns to its normal activity, and the tendency to develop cancer decreases.

Similarly, those human patients who exhibit a strong immune response following surgical removal of a cancer show a much better survival rate than do those patients who exhibit a weak immune response following tumor removal.

So, regardless of its cause—exposure to radiation, to viruses, to cancer-producing chemicals—a cancer takes hold and spreads due to some malfunction of the body's immune system.

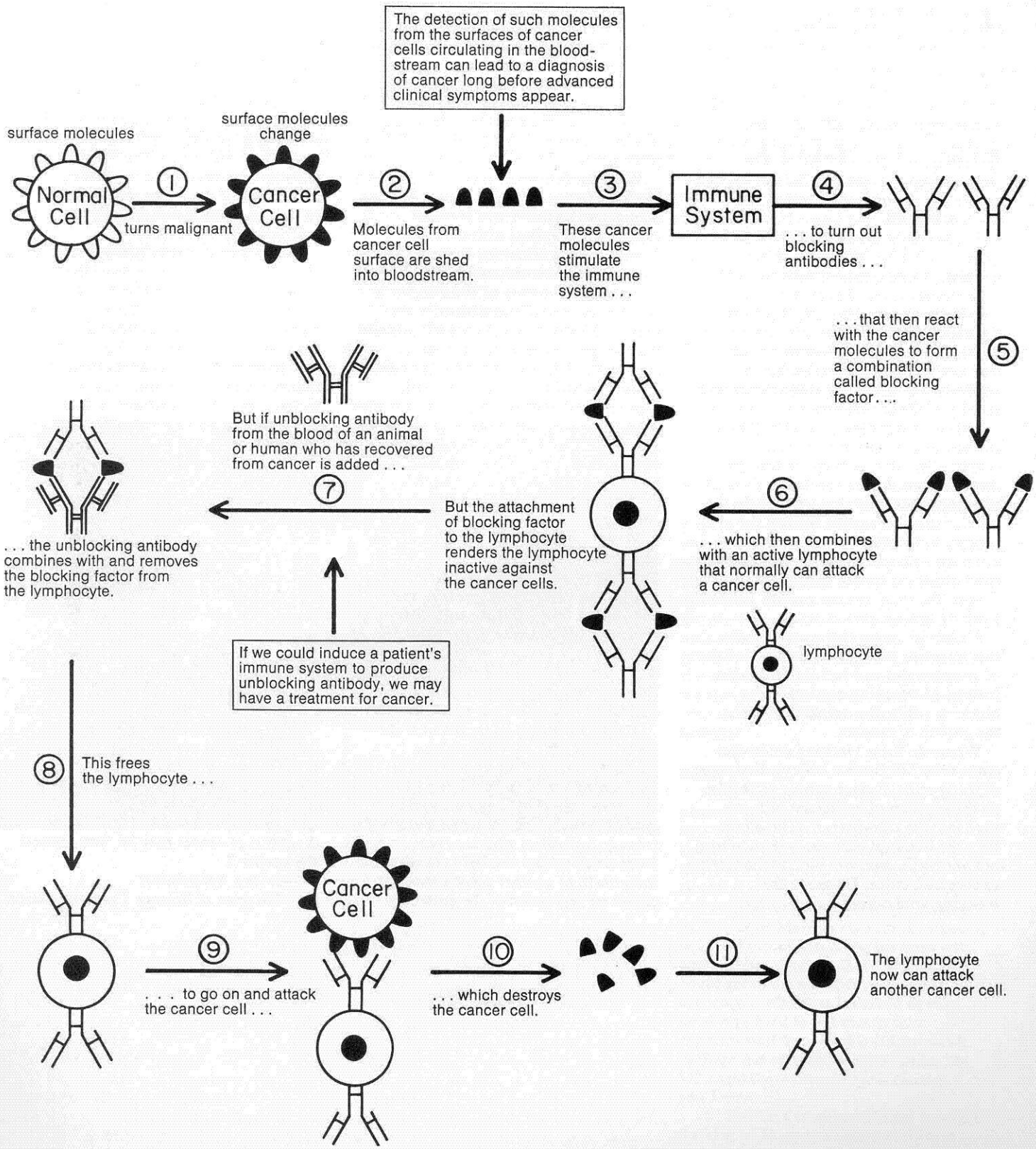
Actually, there are two immune systems. One system consists of *antibodies* that have their origin in the bone marrow or the spleen. They are produced in response to the introduction of a foreign material into the bloodstream. Antibodies are a special class of proteins that can recognize, bind to, and lead to the destruction of foreign invading materials such as bacteria, viruses, or venoms. Because these antibodies are freely circulating molecules dissolved in the fluid part of the bloodstream, this immune system is known as *humoral immunity* (*umor* meaning fluid in Latin).

The other immune system consists of antibodies attached to white blood cells called *lymphocytes*. These antibodies have their origin in the thymus, and they also can recognize foreign invading materials—particularly foreign cells—and can destroy them. Because this behavior involves attack by an antibody-lymphocyte cell combination, this immune system is called *cellular immunity*.

Cellular immunity is the body's anticancer surveillance and defense system. Lymphocytes continually patrol the body and attack and destroy cancer cells which the antibodies attached to the lymphocytes recognize as being foreign. So, even though many normal cells daily may turn into abnormal malignant cells, the lymphocytes eliminate them.

How do lymphocytes recognize the difference between the body's own normal cells—which they do not attack—and cancer cells? The surface of every cell is covered with specific molecules which serve as signals to indicate to the lymphocytes whether the cell is normal or

Cancer and the Immune System



malignant. Thus, the body's own normal cells have surface molecules that are recognized as "self" by the lymphocytes and the cells are left alone.

But, when a normal cell turns malignant, its surface becomes covered with foreign cancer molecules which serve as a specific signal to the lymphocytes that the cell is malignant. The lymphocytes, recognizing the surface of a cancer cell as "non-self," attack and destroy the cell.

Then how do cancers take hold and spread? What has happened to the lymphocytes of a patient with cancer?

In elegant research, carried out in collaboration with his wife, Ingegerd, Karl Hellström has found that the bloodstreams of experimental animals and humans bearing cancers contain an antibody that antagonizes the anticancer activity of the lymphocytes.

This is a surprising discovery. The antibodies of the humoral immune system, since they also attack foreign materials, would be expected to show an anticancer behavior that would help the cellular immune system combat the cancer. Yet, these antibodies actually interfere with and block the lymphocytes from attacking cancer cells. Thus, in cancer, the two immune systems are working against each other.

Hellström refers to these antibodies that interfere with the anticancer activity of lymphocytes as *blocking antibodies.* Instead of attacking cancers, these blocking antibodies actually *enhance* the growth of cancers.

Where do these blocking antibodies come from? Hellström believes that some of the specific, foreign cancer molecules on the surfaces of malignant cells are shed into the bloodstream. This stimulates the humoral immune system to turn out antibodies that will bind to the foreign cancer molecules. These are the blocking antibodies.

When the blocking antibodies combine with the cancer molecules, they form a union or complex that then attaches itself to the antibody attached to a lymphocyte. This prevents the lymphocyte from attacking and destroying cancer cells. The cancer-enhancing combination of blocking antibody and foreign cancer molecule is called a *blocking factor.*

When Hellström extracts and isolates a blocking factor from one cancer-bearing animal and injects it into another experimental animal with the same cancer, the growth of the cancer in the injected animal is enhanced. His laboratory at the University of Washington is now trying to purify and identify the nature of both the blocking antibody and the foreign cancer molecule that, in combination, make up a blocking factor.

But Hellström *also* finds, in both experimental animals and in humans who have recovered from cancers, that there is an antibody in their bloodstreams that opposes and reverses the action of blocking antibody. He refers to this anti-blocking antibody as *unblocking antibody.*

When injected into a cancer-bearing experimental animal or human, unblocking antibody causes the cancer to regress and often to disappear. Presumably, it acts by combining with and removing the complex of the blocking antibody and foreign cancer molecule that is attached to the lymphocyte. This liberates the lymphocyte to attack and destroy cancer cells once again.

The bloodstream of each human or animal that has recovered from a particular type of cancer contains an unblocking antibody that has a specific anticancer effect *only* against that same type of cancer. The unblocking antibody from an individual who has recovered from colon cancer can only antagonize the growth of another colon cancer; it causes no regression of the growth of lung cancer, kidney cancer, or breast cancer.

Obviously, if we knew how to stimulate the humoral immune system of a person bearing a cancer to produce cancer-destroying unblocking antibody—without at the same time producing cancer-enhancing blocking antibody—then we could have an immunotherapeutic technique to treat and cure cancer, particularly if the major mass of cancerous tissue is first removed mechanically by surgery.

But cancer immunotherapy—treatment of cancer by the stimulation of the immune system—is now a hazardous procedure. It could result in the enhancement of cancer growth rather than its regression. Obviously, we need a great deal more research in cancer immunotherapy in animals before we can use such techniques in the treatment of humans.

Although cancer immunotherapy is complex and subtle and seems to lie in the distant future, the use of the immune system to diagnose cancer is imminent.

With immunological techniques it should be relatively simple—using a blood sample taken from a patient—to detect the presence of the foreign surface molecules of cancer cells that are shed into the bloodstream. These molecules are specific for each kind of cancer. Thus, we may soon be able to diagnose whether that patient has a specific form of cancer —colon cancer, lung cancer, breast cancer—long before advanced clinical symptoms of the disease appear. Such an "early warning system" in cancer detection could markedly and favorably affect the survival rate of patients. So, although it may be many years before immune system techniques are used to treat cancer, techniques for the early diagnosis of cancer may be "just around the corner."

—*Irving Bengelsdorf*
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