CLOSING IN ON CANCER

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With exciting new genetic-engineering techniques, researchers are probing ever closer to the causes of this dread disease—and toward promising ideas for treatment and perhaps even prevention

Closing In on Cancer

Condensed from NEW YORK TIMES MAGAZINE
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TWO SUMMERS AGO, when Dr. Robert A. Weinberg was asked what causes cancer, the distinguished molecular biologist at M.I.T. could only hazard a guess—something gone awry in the genetic programming of a normal cell. Nowadays, although many questions remain, there is nothing vague about his answer. The problem has been tracked to specific snippets of DNA (deoxyribonucleic acid), the body's hereditary instructions. Dr. Weinberg can slip one of these microscopic segments into a normal animal cell, and within a day or two the cell will be transformed into a malignant mutant.

"Human cancer research is moving forward faster than anyone believed possible," says Dr. Weinberg. He and other leading investigators attribute this accelerated pace to advances in genetic engineering—the new technology that enables researchers to manipulate life's hereditary blueprint with precision.

A decade ago, scientists showed that a class of enzymes could be used to cut, move, recombine and decipher DNA.* With these "gene-splicing" or recombinant DNA techniques, scientists can now locate cancer at its source. And they have proved what they long suspected: that cancer is the result of an error in our genetic program. This genetic error appears to be inherited in some cases. Far more frequently, however, the disease seems to result from DNA damage that occurs in normal cells over the course of an individual's life. Carcinogens (cancer-causing chemi-

*See "Gene-Splicers on the Cutting Edge," Reader's Digest, September '81.

cals) and, on very rare occasions, viruses attack our DNA. As a result, the normal genes in our bodies can quickly be changed into cancer-causing agents, or oncogenes.

Tiny Triggers. Each human cell contains as many as 100,000 genes spread along six feet of tightly coiled, threadlike DNA, and each gene carries the instructions—or template—for making a single body protein. With genetic engineering's advent, this vast constellation of genes was reduced to manageable size. A suspect gene could be snipped out of a cell and implanted in bacteria, which generated exact copies of it with each cell division.

A recent study by Dr. Weinberg's group at M.I.T. found that the oncogene triggering human bladder cancer differs from its normal cellular counterpart in only one regard—a single variation in one chemical sub-unit among 6000. This tiny change is thought to be enough to turn out a distorted protein. Like an undetected malfunctioning part making its way down a factory assembly line, it is passed along the biochemical pathways of the cell, disrupting normal regulatory processes. "Once the oncogene gets going," says Dr. Weinberg, "it wreaks havoc in the cell—and the end result is cancer."

Although cancer is actually a catchall term for more than 100 diseases, scientists suspect that relatively few genes may be responsible for many cancers. Using recombinant DNA technology, they have tracked down about half a dozen human oncogenes; at least one has been implicated in cancers of both the lung and large intestine.

Looking for Locks. Researchers in cancer treatment are also using genetic engineering, but they are more concerned with the external appearance of the cancer cell. These scientists want to understand how the enemy, the cancer cell, masquerades as a normal cell, slipping past the sentinels of the immune system undetected.

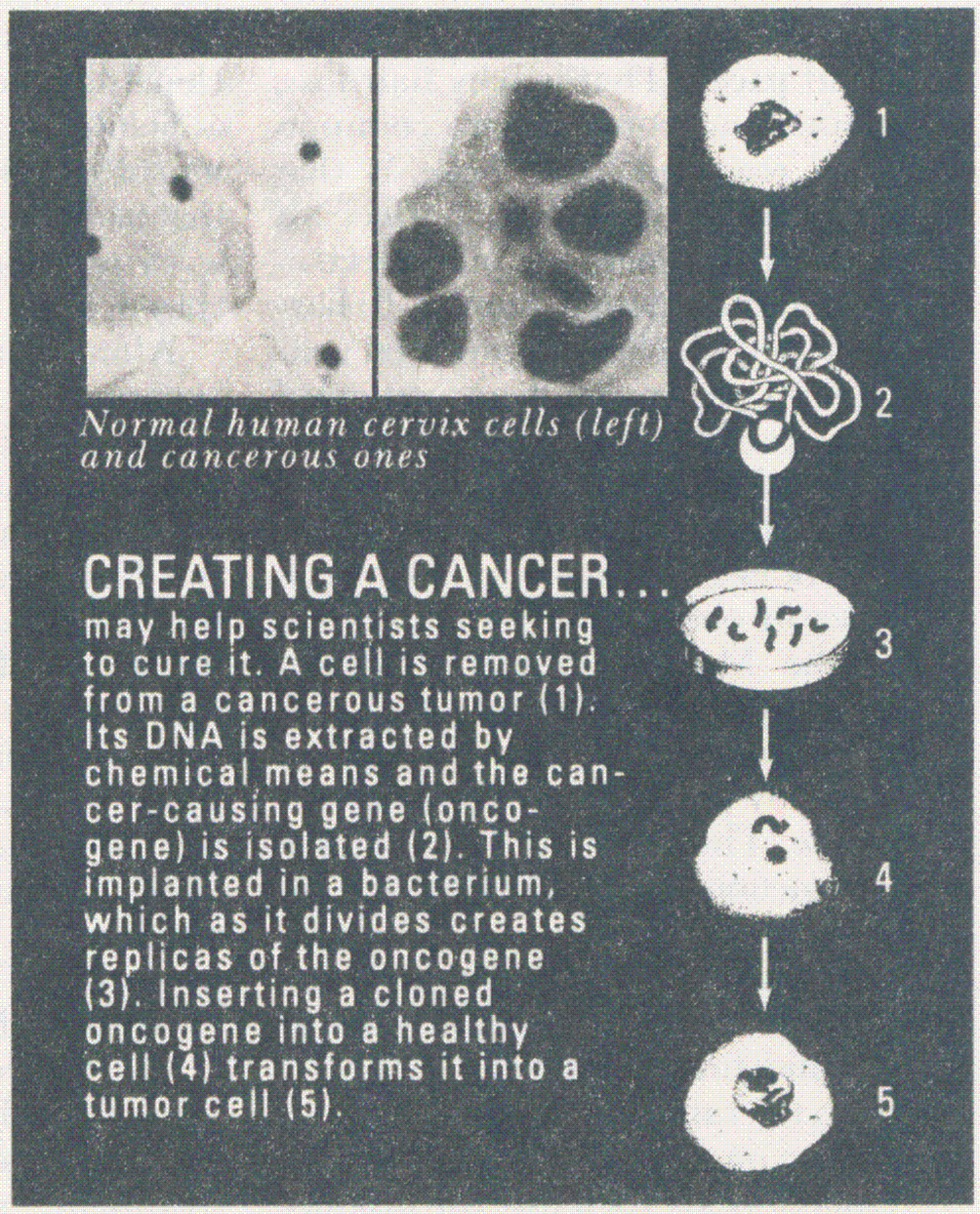
When functioning well, the immune system is capable of making subtle discriminations. The body produces certain proteins called antigens that mark the deadly cells. Thousands of antigens dot the surface of a single cancer cell. In fact, any disease-causing agent, from a virus to a bacterium, is recognized by its characteristic antigen markers. Antibodies that circulate through the bloodstream are on constant patrol for these "tags," like keys traveling around the body looking for locks. As soon as the right antigen "lock" is spotted, the antibody inserts itself into the antigen, forming a chemical bond, and in so doing the cancer cell is marked for death. The body is alerted and dispatches special killer cells and a barrage of chemical artillery to dispose of the threat.

Cancer, then, may result from a breakdown in any one of a complex chain of events. The body may not produce antibodies against tumor

antigens—or it may not deploy them in time. Alternatively, its arsenal of cell-mediated substances like interferon and other biochemical weapons may be deficient.

Anti-Tumor Factories. The new tools of molecular biology may help to identify what goes wrong—and to fix it. Researchers have already identified 50 to 100 proteins that may have anti-tumor effects and have actually located the genes that code for more than a dozen of these. If the immune system is not producing enough defensive proteins, these compounds can be made outside the body. By transferring the appropriate DNA template into bacteria, scientists can create tiny factories that mass-produce promising medicinal substances never before available for clinical study. Among these, interferon—a powerful protein that appears to improve the overall tone and functioning of the body's defense mechanisms—has until recently hogged the limelight.

Interferon, however, has increasingly been upstaged by the new trend in therapy toward greater specificity—the most outstanding property of antibodies. The body synthesizes more than a million different kinds of these molecules, and each variety seeks out only a single antigen target—leaving all other cells unaffected.



Normal human cervix cells (left) and cancerous ones

Frank J. Rauscher, Jr., senior vice president for research at the American Cancer Society, believes that antibodies—with their remarkable homing ability—may eventually allow us "to replace the shotgun approach of chemotherapy

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with a precise rifle shot." Conventional drug treatment blasts the whole body in an attempt to knock out the primary cancer tumors and any new growths. Explains Rauscher, "You also wind up killing hair follicles, gut cells and any other normal tissue that grows at a rapid pace." That is why hair loss, nausea and vomiting are common toxic reactions. The hope is that antibodies will score a perfect hit every time—without side effects.

Miniature Smart Bombs. To harness these biochemical missiles, generations of researchers struggled unsuccessfully to purify them from blood. Now, thanks to cell-fusion technology—another variation of genetic engineering—antibodies can be easily obtained. In 1975, scientists at the Medical Research Council in Cambridge, England, succeeded in fusing a myeloma cell with an antibody-producing white blood corpuscle. The resulting hybridoma (a contraction of hybrid-myeloma) inherited the ability to manufacture one specific antibody from the white-cell parent and the ability to proliferate indefinitely outside the body from the cancer side of the family. It will go on dividing forever, making exact clones of itself that will produce one extraordinarily pure type of antibody, known as monoclonal.

Early clinical trials with monoclonal antibodies have sought to establish safe dosage levels. Though antibodies are also available for therapeutic testing, only a limited number of patients are being accepted into experimental programs. Even these are not always helped.

Yet in one instance results were dramatic. Last March the *New England Journal of Medicine* published the case history of one of the first cancer patients treated with monoclonal antibodies. A 67-year-old man at Stanford University Medical Center suffered from a rare malignancy that had raged through his lymphatic system, spreading to his liver, spleen, bone marrow and blood.

After six months of painstaking experiments, a team headed by Dr. Ronald Levy developed a variety of antibody that would normally be effective against this unusual cancer. Halfway through the patient's four-week-long treatment of eight injections, the fever and chronic night sweats that characterize lymphoma vanished. "Over the next three weeks," the clinicians reported, "the patient's enlarged lymph nodes gradually became smaller, and his liver and spleen returned to normal size." Nearly two years later, without further therapy of any kind, he remains disease-free. "We're on the threshold of developing a whole new form of cancer treatment," says Dr. Ivor Royston, a cancer researcher at the University of California at San Diego.

In many animal studies, best results are achieved with antibodies that are chemically attached to toxic drugs. It is hoped that these "poison-tagged" antibodies will act as miniature smart bombs, delivering

their lethal payload to the diseased tissue—and nowhere else.

Tracer Tools. When many cancers reach the advanced stage, nothing works better than surgery or radiation to reduce the sheer bulk of the tumor mass. The problem is the few stray cancer cells that escape such measures—for even this small foothold is sufficient to launch a new offensive as the cancer cells divide and multiply. Many researchers believe that this is where poison-tagged antibodies will play an invaluable role—killing the cancer cells left behind by conventional treatments.

In a recent study conducted by Drs. Jonathan Uhr, Ellen Vitetta and Keith Krolick at the University of Texas Health Science Center in Dallas, leukemic mice were treated with radiation. Then monoclonal antibodies chemically attached to ricin (a potent toxin extracted from castor beans) were injected to finish the job. Treatment did not begin until a quarter of the animal's body weight was tumor. Yet all 38 mice went into remission, and after six months half remained disease-free. In contrast, all the animals that received radiation alone died within four to six weeks.

Both before and after treatment, the question of metastasis—the spreading of cancer cells to distant locations within the body—remains crucial. Monoclonal antibodies may be able to serve additionally as powerful diagnostic tools that allow the exact size and location of these treacherous growths to be mapped.

One of the first experiments in this area was undertaken in 1981 at the University Hospital of Lausanne in Switzerland. A colon-cancer patient was injected with monoclonal antibodies tagged with trace amounts of a radioactive chemical. They circulated through his body, attaching to malignant cells. When the patient was placed under a scanner 24 hours later, the cancerous growths appeared as bright patches on a screen. For the first time, it was possible to get a clear look at the full extent of his disease. In this way, many cancers may eventually be detected during routine checkups at the doctor's office—long before a single symptom has appeared.

All-Purpose Vaccine. The ultimate victory, of course, would be to banish cancer forever through vaccination. This may sound farfetched but, according to the American Cancer Society's Rauscher, it "is not Buck Rogers stuff."

The technique of vaccination has been modified only slightly in the last century. A dead or inactivated strain of a disease-producing virus or bacterium is injected into the bloodstream. In response, the body generates protective antibodies. Today, we know the whole disease-causing agent is not needed to stimulate immunity; the antigens that normally cling to its surface will suffice. The key question is whether this approach would trig-

ger solid, long-lasting immunity.

More than 15 years ago, a young George Washington University scientist named Ariel Hollinshead determined to find out. After injecting hamsters with antigens extracted from cancer-cell membranes, she learned that the animals were able to fight off implanted tumors. She began to suspect that cancer could be prevented just like viral or bacterial infections.

By 1973 she was ready to undertake the first clinical trials of antigens with her colleague Thomas H. M. Stewart, a physician at the University of Ottawa Medical Center. They selected 52 patients who had recently undergone lung-cancer surgery. After five years, the survival rate among those who had received the antigens was 78 percent; for those who had not, 46 percent. After seven years, the difference was even more pronounced: 78 percent versus 18 percent.

So far, antigens have been administered only after the onset of cancer. Dr. Hollinshead believes the results might be greatly enhanced if the same procedure were applied earlier, as a preventive step in healthy individuals. Her most ambitious plan yet is to protect high-risk populations against cancer. For example, she expects soon (with Food and Drug Administration approval) to immunize a group of heavy smokers at a San Francisco shipyard, where they are exposed to asbestos. "In the future," says Dr. Hollinshead, "cells could be programmed to produce a single anti-cancer vaccine"—one potent injection to protect against many varieties of the disease.

Break With the Past. For now, even the most optimistic investigators agree that genetic engineering, as a technique for treating cancer, remains in the earliest stages of research. None of the scientists working in these areas would deny that expanded clinical trials must be conducted over many years before definitive conclusions can be reached.

Nonetheless, genetic engineering is seen as perhaps the most important advance since the government declared war on cancer 11 years ago. Until now, scientists have approached the disease with the brute-force tactics of surgery, radiation and chemotherapy. And the experience has often been like that of an outside power trying to wage conventional warfare against guerrillas: no matter how many troops and arms are imported, it is impossible to win.

Today's new immunological strategies, if they succeed, will represent a break with everything that has come before. For in principle they work with, rather than against, the body, augmenting its own defense network. It may be that the weaponry needed to fight off cancer has always been close at hand. But until genetic engineering arrived, there was no way to mobilize the powerful natural forces contained within us.