THE GENETIC ASSAULT ON CANCER

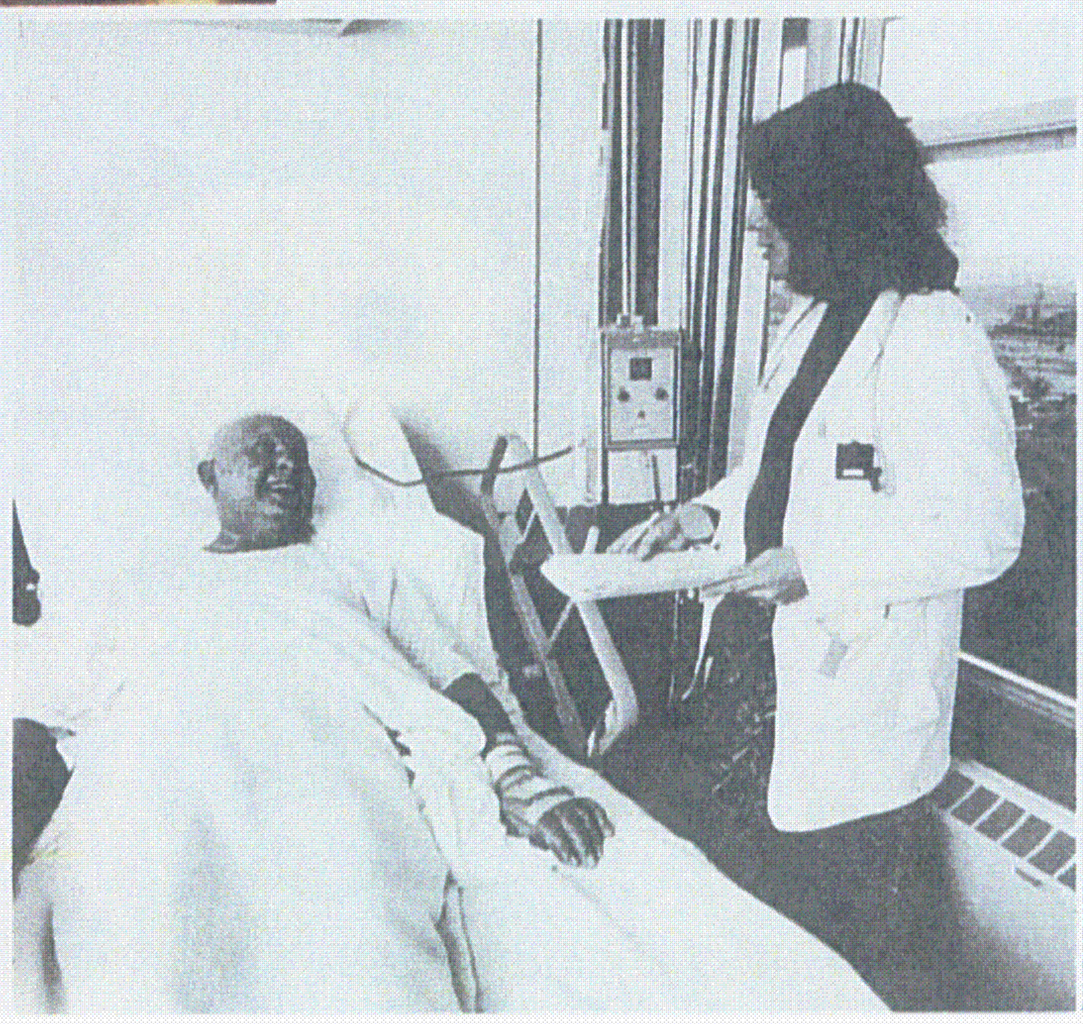
The innovative technology of genetic engineering is providing cancer researchers with new tools to probe the deep-seated causes of the elusive disease, and with new ideas, which are promising but still very experimental, about how to treat it.

By Sharon McAuliffe and Kathleen McAuliffe

Two summers ago, when Robert A. Weinberg was asked what causes cancer, the distinguished molecular biologist at the Massachusetts Institute of Technology could only hazard a guess: Something gone awry in the genetic programming of a normal cell might cause that cell to proliferate out of control. If you pressed him to describe what that "something" might be, he shrugged.

Nowadays, although many questions remain, there is nothing vague or speculative about Dr. Weinberg's answer. The problem has been tracked down to specific snippets of DNA (deoxyribonucleic acid), the body's hereditary instructions. Dr. Weinberg can slip one of these microscopic segments, only one gene in length, into a normal animal cell, and within a day or two the cell will be transformed into a malignant mutant.

"Human cancer research is now moving forward faster than anyone believed possible," says Dr. Weinberg. He and other leading investigators attribute this accelerated pace of discovery to advances in the burgeoning field of genetic engineering — the new technology that enables scientists to manipulate with ease and precision the underlying hereditary blueprint of life.



DAVID SCHARF

A decade ago, scientists showed that a class of enzymes (proteins that catalyze biochemical reactions) could be used to cut, move, recombine and decipher DNA. Since then, these "gene-splicing" or recombinant DNA techniques have opened up a new era in cancer research. Not only can scientists now locate the disease at its source, but they have been able to identify internal defenses that can be manufactured outside the body and used in the fight against cancer. One among many of these substances is interferon, a body protein that was widely touted in the media — prematurely — as a "miracle" cancer treatment. In addition, there is the possibility that there may someday be vaccines prepared through these methods to prevent a number of cancers before they occur. "We're on the

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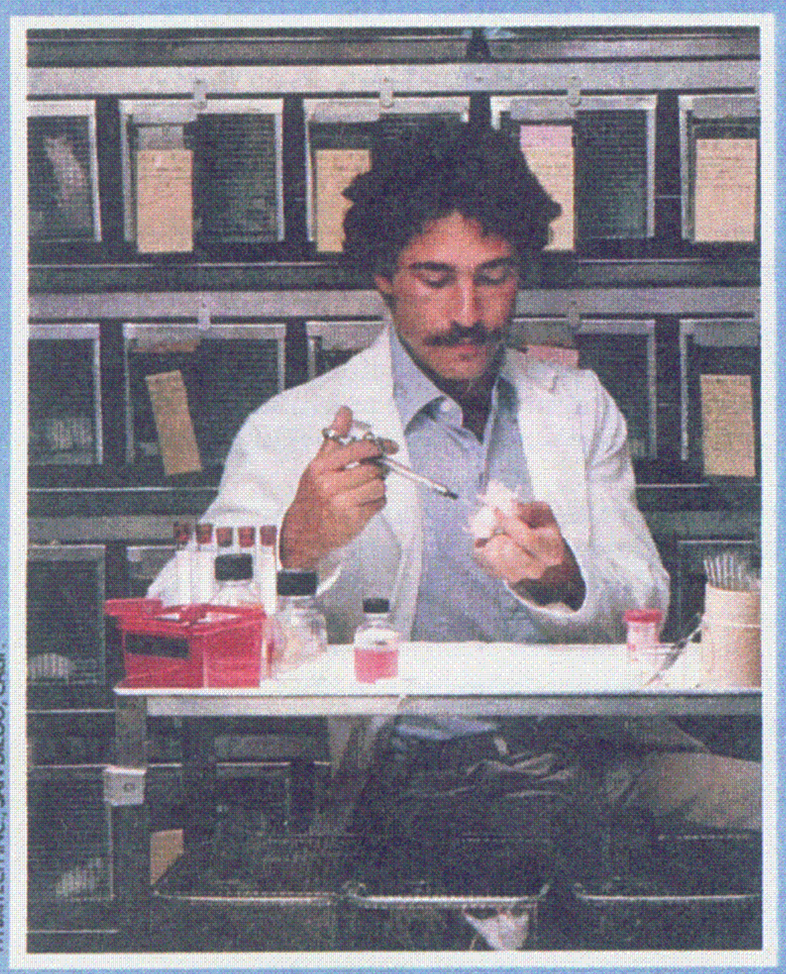
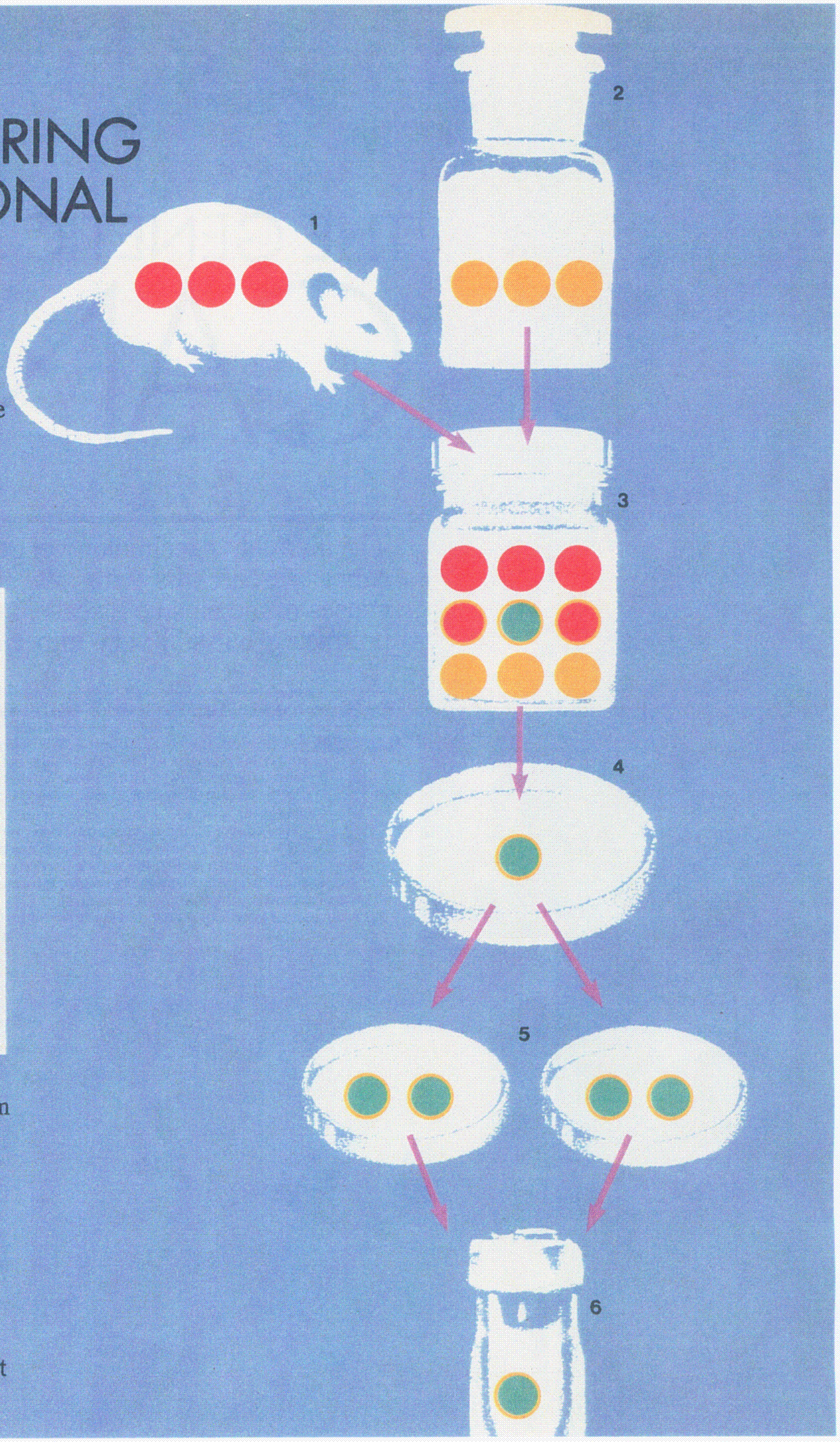
MANUFACTURING A MONOCLONAL ANTIBODY

In order to synthesize the substance that scientists hope may one day prove effective against cancer, researchers use a genetic-engineering technique called 'cell fusion.' A mouse is injected (below) with a cancer-related protein that makes the animal's white blood cells produce antibodies to fight the



HYBRITECH INC., SAN DIEGO, CALIF.

disease. White blood cells containing these antibodies are then extracted from the mouse (1, in the accompanying chart). Next, cancer cells (2) are mixed and chemically fused with the blood cells (3). The resulting hybrid cell, called a 'hybridoma' (4), inherits from the blood cell the capacity to produce a cancer-fighting antibody and from the cancer cell the ability to proliferate indefinitely. The hybridoma continues to divide (5), making clones of itself that can be used to produce monoclonal antibodies in volume (6).



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 (U.C.S.D.).

But along with the enthusiasm inspired by genetic engineering comes a note of caution. Dr. David Baltimore won a Nobel Prize in 1975 for discovering an enzyme that made genetic engineering possible. "As long as I have been in science, there has been some form of new experimentation in treating cancer, and a lot of good things have been done," says Dr. Baltimore, who is an American Cancer Society Professor of Microbiology at M.I.T. "But the cancer cell has more up its sleeve than most people give it credit for. I don't see us solving these problems in the short run." Research into utilizing this new technique for treating cancer is still in its earliest possible stages. None of the scientists working in these areas would deny that expanded, long-term clinical trials must be conducted over the course of many years before any definitive conclusions can be reached.

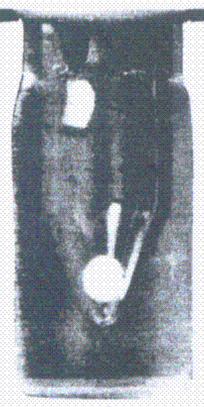
Nonetheless, many scientists see genetic engineering as one of the most important advances since the Government declared war on cancer 11 years ago. According to Dr. Frank J. Rauscher Jr., senior vice president for research at the American Cancer Society and former head of the National Cancer Institute (N.C.I.) in Bethesda, Md., no other scientific tool has such versatile potential applications in treatment, prevention and basic research aimed at unearthing the disease's deep-rooted causes.

In their efforts to trace cancer to its source, researchers began to dissect our genetic machinery, and before long they uncovered one of nature's strangest paradoxes: Normal cellular genes within our bodies can quickly be changed into cancer-causing agents, known as oncogenes. Under ordinary circumstances, they lie peacefully in our cells. Yet exposure to carcinogens (cancer-causing chemicals) and sometimes certain viruses can damage one of these genes, bringing on the unrestrained and often deadly cancer.

We all carry within us the seeds of destruction: Oncogenes appear to be normal genes that have been harmed during an individual's lifetime. At the same time, however, myriad other genes function to prevent this disease by directing the cell to produce defensive biochemicals. Thanks to genetic engineering, these natural anticancer drugs have become accessible for detailed study and further testing.

A human cell contains as many as 100,000 genes spread along the thin, chainlike DNA molecule; each carries the instructions — or template — for the manufacture of a single body protein. It is through the production of these biochemicals that genes actually function. Although it now appears that some of these proteins are involved in cancer, there is also a group of immune proteins that enhance our ability to ward off illness by identifying characteristic markers that lie on the outside of any damaged or diseased cells. Indeed, researchers at the National Institutes of Health in Bethesda, and elsewhere have already identified 50 to 100 proteins that may have antitumor 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 or if it malfunctions in some other way, these compounds can be made outside the body. By transfering the appropriate DNA template into bacteria, scientists can create tiny factories that mass-produce promising medicinal substances never before available for clinical study.

In January 1980, scientists announced that bacteria had been engineered to produce human interferon. This potent protein seems to shrink certain malignant tumors by generally activating elements of the immune system — the body's network of defense against disease. Within the oncology, or cancer-research, community, however, interferon has been increasingly upstaged by antibodies. This



Scientists hope that artifically produced antibodies will complement conventional treatments such as radiation and chemotherapy, destroying the stray cancer cells such treatments often leave behind.

family of proteins makes up the body's first and most powerful line of defense against disease. These antibodies seek out and destroy foreign invaders and malignant growths that attack from within. To harness these biochemical missiles, generations of researchers struggled unsuccessfully to purify them from blood. Now, like interferon, they can be easily obtained from genetically altered cells grown in the laboratory.

Last March, the New England Journal of Medicine published the case history of one of the first cancer patients treated with antibodies from this new source. 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 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; his liver and spleen returned to normal size, [and] the tumors on his scalp disappeared." Nearly a year and a half later, without further therapy of any kind, he remains disease-free.

Doctors are especially wary of generalizing from a single case. It will take five to 10 years to determine the efficacy of this treatment, and no one wants to raise false hopes or expectations. "Progress may actually be fast from a research perspective," says Dr. Robert K. Oldham, the director of the Biological Response Modifiers Program, which encompasses both interferon and antibody studies at the National Cancer Institute. "Unfortunately, this is going to be of little consolation to the cancer patient whose life is being measured in weeks or months and who is searching for help today."

At this point, however, many experts share a growing belief that if antibodies can be perfectly matched to the many different forms of cancer, medicine may then have "magic bullets" that can slay the diseased tissue while leaving the rest of the body in peace. "Someday," says Dr. Royston of U.C.S.D., "people may look back at conventional chemotherapy and say, 'My God, they used to poison the entire body to kill off malignant cells!' "

Still other scientists are searching for treatments that would actually prevent cancer. Within the next several months, a George Washington University oncologist will vaccinate a high-risk population in an attempt to immunize them against lung cancer. Once again, genetic engineering is at the center of this work.

Only in the last four years have scientists proved what they have long suspected: that cancer is the result of an error in our hereditary program. A single cell suddenly begins to divide at a faster-than-normal clip, eventually forming a tumor mass. Soon, mutant cells may break off to form new colonies in distant locations and, in time, choke the very body that gave them life. It is as if the malignant cells have returned to a primitive embryonic state characterized by rapid cell division.

In some cases, this genetic error appears to be inherited. Far more frequently, however, the disease seems to be the result of DNA damage that occurs over the course of an individual's life. For example, carcinogens are chemicals that attack our DNA. And on very rare occasions (less than 5 percent of the time), human cancers are thought to be caused by viruses that insinuate themselves into the genetic machinery of cells.

By the early 1970's, all the circumstantial evidence pointed to damaged genes. Yet, recalls Dr. Rauscher, "there was no way to isolate individual genes or determine their expression. When we are babies, our genes make all kinds of products. And when the job is done — when our tissues are fully developed — a number of them are switched off. Later on in life, it appears that some of those genes may be turned on again to cause cancer — in one of four of us, it seems. Why? What happens? Is it the automobile exhaust on Third Avenue? Is it asbestos? Is it a virus? We couldn't even ask those questions before we had the power to excise genes."

Researchers were restricted to what Dr. Edward M. Scolnick, a tumor virologist at the Merck, Sharp & Dohme Research Laboratories near Philadelphia, calls "black-box" science: "We could dump chemicals onto cells to see if they caused cancer, and test drugs to see if they would kill tumors," says Dr. Scolnick, who recently left the National Cancer Institute, "but there was no way to understand what was going on at the level of the gene. We didn't have the tools to attack the fundamental question of transformation — how a normal cell becomes malignant."

Each human cell contains six feet of tightly coiled, threadlike DNA. In fact, if all the DNA in the human body were laid end to end, it would stretch from here to the sun and back 400 times. With the advent of genetic engineering, this vast constellation of genes was reduced to manageable size. For the first time, a suspect gene could be snipped out of a cell and implanted in bacteria, which can generate an exact copy of it with each cell division. (See diagram on page 43.) Within a few days, scientists could easily obtain a milligram of a human gene and plenty of its protein product. "Overnight," says Dr. Scolnick, "we were able to take a huge jump forward, replacing the witchcraft of cancer-biology research with a rational, scientifically based approach."

Cancer is not one disease; it is a catchall term for more than 100. Lung, breast and other tumors all come in a number of different forms that vary in their ability to spread, the ease with which they are spotted by the body's immune system and their responsiveness to different treatments. Scientists suspect, however, that relatively few genes may be responsible for many cancers. Using recombinant DNA technology, teams from M.I.T., Harvard University's Sidney Farber Cancer Institute, Cold Spring Harbor Laboratory on Long Island and N.C.I. have tracked down about half a dozen human oncogenes, and at least one has already been implicated in both cancers of the lung and large intestine.

Normal cellular genes that can become oncogenes have also been found in the DNA of fish, birds and even the lowly fruit fly, which suggests that

they existed in a common ancestor early in evolutionary history — perhaps as long as a billion years ago. And since only vital genetic information is kept over time, they are probably crucial to the well-being of the species in which they persist.

The trouble arises when the gene or its regulatory mechanism is altered. A recent study by Dr. Weinberg's group at M.I.T. found that the oncogene that triggers human bladder cancer, for example, differs from its normal cellular counterpart in only one regard: There is just a single variation in one chemical subunit among 6,000. This tiny change, however, is thought to be enough to turn out a distorted protein. And like an undetected malfunctioning part that makes 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."

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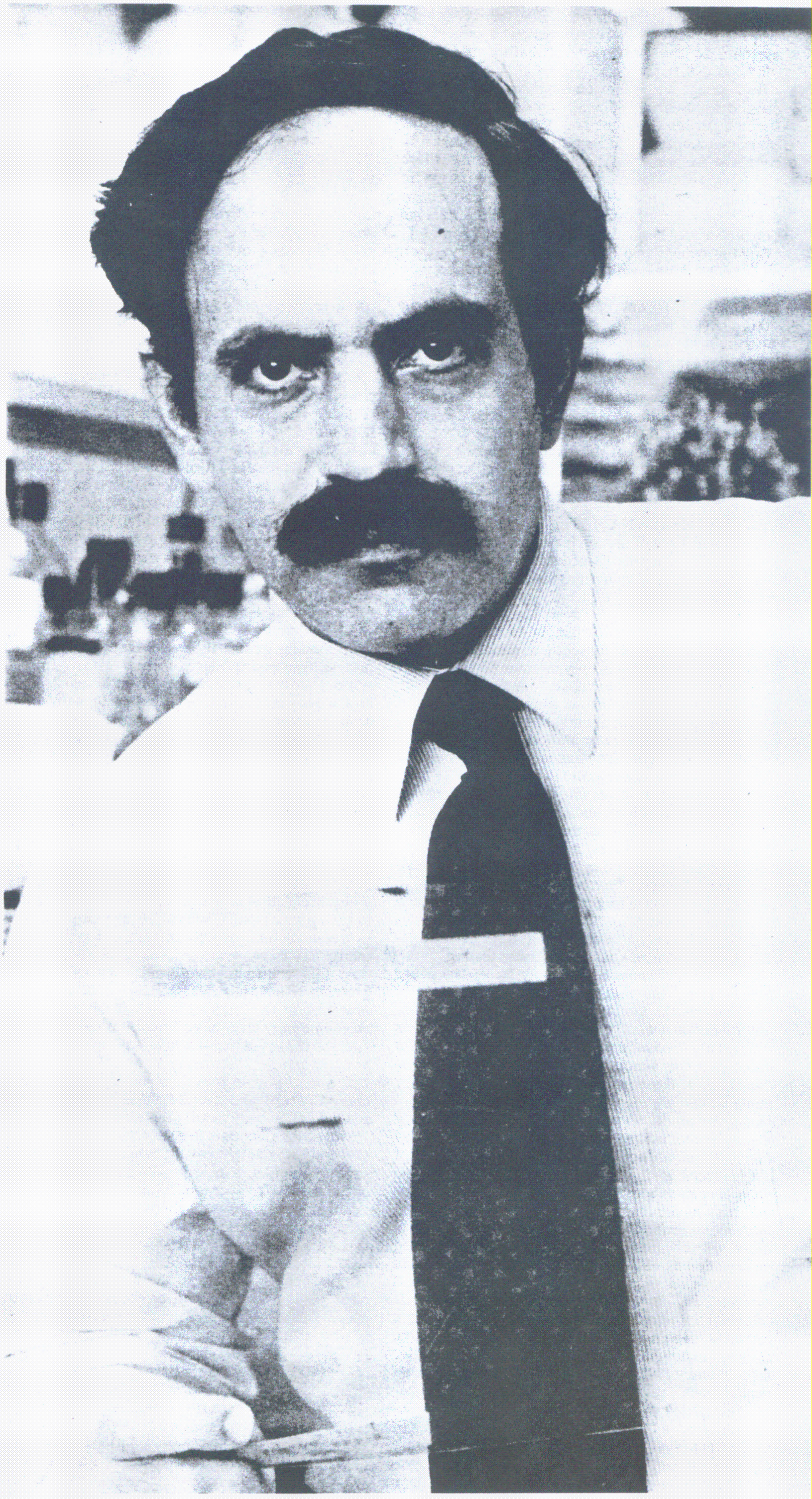
Scientists in the field of cancer treatment are also using genetic engineering, but they are more concerned with the external appearance of the cancer cell than with its internal makeup. These researchers want to understand how the enemy masquerades as normal, slipping past the sentinels of the immune system undetected. This mystery is baffling, since even the untrained eye can readily spot the difference between normal and cancerous tissue. Under the microscope, healthy cells appear exquisitely chiseled. Like Roman columns, they

TERRY COCKERHAM

Dr. Ellen Vitetta at the University of Texas is testing the effects of monoclonal antibodies on leukemic mice.

form neat, orderly rows with a distinctive architecture. A malignancy, on the other hand, is composed of lumpy, malformed cells that haphazardly clump together. Why, then, doesn't the body recognize that something has gone terribly awry?

No one is sure why we seem able to outwit cancer cells much of the time and then, on a single, crucial occasion, have our bodies fail us. Part of the problem appears to be that a malignancy — in direct contrast to a microbial invader — is descended from normal tissue. Despite its ugly appearance and unruly conduct, the cancerous growth shares many physical traits with the healthy cells that surround it, and thus it may be successfully camou-



A WYMAN

When functioning well, however, 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 a key traveling around the body looking for a lock. 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 quickly 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 interferon and other biochemical weapons may be deficient. But the new tools of molecular biology may help to identify what goes wrong — and to fix it. Since the chemical components of our defense system are manufactured from genetic templates, these natural drugs can be artificially produced in specially engineered cells. This means that medical researchers can begin to test their therapeutic effects and deduce where the immune system malfunctions.

According to Dr. Oldham of the National Cancer Institute, the body may produce literally hundreds of substances with antitumor effects. Until very recently, however, interferon seemed to hog the scientific limelight. Like a multipurpose tonic, this powerful protein appears to improve the overall tone and functioning of the body's defense mechanisms. Interferon has not yet lived up to its advance billing as the "new wonder drug against cancer." Nonetheless, it has shrunk tumors markedly in about 25 percent of patients with lymphoma and multiple myeloma (a cancer of the blood-forming tissue) and has worked to a lesser degree against cancers of the breast, ovary, prostate, colon and cervix. At present, its performance is no better than that of conventional therapies, but scientists are hopeful that this will improve as research continues.

The new trend in therapy, however, is 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. Their remarkable homing ability can readily be demonstrated in the controlled environment of a test tube: Antibodies will zero in on every single cancer cell but leave all other cells unaffected. N.C.I. considers the properties of antibodies so promising that it has commited close to one-fourth of the $18 million to $20 million annually allotted to its Biological Response Modifiers Program for their study — a distinct shift from its original emphasis on interferon research.

Studying bladder cancer at M.I.T., Dr. Robert Wein-

Dr. Rauscher of the American Cancer Society believes that antibodies may eventually allow us "to replace the shotgun approach of chemotherapy with a precise rifle shot." Conventional drug treatment blasts the whole body in an attempt to knock out the primary tumors and any new growths. "In the process," explains Dr. 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. Morever, this blunt approach is relatively ineffective against slow-growing solid tumors or those in temporary resting state. In contrast, some scientists hope that antibodies will score a perfect hit every time — and without any side effects.

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Until 1975, there was no way to obtain large quantities of antibodies for therapeutic use. It was then that cell-fusion technology — another variation of genetic engineering — opened up a new route outside the human or animal body for the production of antibodies. Cell fusion mates the unmatable: By chemically dissolving the cells' outer membranes, scientists have merged the entire contents of two cells from different organisms.

This new method of mixing genes is less precise than recombinant DNA technology, but as Cesar Milstein and Georges Köhler discovered in their work at the Medical Research Council in Cambridge, England, it can be more effective in reaching certain goals. They succeeded in fusing a cancerous myeloma cell with an antibody-producing white blood corpuscle. (See diagram on page 40.) 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. This hybridoma begins to divide and will go on dividing forever, making exact copies or clones of itself that will produce one extraordinarily pure type of antibody, known as a monoclonal. In an ironic twist, scientists have created man-made tumors to "fight fire with fire."

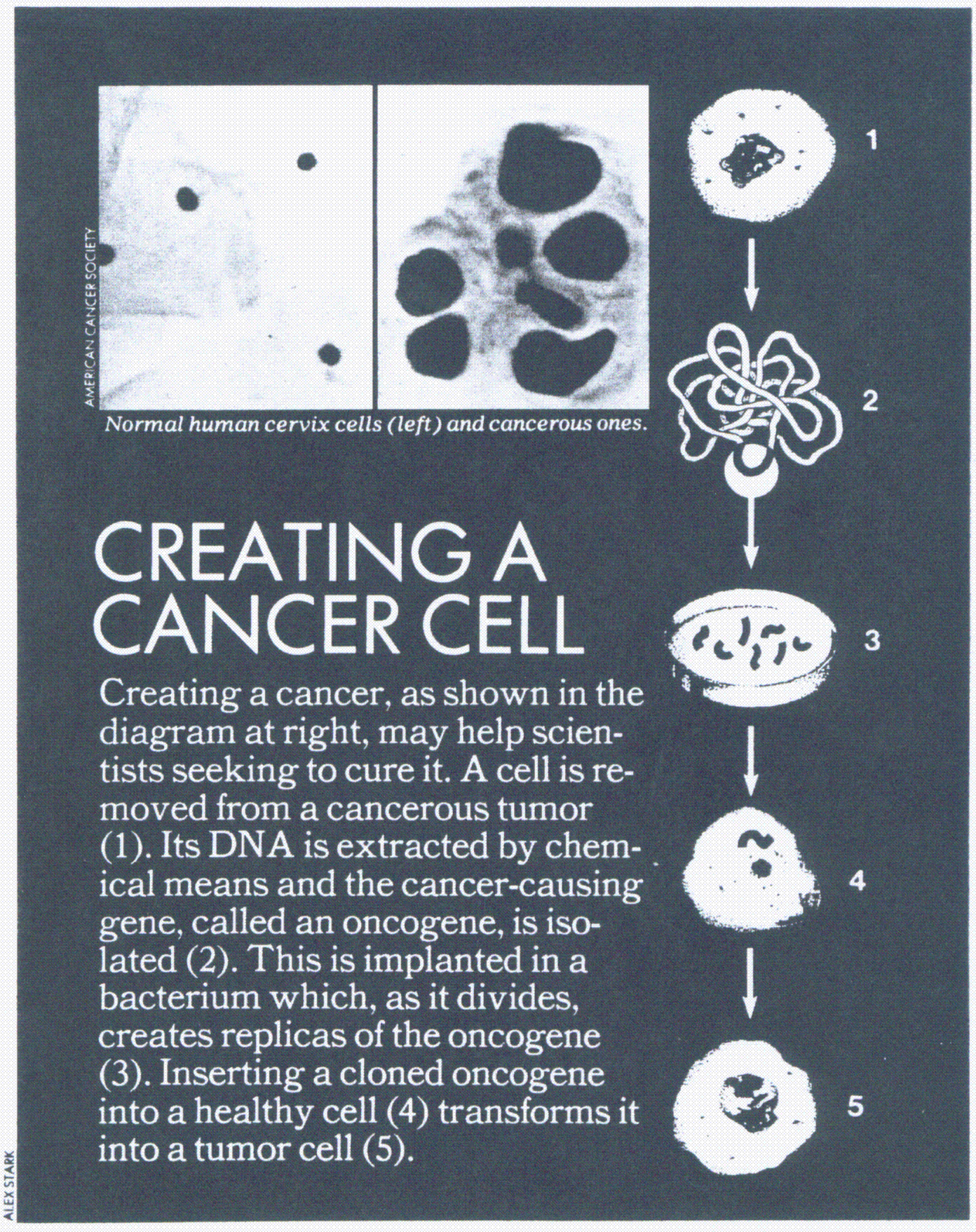
To date, only a few dozen cancer patients have been given monoclonal antibodies. The early work has tended to focus on leukemia and lymphomas. Unlike solid carcinomas, such as those of the bowel and breast, these tumors are present in the circulatory system and are therefore readily accessible to injected antibodies. But in the coming months, there are plans to tackle a whole range of representative tumors in man.

Clinical trials, which began in 1980, have thus far sought to establish safe dosage levels for the antibodies rather than to determine their actual therapeutic effectiveness. Yet even in the small amounts administered until now, these pure antibodies have shown promising results. At least partial remissions have been reported in several patients in advanced stages of cancer who had ceased responding to other forms of treatment — and without any evidence of adverse side effects.

In many animal studies, the best results have not been achieved with antibodies alone. Rather, antibodies are most effective when used in a far more refined version of standard chemotherapy. In conventional drug treatment, toxic chemicals are introduced into the body and allowed to roam freely through the circulatory system, where they inflict damage in many areas. Now scientists are chemically attaching such substances directly to monoclonal antibodies. 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 in the body.

When many cancers (cont'd pg 43)

> Although the dream of developing a vaccine to prevent cancer before it occurs seems farfetched, one scientist insists research toward this end 'is not Buck Rogers stuff.'



Normal human cervix cells (left) and cancerous ones.

AMERICAN CANCER SOCIETY

CREATING A CANCER CELL

Creating a cancer, as shown in the diagram at right, may help scientists seeking to cure it. A cell is removed from a cancerous tumor (1). Its DNA is extracted by chemical means and the cancer-causing gene, called an oncogene, is isolated (2). This is implanted in a bacterium which, as it divides, creates replicas of the oncogene (3). Inserting a cloned oncogene into a healthy cell (4) transforms it into a tumor cell (5).

ALEX STARK

CANCER

Continued from Page 43

THOM VOLLENWEIDER

Dr. Ivor Royston made the antibody being used experimentally on cancer patients at the University of California at San Diego.

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. Even this small foothold is sufficient to launch a new offensive and regain control of the body, as the cancer cells divide and multiply. Many researchers believe that this is where poison-tagged antibodies will play an invaluable role. By killing the cancer cells left behind by conventional treatments, they may dramatically enhance the patient's chance of survival.

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 first treated with radiation. Then monoclonal antibodies chemically attached to ricin (a potent toxin extracted from castor beans) were injected to finish the job. "This form of leukemia is so lethal that the disease will often start up again if just a single malignant cell is missed," Dr. Vitetta explains. Treatment did not begin until a quarter of the animal's body weight was tumor. Yet all 38 of the mice went into remission, and after six months half of this group remained disease-free. In contrast, all the animals that received radiation alone died within four to six weeks.

Although the particular leukemia under study closely resembles a human variety, Dr. Vitetta cautions that there is still a large gap between animal and human subjects. "There are many unknowns," she says, "but antibodies attached to toxic agents may someday substitute for everything now in use."

One of the most exciting potential applications of antibodies recently came to light in the area of bone-marrow transplantation. Blood cells are manufactured in the bone marrow, and if this tissue becomes cancerous, the result is leukemia. If conventional treatment fails with someone suffering from this disease, a drastic technique is sometimes tried: The patient is brought into temporary remission via radiation or chemotherapy, then a sample of bone marrow is surgically removed, frozen and stored. When the cancer does flare up again, supralethal doses of

'The crab is the wrong symbol for cancer,' says one physician. 'They should have used a chimera, a mythical monster that has a goat's body, a serpent's tail, a lion's head and breathes fire. It is much more dangerous than the crab.'

radiation and chemotherapy are applied to wipe out all the remaining marrow in the body and the reserve material is implanted to replenish the blood, lymph nodes and spleen. Long remissions have been achieved with this strategy, but failures are commonplace, for marrow taken when the disease is not evident often contains undetectable malignant cells that enable the cancer to strike back.

This is where monoclonal antibodies enter the picture. They may be used to cleanse the bone marrow of any lingering tumor cells before it is returned to the patient. Dr. Vitetta's group used poison-tagged antibodies on implants given to 20 leukemic mice. After treatment ended, 15 of these animals appeared to be totally disease free. And at the Sidney Farber Cancer Institute in Boston, a team headed by Dr. Stuart Schlossman used a related approach to treat 10 victims of childhood leukemia. Seven improved dramatically, showing no signs of the disease for periods now ranging up to two years. While these results are encouraging, scientists stress that this research is still at the most preliminary stage.

Monoclonal antibodies are also being studied in human therapy at University of California at San Diego, Stanford University, the Fred Hutchinson Cancer Research Center in Seattle and the Wistar Institute of Anatomy and Biology in Philadelphia. And by the end of the year, another 10 experimental treatment programs are expected to be in operation.

Years of research and testing, as well as plenty of money, will be required to determine whether antibodies can be translated from the experimental stage to the realm of standard medical practice. Oncologists are already concerned that the public will expect too much too quickly.

As publicity picks up, says Dr. Royston of U.C.S.D., "more and more people are coming to the hospital and demanding that new drug, 'monoclonal antibodies.' We've even heard rumors that people are pretending to dispense antibodies at private clinics." Though antibodies are available for therapeutic testing, only a limited number of patients are being accepted into experimental programs.

Even those who do manage to get antibody treatment are not always helped. At U.C.S.D., a 73-year-old retired Goodyear Tire and Rubber Company executive waited for weeks to begin a six-month-long series of injections. While the therapy did seem to provide some relief from the terrible itching and rashes that characterize his form of lymphoma, and there was a reduction in the level of tumor cells found in the blood, the effects were not long lasting.

The most formidable task ahead is to develop a whole line of monoclonal antibodies effective against particular cancers. But the picture is even more complex than it first appears. Recent evidence indicates that as a tumor grows, even a single form of cancer will display somewhat different clusters of antigen markers, so that an antibody that has successfully been attacking the cancer suddenly becomes ineffective. Most damaging of all is the group of cells that metastasize, spreading to distant locations in the body. "The crab is the wrong symbol for cancer," says Dr. Paul Calabresi, the head of the department of medicine at Roger Williams General Hospital in Providence, R.I.

"They should have used a chimera, a monster in Greek mythology that has a goat's body, a serpent's tail and a lion's head, and is often shown breathing fire. It is a much fiercer and more dangerous animal than the crab." In order to outwit the beast, physicans will have to be able to vary the antibody formula constantly as treatment progresses.

Both before and after treatment the question of metastasis remains crucial. As well as delivering lethal warheads, monoclonal antibodies may be able to serve as highly sensitive probes — powerful diagnostic tools that allow the exact size and location of these treacherous growths to be mapped. Now physicians may finally be able to get a good look at the enemy before deciding on a mode of therapy. And, once treatment begins, they may be able to monitor the patient closely for any sign of the cancer's return.

One of the first experiments in this area was undertaken in 1981 at the University of Lausanne in Switzerland. A colon-cancer patient was placed under a scanning machine that detects radiation. Some 24 hours before, he had been injected with monoclonal antibodies tagged with trace amounts of a radioactive chemical. They circulated through his body, attaching to malignant cells. When the scanner was activated, 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 the future, many cancers may be detected during routine check-ups at the doctor's office — long before a single symptom has appeared. A number of tumors are known to shed characteristic antigens into the circulatory system as they grow. If matching antibodies are mixed with an ordinary sample of the patient's blood, physicians may be able quickly to detect the disease. With the advent of new test kits that use monoclonal antibodies to "fish out" tumor antigens from the blood, hidden cancers could be detected at the earliest possible stage. There are estimates that 70 companies are now funding antibody research, and several of these are known to be involved in efforts to develop diagnostic tests for cancers of the pan-creas, stomach, colon and prostate gland.

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While monoclonal antibodies may be used to detect and destroy the cancer, the ultimate victory would be to banish it forever. It is the dream of some researchers that cancer may someday be relegated to the same fate as smallpox, polio and numerous other diseases eradicated through vaccination. Immunizing against cancer may sound farfetched but, according to Dr. Rauscher, "This 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. The body generates antibodies to fend off the harmless agent and is thus primed to combat an attack by its living counterpart. Today, we know the whole disease-causing agent is not needed to stimulate immunity; the antigens that normally cling to its surface will suffice. In the future, inoculants may consist solely of antigens — whether they are plucked from the outer coat of a virus or a human tumor.

This seemingly minor innovation may be the key to developing cancer vaccines. No clinician would chance introducing intact malignant cells — even dead ones — into the body merely as a preventive measure. But now it may be possible to substitute antigens prevalent on the surface of tumors without incurring any risk. In the future, it may not even be necessary to handle cancer cells while preparing a vaccine. Bacteria implanted with human genes could be converted into microscopic factories that would obediently crank out the specified antigen. The key question is whether this approach would actually trigger 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 the antigen-rich membranes of cancer cells, she learned that they were able to fight off implanted tumors. She began to suspect that cancer could be prevented just like viral or bacterial infections. At the time, there was little interest in the antigenic properties of cancer cells and Dr. Holling-

head had difficulty obtaining grants.

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

Further tests in this area are now under way at more than a dozen medical centers in the United States, Canada, England and France. In addition, Dr. Hollinshead is supplying researchers with antigens isolated from melanoma cells and tumors of the colon and ovaries to determine whether patients suffering from these forms of the disease can also be helped. While she and other oncologists are optimistic about the possibility of using cancer antigens therapeutically, they caution that it is too early to draw any definite conclusions about their effectiveness. The completion of long-term clinical studies by a number of different investigators is needed to confirm these early encouraging results.

This line of study, however, continues to move in intriguing new directions. So far, antigens have been administered only after the onset of cancer, when the immune system has already been weakened by the disease. 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. The Food and Drug Administration has given the go-ahead for trials with a group of individuals considered extremely susceptible to lung cancer. Within a year, Dr. Hollinshead plans to immunize a group of heavy smokers at a San Francisco shipyard, where they are exposed to asbestos.

While continuing these studies, she is also using monoclonal-antibody probes to chart the constellation of antigens found on cancer cells. She says she can envision a day eventually when molecular cartographers have mapped each and every surface marker associated with the disease. One day, it may even be possible to design a "superbug," a genetically engineered bacterium that will churn out a mixture of key antigens. "In the future," says Dr. Hollinshead, "there could be a single anticancer vaccine" — one potent injection that would protect against many varieties of the disease.

In the meantime, researchers hope to begin testing a batch of vaccines that may provide resistance to a small group of viruses that are linked to human cancer. These include hepatitis B, associated with the delayed onset of liver tumors; Epstein-Barr virus, the most common cause of childhood cancer in Africa; and herpes simplex II, tied to malignancies of the cervix. Genetic engineers hope to have the first of these inoculants ready for testing within the next two years.

As the excitement grows, Dr. Baltimore, the Nobel Prize winner who is also the director of the Whitehead Institute for Biomedical Research in Cambridge, Mass., inserts a note of cautious skepticism. "Cancer is the most difficult problem medical science has ever faced," he says. "It is very hard to appreciate how easily cancer cells can slip through the net. A lot more experiments still need to be done."

Even the most optimistic of investigators agree that the research is still in its earliest stages. But for years scientists have approached cancer 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 principal, 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. ■