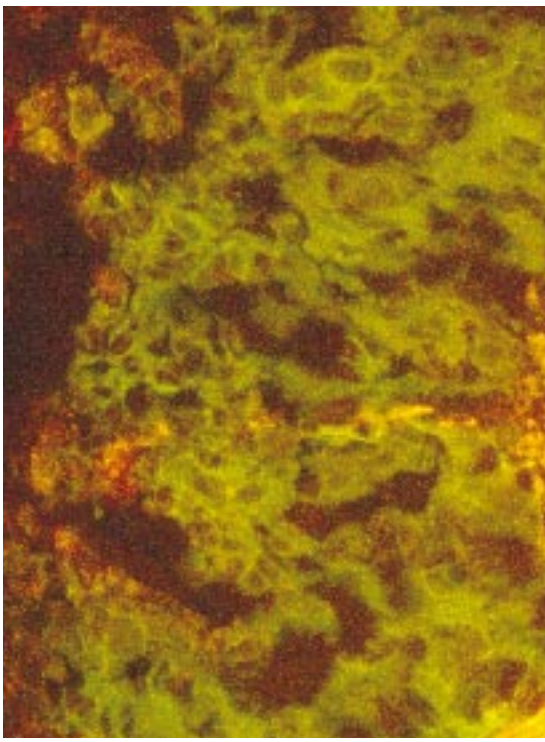
Immunotherapy for Cancer

As knowledge about the immune system grows, scientists are devising ways, using the body's own defenses, to attack cancer

by Lloyd J. Old



During the past century, excitement has waxed and waned over the possibility that the extraordinary disease-fighting prowess of the immune system might be enlisted to destroy cancers. Today doubts have vanished, and countless investigators are working to translate the notion into potent new biological therapies.

Clinical support for the idea that the immune system might restrain the development of cancer emerged in the 1800s, when physicians noticed that tumors sometimes regressed in cancer patients who contracted bacterial infections. William B. Coley, a surgeon at Memorial Hospital in New York City from 1892 to 1936, dedicated his life to creating therapies based on this observation. He made deliberate attempts to infect cancer patients with bacteria and later devised a vaccine consisting of killed bacteria to prompt a tumor-killing response. These treatments—which we would now consider immunotherapies because they aimed to attack disease with the body's own defenses—brought about complete tumor regressions in some individuals. But they were not broadly accepted, because the results were unpredictable.

Early in this century other investigators also attempted to develop immune-based therapies, but none showed a convincing benefit. Still, the link between immunity and cancer remained firmly fixed in the minds of many people. During the 1960s and 1970s, for example, there was wide acceptance of the "immunosurveillance" model put forth by Lewis Thomas of New York University and MacFarlane Burnett of the Hall Institute in Melbourne, Australia. This theory held that the immune system constantly seeks out and destroys emerging cancer cells. Tumors, it proposed, arise when this policing mechanism fails. In the following years, however, accumulating evidence suggested that the immune system attacked only tumors caused by viral infections. Because such cancers account for a minority of all cases, the theory appeared flawed.

Recently, though, new insights have generated a resurgence of interest in immunotherapies for cancer. In particular, the science of immunology has undergone revolutionary changes. Researchers have discovered and isolated the cells and chemicals that enable the immune system to defend the body against attack and to prune away infected and damaged tissues. By studying these components, immunologists have gained a deep understanding of the workings of the normal immune system. And cancer immunologists have gained knowledge of mechanisms and molecules by which they may someday control cancer.

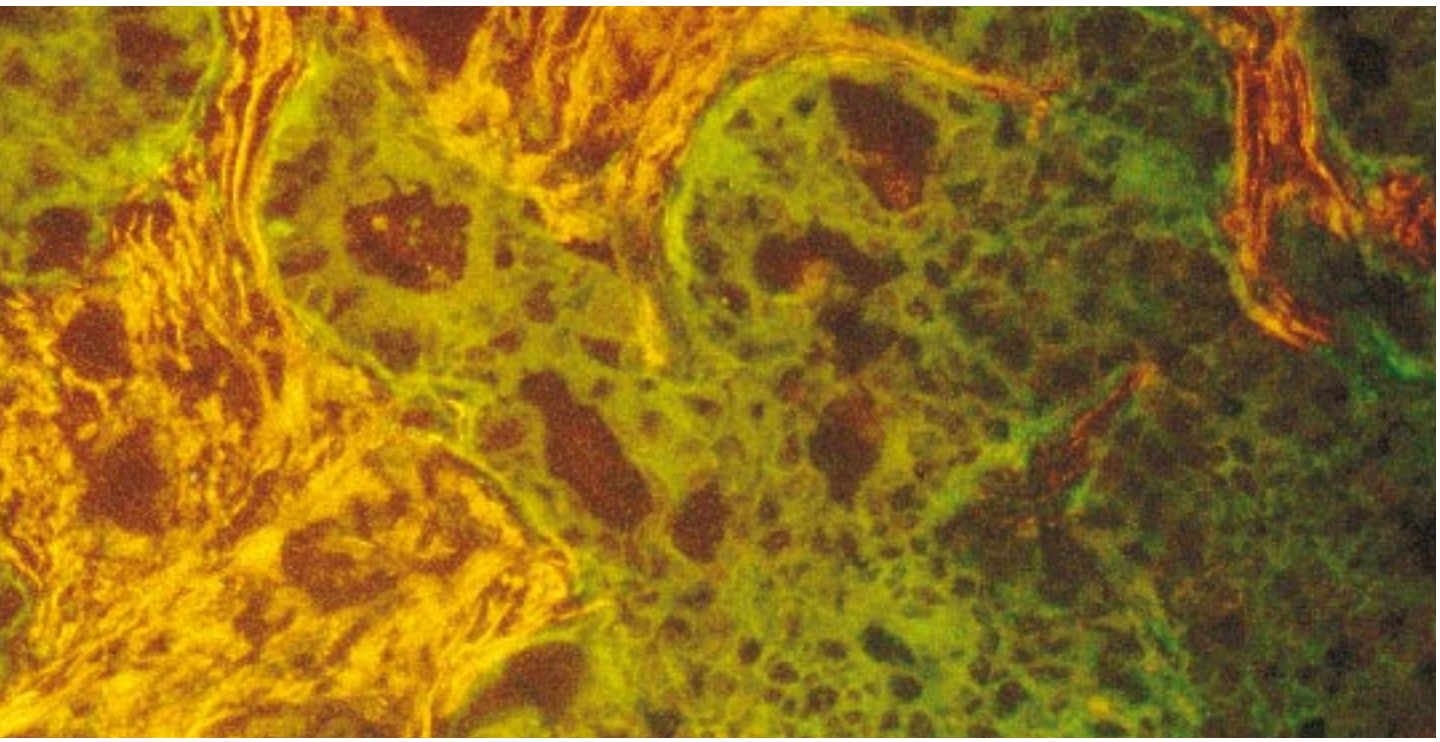
Activating the Immune System

Today we would describe Coley's approach to cancer therapy as nonspecific: it strengthened the overall activity of the immune system instead of selectively arousing those elements most able to combat cancers. During the past decade, scientists have developed a range of other nonspecific immunotherapies. The strategy behind all these interventions has been likened to kicking the television set to make it work: give the immune system a good jolt, the thinking goes, and its capacity to rid the body of cancer cells may increase. Exactly which component, or combination of components, accounts for the killing remains unknown. Even so, the tactic has had some real success.

For instance, cancer occurring on the inner wall of the bladder—superficial bladder cancer—responds well to a vaccine, called Bacillus Calmette-Guérin, or BCG, used to combat tuberculosis. These microbes do not cause disease, because they evoke a strong immune response. Superficial bladder cancer typically recurs after surgery and, in its later phases, invades the bladder wall and beyond. But instilling BCG into the bladder by way of a catheter elicits a chronic inflammatory response—a prolonged activation of immune cells that fight invaders. Just how the inflammatory cells work is not understood in detail, but the end result is that the immune cells and the substances they secrete kill preexisting and developing cancer cells in the bladder wall. Consequently, patients who receive BCG postoperatively face a much lower risk of recurrence.

Although this vaccine illustrates the potential of nonspecific immunotherapies, it acts locally—provoking inflammation only in the bladder. Most cancers become lethal because they spread

Copyright 1996 Scientific American, Inc.



COURTESY OF PILAR GARIN-CHESA *Memorial Sloan-Kettering Cancer Center*

COLON CANCER SPECIMEN was stained using two monoclonal antibodies of different hues. Each antibody binds to distinct proteins on the surface of different cell populations. In this case, green marks cancer cells, and orange reveals the connective tissue (stroma). Because antibodies recognize specific cells, they can be used to find and selectively destroy tumor cells as well as the tissues that support and nourish such growths.

and give rise to tumors at distant sites. To eliminate those growths, immunotherapies must be capable of seeking out incipient tumors in all parts of the body. To accomplish this, many research oncologists turned in the 1970s and 1980s to molecules that the body produces in response to viral and bacterial infections; these molecules, now called cytokines, help to orchestrate the defense response. The cytokines include such proteins as interferons, interleukins and tumor necrosis factor (TNF). Investigators were initially very hopeful that cytokine therapy would be of great value. Extensive clinical testing of this nonspecific approach, though, has dampened enthusiasm. Relatively few patients appear to benefit from cytokine therapy alone.

Cancer Antigens

Cytokines may prove more valuable in combination with one another or with other treatments. Meanwhile, however, researchers have sought more specific ways to battle tumor cells. To single out cancer cells, an immunotherapy must be able to distinguish them from normal cells. One way the immune system can recognize differences among cells is by molecules, called antigens, that appear on the cell surface. Long ago scientists speculated that cancer cells might display molecules that signaled their abnormality. If such cancer-specific antigens were found, investigators could presumably devise means to make them more visible to the immune system. In other words, the antigens could be made to serve as targets for an immune attack—just as bacterial and viral antigens alert the body to disease-causing invaders.

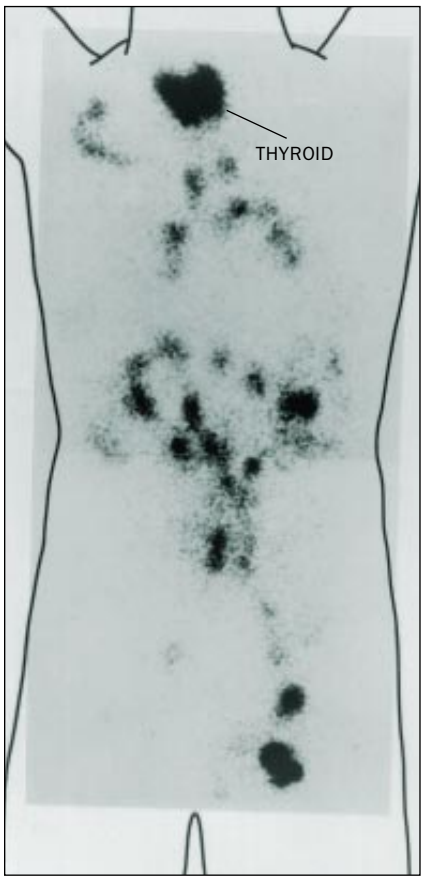
The discovery of antibodies at the end of the 19th century provided the means to search for such cancer-specific antigens—and later opened the way for extensive studies of antibodies as potential immunotherapies for cancer. Antibodies, a critical component of the immune system, circulate in the blood and bind to foreign antigens. In so doing, they mark antigen-bound invaders for destruction by scavenger cells called macrophages, by other cells and by special blood protein components, collectively called complement.

The ability of antibodies to recognize fine distinctions between molecules is what has made them extremely useful in the search for cancer antigens. Over the past century, investigators injected human cancer cells into innumerable horses, sheep, rabbits, mice and rats, closely analyzing the antibodies the animals produced in response. If the immune systems of the animals reacted to the foreign tumor cells by producing antibodies that did not react with normal cells, this finding would signal the presence of antigens that could subsequently be identified and pressed into service as targets for antibody-based therapies. Many workers tried this approach and claimed to identify cancer-specific antigens. Unfortunately, none of these claims held up to careful scrutiny.

The Era of Monoclonal Antibodies

The search for cancer antigens became easier in 1975, thanks to a discovery made by César Milstein and Georges J. F. Köhler of the University of Cambridge. These researchers demonstrated that antibody-producing cells could be made to survive indefinitely if they were fused with cancer cells. The technique, which earned Milstein and Köhler a Nobel Prize, enabled scientists to produce unlimited supplies of identical antibodies, or monoclonal antibod-

Copyright 1996 Scientific American, Inc.



COURTESY OF SYDNEY WELT *Memorial Sloan-Kettering Cancer Center*

COLON CANCER METASTASES in the abdomen and elsewhere are dark on this scan because they have absorbed and concentrated the monoclonal antibody A33, labeled with a radioactive isotope. Normal intestinal cells also take up A33 but do not retain it. (Thyroid takes up released radioactive isotope.) It is this selective accumulation of monoclonal antibodies in tumors that raises hopes of targeted therapies having fewer side effects than conventional chemotherapies.

ies, because any given antibody-producing cell produces only a single species of antibody. The method had a profound effect on cancer immunology for several reasons. First, it provided a powerful new method to search for cancer antigens. And second, workers could at last produce defined antibodies in sufficient amounts to put antibody-based therapies to the test.

Naturally, this spectacular technology gave rise to high expectations as well as to premature and unrealistic assertions about antibodies as "magic bullets." It was hoped that monoclonal antibodies would home in on cancer cells (by recognizing specific antigens) and trigger an immune attack that destroyed the target cells but ignored normal cells lacking the cancer antigens. Many expected that these bullets could be made more deadly by loading them with toxic chemicals; the antibodies would carry the toxins directly to tumors, where the poisons would kill cancer cells. Excitement prompted industry and private investors to spend vast sums of money. But when the claims could not be substantiated as quickly as everyone hoped, opinion swung in the other direction, prompting many analysts and investors to declare that the technology had failed. The reality of the situation is far more positive. The concept remains sound, and slow, steady progress is being made in developing antibody therapies.

Monoclonal antibodies have revealed a large array of antigens that exist on human cancer cells. Regrettably, virtually all these antigens are also found on normal cells, which might therefore be damaged by an antibody-based therapy. This overlap, however, does not preclude their use as therapeutic targets for several reasons: the antigen in normal tissues may not be accessible to blood-borne antibodies; the cancer cells may express more antigen than normal cells do; and antibody-induced injury of normal cells may be reversible.

In addition to targeting cancer cells, antibodies can also be designed to act on other cell types and molecules necessary for tumor growth. For instance, antibodies can neutralize growth factors—chemicals needed by cancer cells and their blood supply—and thereby inhibit a tumor's expansion. And antibodies can target the stroma, the connective tissue between tumor cells.

Without the stroma, which can make up 60 percent or more of a cancerous mass, a tumor cannot exceed a harmless, microscopic size. At the Memorial Sloan-Kettering Cancer Center in New York City, Wolfgang J. Rettig, Pilar Garin-Chesa and I have identified an antigen called FAP-alpha that is strongly expressed by stromal cells in a wide range of human cancers. This and other antigens that mark tumor stroma or tumor blood vessels have become attractive targets to researchers devising antibody-based therapies.

Today monoclonal antibodies are most often obtained from mice that have been immunized with human cancers. In clinical tests, human subjects generally mount an immune reaction that inactivates the injected mouse-derived molecules. Scientists have therefore begun to construct human therapeutic antibodies that should evade immune recognition. In the meantime, workers are disguising the murine antibodies, refashioning them into something more resembling human antibodies. They do so by replacing all the nonessential structures in the mouse antibody with the corresponding human parts. This trick, called humanization, has yielded antibodies that in initial clinical tests have sneaked past the human immune system. Antibody engineers are also refining other characteristics of the humanized molecules to make them better able to bind to antigens and penetrate tumors.

Testing Antibodies in the Clinic

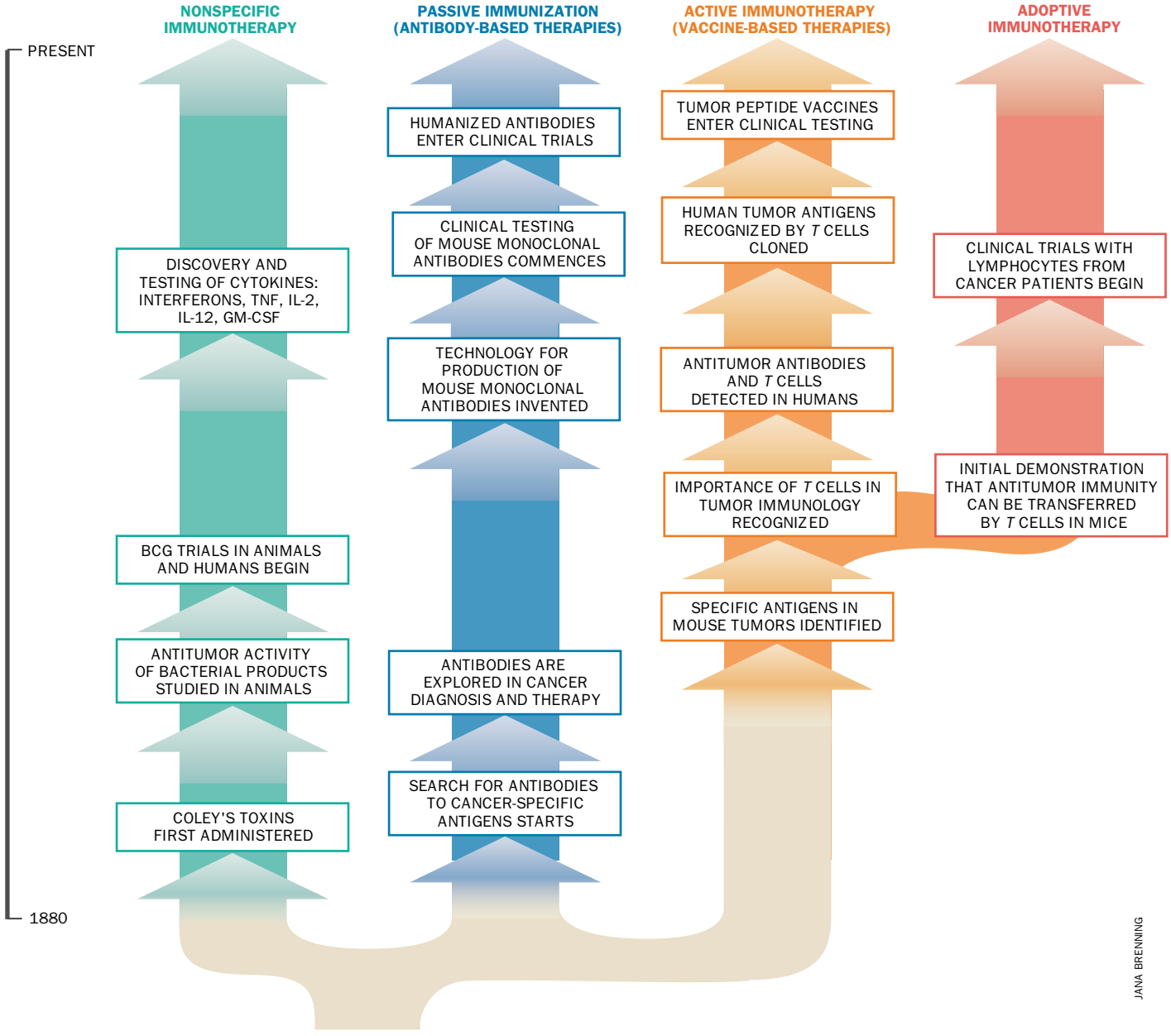
Once a target antigen is identified and an antibody construct selected, antibody engineers must decide what kind of toxic message they wish to deliver to a tumor. Here lie two distinct approaches. One exploits the ability of antibodies themselves to destroy cancer cells. The other, as envisioned from the start, uses antibodies as vehicles to carry a toxic agent—be it a chemotherapeutic agent or a radioactive compound, a plant or a bacterial toxin—to a tumor site. Many new antigenic targets and antibody constructs have emerged—so many, in fact, that they cannot all be tested in the clinic.

One criterion for deciding which antibody to test as a therapy is the likelihood that it will be taken up by a tumor in significantly greater amounts than by normal tissues. To see if an antibody meets this requirement, it is tagged with a radioactive isotope of iodine (^{131}I), injected into human volunteers and followed in the body using imaging techniques. For a more accurate assessment of the antibody's accumulation in the tumor, a biopsy is taken. Because none of the antigenic targets studied so far exist exclusively on tumors, imaging studies are also critical for discerning how much antibody attaches to normal tissues. Antibodies showing favorable characteristics in these studies are the best candidates for therapeutic trials.

To develop even one antibody-based therapy requires tremendous effort and time, which explains why translating good ideas into useful therapies can proceed much more slowly than anyone

Copyright 1996 Scientific American, Inc.

Landmarks in the History of Tumor Immunotherapy



would like. Consider the ongoing studies of a mouse monoclonal antibody called A33, carried out by Sydney Welt and our group at Memorial Sloan-Kettering. This antibody detects an antigen that is expressed by normal cells in the intestine and by virtually all colon cancers. Clinical studies using A33 labeled with a trace of radioactive isotope showed substantial uptake in colon cancers. Up to one hundredth of a percent of the injected antibody accumulated in the tumor mass. Moreover, the antibody was able to penetrate the core of the tumor.

These favorable results justified taking A33 to the next step: clinical trials with a therapeutic aim. We loaded the antibody with much higher doses of radioisotope, designed to irradiate and destroy cancer cells, and asked two key questions: Can enough antibody reach the tumor, and what effect will the isotope-carrying antibody have on normal cells in the gastrointestinal tract? Because the human subjects in the trial mounted an immune response that neutralized the mouse-made A33, only a single injection of the molecule could be given. (Follow-up injections would be useless because the immune system would recognize and eliminate the antibody before it had the opportunity to come near a tumor.) Even with such limited dosing, the tumors in some patients shrank.

Most important and surprising, we observed that the antibody caused no toxicity in the gut even though it accumulated there. We believe the gut cells are not harmed by the antibody because they rapidly excrete it. In contrast, the tumor cells retain it. A humanized version of A33 has been developed and is now being tested in the clinic. To give some idea of the timescale involved in these studies, the antigen was identified in 1982; the first clinical study started in 1988; the therapeutic trials commenced in 1991; and the first patients

Copyright 1996 Scientific American, Inc.

Tumor-Killing Agents Delivered by Antibodies

Acting alone, antibodies bind to antigens on the surface of cancer cells. In doing so, they mark these cells for destruction by other immune components or cause them to self-destruct. Antibodies can similarly target and attack the blood vessels feeding a tumor or the connective tissues (or stroma) supporting it. And antibodies can neutralize or block the action of growth factors—chemicals that a tumor needs to grow. In addition, antibodies are used as guided missiles of sorts. They can deliver an array of damaging compounds (some of which are listed below) to tumor sites.

RADIOACTIVE ISOTOPES, such as iodine 131 or yttrium 99, kill cancer cells by damaging their DNA.

OTHER TOXINS travel to a tumor site by way of antibodies. One well-studied example is ricin, which is made from castor beans; it inhibits protein synthesis and thwarts tumor growth. Toxic products from bacteria and other microorganisms also stall cancer cells in experiments. And many other highly tumoricidal drugs too toxic to be used alone—including CC-1065, calicheamicin and maytansinoids—may be effective if targeted by an antibody.

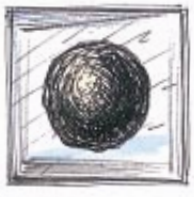
CHEMOTHERAPEUTIC DRUGS often reach tumors in larger, and so more lethal, doses when delivered by an antibody.

ENZYMES that can convert innocuous "prodrugs" into cell killers will home to tumors when attached to antibodies. Because the enzymes activate the prodrugs only at tumor sites, healthy tissues in the body remain unharmed.

GENETIC DRUGS come in several forms. So-called antisense DNA molecules block the production of proteins needed by cancer cells. Other gene constructs give rise to proteins that kill tumor cells; the genes can be linked to antibodies directly or packaged into viral particles engineered to have targeting antibody on their surface.

INFLAMMATORY MOLECULES, which include tumor necrosis factor (TNF) and other messenger molecules of the immune system as well as certain microbial products, can bring about an inflammatory reaction that destroys tissues at the tumor site.

IMMUNE CELLS guided by antibodies, such as genetically engineered *T* cells, can prompt tumor cell dissolution, or lysis.



JENNIFER C. CHRISTIANSEN

were injected with the humanized antibody in 1995.

Perhaps the major success in the field to date comes from studies of an antibody that binds to an antigen on both healthy *B* cells—immune cells that, once activated, manufacture antibodies—and on lymphomas of *B* cell origin. Stuart F. Schlossmann of the Dana-Farber Cancer Institute in Boston originally described this antigen target, called CD20, and it has since been studied by a number of groups, including that of Mark S. Kaminski of the University of Michigan and Oliver W. Press of the University of Washington School of Medicine. The results are quite exciting. The antibody alone can bring about tumor regressions, and when it is combined with ^{131}I, these regressions are substantial and prolonged. Equally important, the therapy produces few side effects. Thus, we know that even if an antigen is expressed on normal cells, it can, as had been hoped, still serve in some cases as a useful target for therapy.

As with most experimental therapies for cancer, those based on antibodies are generally tested in patients who have advanced forms of the disease. But these therapies may be far more effective if used sooner. Gert Riethmüller of the University of Munich has in fact studied the effect of a monoclonal antibody called 17.1A in patients who have colorectal cancer in fairly early (basically localized) stages. He started antibody therapy in these individuals immediately after they had their visible tumors removed by surgery. Despite surgery, some patients remain at high risk because of residual cancer cells. But in Riethmüller's study, the antibody-treated patients had a significantly lower recurrence rate. Treating the cancer cells left behind after surgery—or those beginning to spread to some other site—makes much sense, and all forms of immunotherapy will undoubtedly focus on this goal in the future.

The Promise of Vaccines

In the antibody-based therapies we have been discussing, the injected antibody derives from an animal; in the future, it may be made in a test tube. Either way, the treatment is considered passive immunotherapy: the immune molecules are given to patients, who do not produce them on their own. A vac-

Copyright 1996 Scientific American, Inc.

cine, on the other hand, is deemed active immunotherapy because it rouses an immune response in the individual who needs protection.

Efforts to treat cancer with vaccines date back to the very origins of immunology. Over the years, doctors have vaccinated many hundreds of cancer patients with malignant cells—either the patients' own cells or those taken from another patient—usually irradiated to prevent further growth. Although occasional responses were observed, this early vaccination strategy suffered from major deficiencies. Most significant, it offered no way to monitor the vaccine's effect on the immune system. When vaccines against infectious diseases such as poliomyelitis were developed, their impact could be readily detected by looking for the specific antibodies they elicited. But until recently, scientists had no comparable information about cancer antigens and the immune response they provoke. Without such knowledge, investigators had no hope of understanding why the treatment seemed to work in some cases but not in others. Steady progress over the past several decades has now brought us to a point where we can place the development of cancer vaccines on a firm scientific basis.

SKIN TESTS offer one way to tell if a patient's immune system recognizes peptide antigens expressed by tumor cells. If so, irritation in the form of a so-called delayed hypersensitivity reaction appears on the skin. The initial skin reaction (*left*) in this melanoma patient became more pronounced after the injection of an immune-boosting cytokine, GM-CSF (*right*). This response resembles the tuberculin reaction that follows a tuberculosis vaccination and can be used to monitor whether a vaccine is stimulating a patient's immune system as intended.

COURTESY OF ALEXANDER KNUTH *Northwest Hospital, Frankfurt*

The modern vaccine story starts in the 1940s and 1950s with a fundamental discovery of tumor immunology. Scientists found that when chemicals or viruses induced tumors in mice, the tumors bore antigens that could immunize other mice of the same strain against transplants of the tumors. Subsequent studies showed that immune system cells known as *T* lymphocytes taken from immunized animals could transfer immunity against tumors to healthy animals of the same strain. And workers devised techniques to show that the *T* cells from the immunized mice could kill tumor cells grown in test tubes as well. In contrast, antibodies elicited by the tumor cells generally failed to transfer immunity or kill tumor cells.

As a next step, we needed to see if comparable immune reactions would take place in humans. For ethical and practical reasons, we could not apply the same approach used in the animal studies described above. And so the focus was on immune reactions that could be extensively analyzed in test tubes. Our group chose to examine melanoma cells, in part because they can be easily grown in the laboratory. Over a 10-year period, we studied a large number of melanoma patients, seeking evidence of antibodies or *T* cells in these patients that reacted with their own melanoma cells. We found that a small proportion did mount a specific immune response against their own tumor cells. And we also formed the impression that these patients followed a more favorable clinical course.

The next challenge was to isolate the tumor antigens recognized in this system so that they might be tested in a vaccine. Thierry Boon and his colleagues at the Ludwig Institute for Cancer Research in Brussels developed a method to do just that for *T* cell recognized antigens [see "Teaching the Immune System to Fight Cancer," by Thierry Boon; SCIENTIFIC AMERICAN, March 1993]. This technique has revealed two main categories of tumor antigens that evoke a *T* cell response in melanoma patients. The first includes antigens called MAGE, BAGE and GAGE that are produced by tumor cells but not by any normal cells outside the testes. The other category of antigens, including tyrosinase and Melan A, are so-called differentiation antigens; they are made by both melanoma cells and melanocytes, normal cells from which the tumor cells arise.

T cells do not "see" the whole protein antigen on the cancer cell, but only pieces of it, termed peptides. When the tumor cell processes the protein, it presents these peptides on the cell surface in conjunction with so-called histocompatibility antigens. Scientists are now creating a rapidly growing list of protein and peptide tumor antigens, identified using the method developed by Boon and his group to clone tumor antigens. All these molecules are prime candidates for use as vaccines. Even newer techniques promise to extend the list of possible vaccines.

Another source of information about potential tumor antigens comes from the avalanche of discoveries concerning genetic changes in cancer cells. Any alteration in a cancer cell that can be recognized by the immune system is grist for the cancer immunologist's mill. Among the most attractive targets for vaccines are abnormal proteins that are made when genetic mutations turn normal genes into cancer-promoting versions. A long list of cancer-related genes—known as oncogenes and tumor suppressor genes—is now being compiled [see "How Cancer Arises," by Robert A. Weinberg, page 62]. And, of course, human cancers caused by viruses, such as cervical cancer, are prime targets for vaccine-based therapies.

As is the case with monoclonal antibody therapies, there are now more vaccine-based therapies than anyone can test in patients. And, although medicine's vast experience with vaccines against infectious diseases will help guide cancer vaccinologists, much uncharted territory lies ahead. Whole-cancer-cell vaccines, whether genetically engineered or not, will probably give way to vaccines that contain defined tumor antigens. Moreover, because peptide vaccines are easy

Copyright 1996 Scientific American, Inc.

Categories of Cancer Vaccines

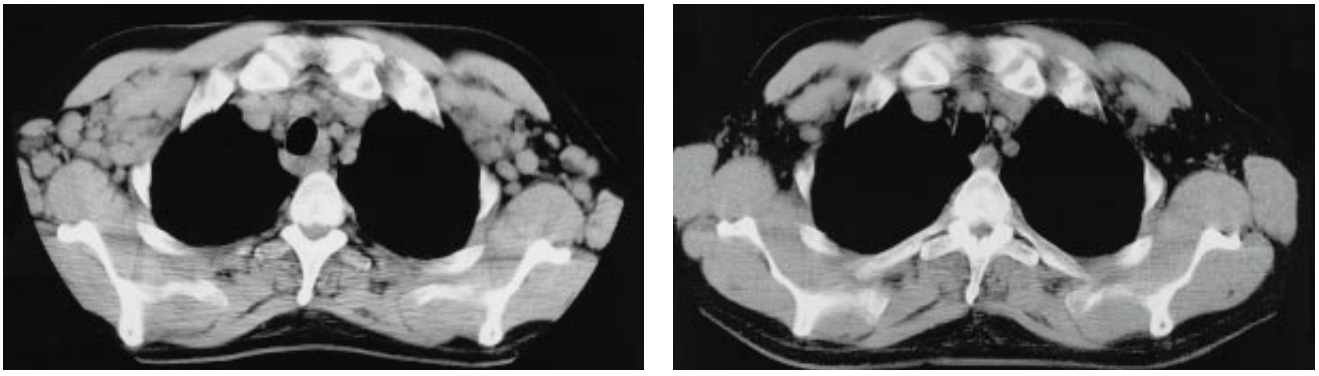
Cancer vaccines are intended to induce *T* cells or other components of the immune system to recognize and vigorously attack malignant tissue.

Whole Cancer Cells	Inactivated cancer cells and their extracts can jump-start the immune system. Cancer cells engineered to secrete cytokines, such as IL-2 or GM-CSF, similarly heighten antitumor immunity. Cells designed to express co-stimulatory molecules, such as B-7, enhance the ability of *T* cells to recognize tumor cells.
Peptides	Tumor peptides, fragments of tumor proteins recognized by *T* cells, are injected alone or with immune-boosting adjuvants.
Proteins	Antigen-presenting cells take up injected tumor proteins and break them down into a range of peptide fragments recognized by *T* cells.
Dendritic Cells	These antigen-presenting cells are isolated from the blood, exposed to tumor peptides or engineered to produce tumor proteins and then reinjected.
Gangliosides	Humans can produce antibodies to these molecules, such as GM2, found on the surface of tumor cells. Clinical studies have shown that melanoma patients with GM2 antibodies have a better prognosis.
Heat-Shock Proteins	These cellular constituents ordinarily bind peptides. Injecting heat-shock proteins isolated from tumors rouses antitumor immunity in mice.
Viral and Bacterial Vectors	Genes coding for tumor antigens are incorporated into viral or bacterial genomes. When injected, these altered infectious agents draw immunity against themselves and the encoded antigens.
Nucleic Acids	DNA and RNA coding for tumor antigens prompt normal cells to begin producing these antigens.

to synthesize, they are taking center stage in clinical trials. In early tests, some tumor regressions have already been noted. Some cancer immunologists theorize that whole proteins will be more effective as vaccines because they can provoke the immune system with a range of different peptides. Scientists eagerly await large supplies of pure tumor antigens to test the idea.

Yet another approach to immunotherapy is under study. Known as adoptive immunotherapy, it involves stimulating *T* cells by exposing them to tumor cells or antigens in the laboratory and then injecting expanded populations of the treated cells into patients. In contrast to the studies in inbred mice, where *T* cells from one mouse can be given to any other mouse of the same strain, *T* cells from one person would generally be rejected by another person. For this reason, patients serve as both donor and recipient of their own *T* cells. Steven A. Rosenberg of the National Cancer Institute spearheaded the clinical testing of this approach, and efforts continue to make this therapy more effective and less time-consuming and expensive.

Adoptive immunotherapy may have its greatest value in treating viral infections and tumors in patients whose immune systems have been weakened by disease and therapy. For instance, before leukemia patients receive bone marrow transplants, they receive massive



MARK S. KAMINSKI *University of Michigan*

COMPUTED TOMOGRAPHIC SCANS show a cross section of a 41-year-old man's upper torso before and after treatment for lymphoma with CD20 antibody-based radioimmunotherapy. The large black circles are the lungs. Despite earlier chemotherapy regimens, the patient had extensive disease, marked by many enlarged lymph nodes (*left*). After a single CD20 treatment (*right*), however, all disease disappeared. The patient continues to be in complete remission two years later.

Copyright 1996 Scientific American, Inc.

doses of chemotherapy and radiation to destroy all leukemia cells. This leaves the individuals immunosuppressed and vulnerable to infections, such as cytomegalovirus infection (CMV). But there are now indications that an injection of CMV-specific *T* cells can reduce the risk of CMV infection in such transplant patients. In addition, dramatic regressions of virus-related lymphomas arising in transplant patients can be brought about by simply injecting lymphocytes from normal donors. Because these immune cells are spared the effects of the immunosuppressive drugs, they retain their ability to combat the lymphoma cells.

The Hurdles Ahead

Despite the great hope of immunotherapy, a dark cloud hangs over all our attempts to control cancer by immune mechanisms. Cancer cells are masters of deceit and disguise—veritable Houdinis that can readily alter themselves to evade immunologic recognition and attack [*see box at right*].

Because the race is between immune control and escape, the best strategies to combat cancer will need to attack it on several fronts. Opportunities being explored include constructing vaccines that combine a variety of antigens (called polyvalent vaccines); testing how well antibody- and vaccine-based approaches work together; and combining nonspecific and specific immunotherapies and other cancer therapies.

Other potential obstacles need our attention as well. As noted with antibodies, it is conceivable that cancer vaccines may injure normal cells to some degree. There are a number of disease states, called autoimmune diseases, that arise when the immune system turns against normal tissues in the body. Examples include rheumatoid arthritis, multiple sclerosis and certain forms of kidney disease. It may turn out that some modest degree of autoimmunity is the price we pay for a successful cancer vaccine.

Given the long history of tumor immunology—marked by recurrent cycles of high expectations and disappointments—we need to exert considerable caution in making any predictions. But many promising opportunities wait to be studied, and they give us reason to expect that powerful immunologic therapies will one day become a reality.

Perhaps these therapies will yield cures—the universal objective of cancer researchers, health care providers and, of course, patients. A more achievable aim, though, may be developing therapies that can change the nature of cancer from a progressive and lethal disease to one that can be controlled throughout a long life. That result would be less than ideal, but it could make a world of difference for many afflicted with tumors not readily treatable today. SA

Tactics Tumors Use to Evade Immune Attack

Altering Their Characteristics
Under attack by the immune system, tumor cells generate variants lacking those features that mark them for destruction by *T* cells, other killer cells and antibodies. The process, called immunoselection, can lead to tumor cells that do not have tumor antigens or major histocompatibility antigens, which present tumor antigens to immune cells. Tumor cells can also lack co-stimulatory molecules, which activate *T* cells, and signaling molecules needed to respond to cytokines, such as gamma-interferon, that promote tumor cell killing by immune mechanisms.

Suppressing the Immune Response
Tumor cells can effect changes in the host that diminish or abrogate an effective immune response against them. Specific immunosuppression occurs when tumor cells deliver inappropriate or ineffective signals to *T* cells, reducing their number or ability to respond. Nonspecific immunosuppression is caused by other tumor cell products, such as TGF-beta, or by cancer drugs or irradiation.

Hiding from the Immune Response
Immune reactions are less effective or absent in several sites in the body, such as the brain, and so tumors there avoid immune attacks. Also, a dense tumor stroma consisting of connective tissues can shield tumor cells from immune recognition and destruction.

Exploiting the Immune System's Ignorance
Tumor cells may grow without eliciting any immune response. But an effective immune response can be generated by immunizing against tumor antigens—indicating that the potential for immune attack is not always activated.

Outpacing the Immune Response
Tumor cells can simply proliferate so quickly that the immune response is not fast enough to keep their growth in check.

The Author

LLOYD J. OLD received his medical degree in 1958 from the University of California, San Francisco. He then joined the Memorial Sloan-Kettering Institute for Cancer Research, where he became associate director of research from 1973 to 1983. Old is now director and CEO of the Ludwig Institute for Cancer Research in New York City. This is his fourth article for *Scientific American*.

Further Reading

TUMOR ANTIGENS RECOGNIZED BY T LYMPHOCYTES. T. Boon et al. in *Annual Review of Immunology*. Edited by W. E. Paul, C. G. Fathman and H. Metzger. Vol. 12, pages 337–366; 1994.
HUMAN NEOPLASMS ELICIT MULTIPLE SPECIFIC IMMUNE RESPONSES IN THE AUTOLOGOUS HOST. U. Sahin et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 92, No. 25, pages 11810–11813; December 5, 1995.
BIOLOGIC THERAPY OF CANCER. Edited by V. T. DeVita, Jr., et al. Lippincott-Raven, 1994.
MONOCLONAL ANTIBODIES. J. P. Mach in *Oxford Textbook of Oncology*, Vol. 1. Edited by J. Peckham, M. Pinedo and U. Veronesi. Oxford University Press, 1995.
CANCER THERAPY WITH RADIOLABELED ANTIBODIES. Edited by David M. Goldenberg. CRC Press, 1995.

Copyright 1996 Scientific American, Inc.