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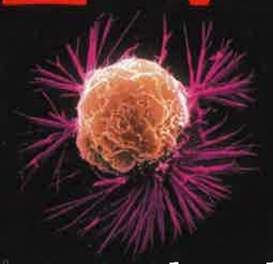
TIME

THE OPPENHEIMER FILES
Revelations of a KGB spymaster



IT BEGINS as a single cell and grows into a merciless disease that claims more than half a million Americans a year. But scientists are steadily unlocking its mysteries, and the fight against it may now have reached a turning point. New discoveries promise better therapies and

HOPE IN THE WAR AGAINST CANCER

■ SCIENCE

STOPPING CANCER IN ITS TRACKS

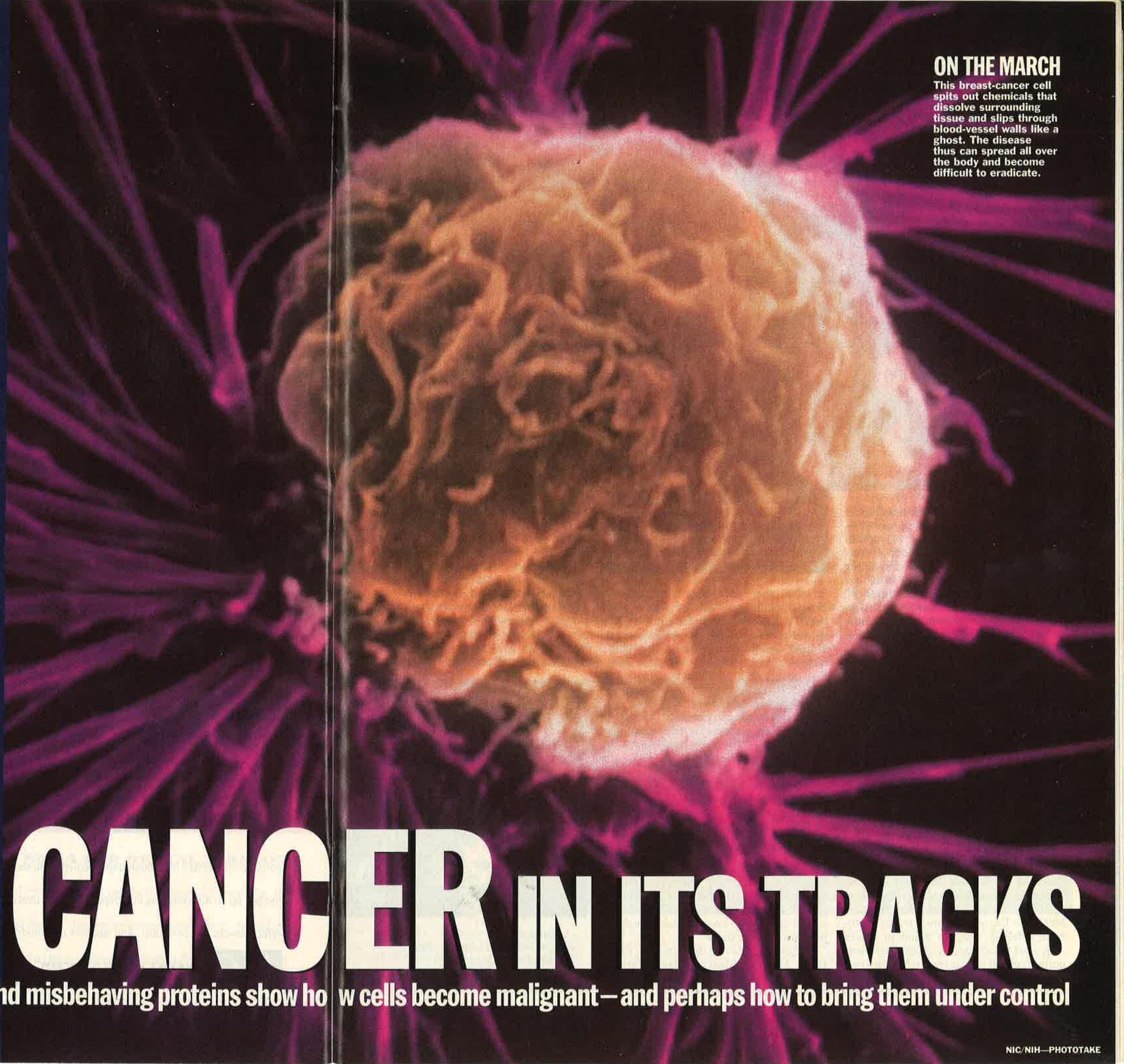
New discoveries about wayward genes and misbehaving proteins show how cells become malignant—and perhaps how to bring them under control

BY J. MADELEINE NASH/CHICAGO

STEALTHY AS A PIRATE SLIPPING FROM A COVE, the cancer cell severs the moorings that attach it to surrounding tissue. Slowly it extends one, two, three fingerlike probes and begins to creep. Then it detects the pulsating presence of a nearby capillary and darts between the cells that compose the blood-vessel wall. It dives into the red river that courses through lung and liver, breast and brain. An hour or so later, it surfaces on some tranquil shore, settles down and—at the expense of its hapless neighbors—begins to prosper.

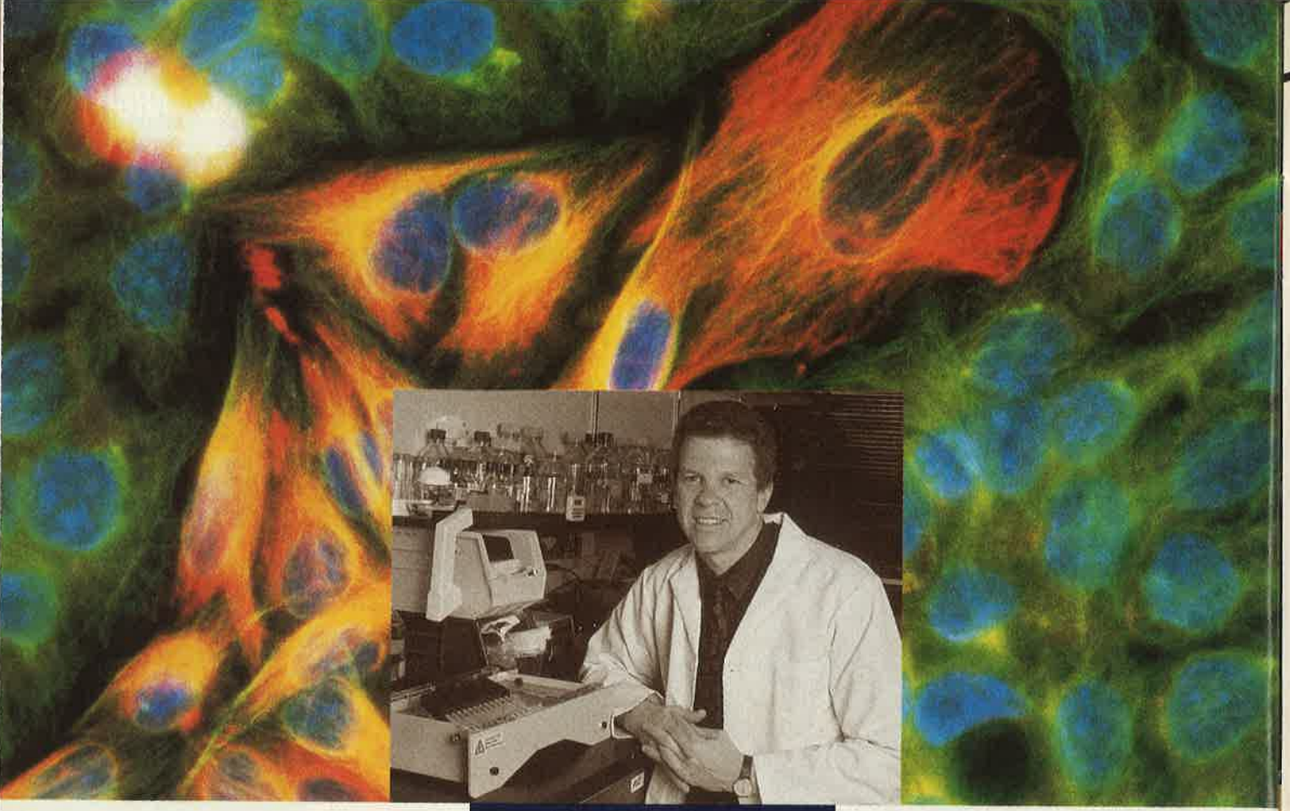
Gradually the cancer cell invades the turf occupied by its normal counterparts, killing all those in its path. It tricks nearby cells into forming food-bearing blood vessels, then compels them to churn out growth-spurring chemicals. To shield itself from patrolling immune cells, the cancer cell sprouts spiny armor like a sea urchin's. To expel the agents physicians send to kill it, the cancer cell deploys along its membrane a battery of tiny pumps. Is there a way to fight such a foe?

Until now, medicine has tried to overwhelm the cancer cell with brute force, slicing it out with surgery, zapping it with radiation or poisoning it with chemotherapy. All too often, however, a few cells manage to survive the onslaught and germinate, sometimes years later, into tumors that are impervious to treatment. The ability of the cancer cell to outmaneuver its attackers has long been reflected in mortality statistics. Despite gains made against cancers such as childhood leukemia and Hodgkin's lymphoma, the overall death rate remains dismally high. This year more than half a million Americans will succumb to cancer, making it the nation's second



ON THE MARCH
This breast-cancer cell spits out chemicals that dissolve surrounding tissue and slips through blood-vessel walls like a ghost. The disease thus can spread all over the body and become difficult to eradicate.

NIC/NIH—PHOTOTAKE



GEORGE FREY FOR TIME; BACKGROUND: NANCY KEDERSHA—IMMUNOGEN/SPL/CUSTOM MEDICAL STOCK

MALFUNCTION The multiple tumor-suppressor gene that Alexander Kamb and his colleagues discovered may explain why these melanoma cells went astray.

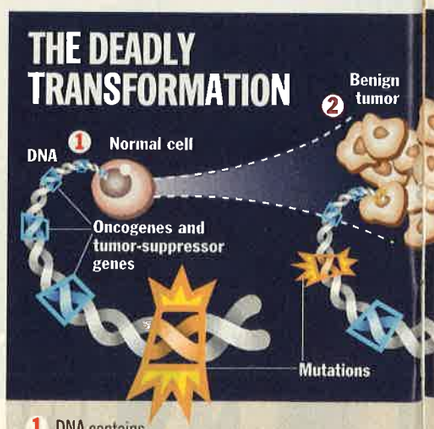
leading killer after cardiovascular disease.

Yet despite the continuing casualties, there is reason to believe the war against cancer has reached a turning point. During the past two decades, a series of stunning discoveries has pried open the black box that governs the behavior of the cancer cell and revealed its innermost secrets. Now the insights gleaned from basic research are being translated into novel approaches to cancer therapy. It still looks difficult to eradicate malignant cells, but scientists are exploring ways to tame them, to make them behave and thus greatly prolong the lives of people with the disease. The new therapies carry the promise of being not only more effective than the current slash-and-burn strategy but also much gentler to the patients who must endure the treatment. Exclaims Dr. Dennis Slamon, a UCLA cancer specialist: "This is the most exciting time imaginable!"

The excitement was running especially high last week, as encouraging news poured out of several labs all at once. From Thomas Jefferson University in Philadelphia came word that an experimental vaccine had given patients unusually long remissions from advanced melanoma, a deadly form of skin cancer. From Canada's McMaster University came a report identifying a telltale enzyme found in cancer cells—but conspicuously absent from most normal cells. If cancer researchers can find a way to deactivate this enzyme, known as telomerase, they may at last have the magic bullet they have long been seeking. Equally tantalizing was the article published in *Science* by molecular biologist Alexander Kamb and his colleagues at Myriad Genetics, a Salt Lake City, Utah, biotech firm. A majority of cancer cells, they found, lack functioning copies of a gene that serves as a circuit breaker and shuts down the abnormal cell growth that causes malignancy. Already Kamb is dreaming up ways to fix this seemingly simple glitch. "The route to therapy," he says, "seems surprisingly clear."

GOOD GENES GONE BAD The conceptual revolution that is just now sweeping into the clinic began in the 1960s, when researchers started to realize that cancer is a disease of DNA, the master molecule that encodes the genetic script of life. One of DNA's most important jobs is to govern cell division, the process by which a cell makes a copy of itself and splits in two. Ordinarily, cell division is tightly regulated, but a cancer cell divides uncontrollably, pushing into surrounding tissue.

A pivotal discovery came in 1976, when Drs. J. Michael Bishop and Harold Varmus at the University of California, San Francisco, made a startling observation. They saw that a viral gene known to cause cancer in chickens was practically a carbon copy of a normal gene found in animal and human cells. The virus had somehow stolen a perfectly good gene and put it to bad use. This finding helped lead to a general conclusion: cells become cancerous because their normal genetic machinery goes awry. The culprits that initiate the damage can be viruses, radiation, environmental poisons, defective genes inherited from parents—or a combination of all of the above.



1 DNA contains oncogenes and tumor-suppressor genes. In a normal cell, these genes work together to control cell growth.

2 Defects in these genes, either inherited or caused by radiation, chemicals or viruses, eventually let the cell grow into a tumor.

3 More mutations may cause the cells to become malignant.

4 The malignant cells stop producing a chemical that prevents blood vessels from forming. New capillaries then grow into the tumor, providing it with nutrients. This also creates a route for malignant cells to break away from the main tumor mass and travel to other parts of the body, where they start new cancers.

5 Chemotherapy can kill the malignant cells, but if there is even one cancer cell that is resistant to the treatment, it will survive and grow into a new tumor. This new cancer will be impervious to the treatment.

TIME Diagram by Joe Lertola

By last week researchers had found perhaps 100 cancer genes, at least three dozen of them important in human tumors. Some, known as oncogenes, turn on cell division, whereas others, called tumor-suppressor genes, are responsible for switching the process off. In their normal form, both kinds of genes work as a team, enabling the body to perform such vital tasks as replacing dead cells or repairing defective ones. But mutations in the chemical makeup of these genes, whether inherited or acquired later in life, can disrupt these finely tuned checks and balances. A cell containing a faulty oncogene is often likened to a car with a stuck accelerator, a cell with a damaged tumor-suppressor gene to a car with no brakes.

Scientists have thus stripped away cancer's mystery and revealed the malignant cell for what it is: not an intrinsically evil villain but an ordinary machine that has broken down in very specific, and potentially reparable, ways. They have studied the life history of a cancer cell and found errant genes at almost every step of the way, from the initial formation of a tumor to the advanced stages of metastasis, the lethal spread of the disease through the body.

FATAL FLAWS Cancer is not a modern disease. Some of our apelike ancestors undoubtedly suffered from it; so did the dinosaurs. In fact, says Robert Weinberg, a molecular biologist at the Massachusetts Institute of Technology, "it is a risk all multicellular organisms run." Each time a human cell divides, it must replicate its DNA, a biochemical manuscript some 3 billion characters long. In the course of transcribing such a lengthy document, even a skilled typist could be expected to make mistakes, and cells, like typists, occasionally err. More often than not, the mistakes they make are minor and quickly repaired by proteins that serve as miniature mechanics. Occasionally, though, cells with defects in their DNA will continue to divide, eventually forming small growths. The more cell-division cycles an organism undergoes, the more likely it is to accumulate colonies of abnormal cells, each the offspring of a single progenitor. By the time humans reach middle adulthood, then, their bodies contain millions of cells that have taken at least one step toward cancer.

EVEN SO, CANCER IS HARDLY INevitable. For example, 50% of Americans will develop at least one precancerous polyp in their colon at some point, but only a fraction of such polyps will develop into aggressive tumors. Why? Usually it takes so long for colon cancer to unfold that most people end up dying of other causes. Indeed, contrary to popular perception, getting cancer is not at all easy. To begin with, a cell must accumulate mutations not in just one or two genes but in several. In the case of colon cancer, Dr. Bert Vogelstein and his colleagues at Baltimore's Johns Hopkins Oncology Center have shown that a cell must sustain damage to at least three tumor-suppressor genes and one oncogene. The first mutation spurs the growth of the cell, triggering the formation of a benign polyp. Later changes cause the polyp to expand and become increasingly irregular in shape. By the time a cell in this growing mass suffers a final, fateful hit to its DNA, many decades may have gone by.

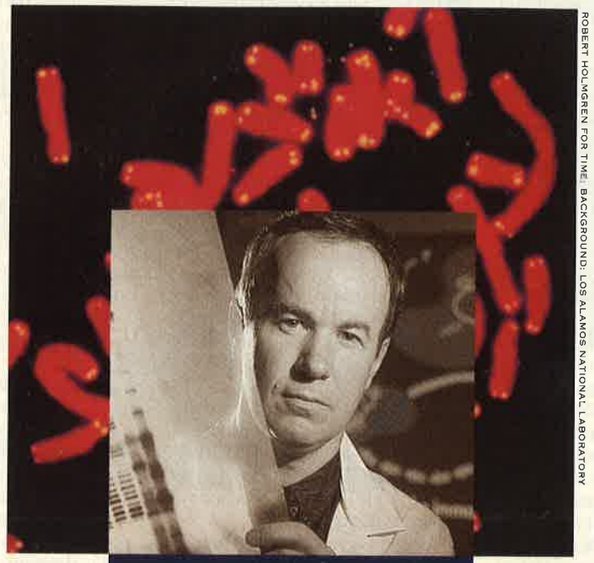
Clearly, however, some people are at a much higher risk of developing cancer than others, and at an earlier age. For them, heredity plays a major role. Over the past five months, competing teams at Johns Hopkins and Boston's Dana-Farber Cancer Institute have identified four new genes associated with a form of early onset colon cancer known to afflict particular families. These genes are carried by as many as 1 in every 200 Americans, making them the most common cause of cancer susceptibility yet discovered. In their normal form, these biological versions of computerized spelling checkers produce proteins that scoot along strands of replicating DNA, searching for tiny typos. When a protein finds an error in one of the words spelled out by DNA's four-letter chemical alphabet, it flashes an alarm. A person born with only one good copy of any of these genes is fine, until some cell in his or her colon loses or mutates its backup copy. Without a spelling checker, mutation piles upon mutation, telescoping the time it takes for cancer to develop.

BENT OUT OF SHAPE Cancer-causing mutations can occur quite by accident. But chronic exposure to carcinogens—chemicals whose by-products bind to DNA and damage it—greatly accelerate the rate at which dividing cells make errors. Proven carcinogens include asbestos, benzene and some ingredients of cigarette smoke. Many carcinogens, it turns out, are not blunderbusses but leave highly individualized fingerprints in the DNA they touch. At the National Cancer Institute, Dr. Curtis Harris, a molecular epidemiologist, has been examining cells from liver- and lung-cancer patients, searching for mutations in a tumor-suppressor gene known as p53 (p stands for the protein the gene makes and 53 for the protein's molecular weight). Smokers who develop lung cancer, Harris has found, show tiny alterations in the p53 gene that differ from those in nonsmokers. They also vary from the changes found in Chinese

liver-cancer patients. In the latter group, aflatoxin, a fungal contaminant of food, is the carcinogen, and it alters DNA in an exquisitely precise way, substituting in a single location a *T* (thymine) for a *G* (guanine) in DNA's four-letter chemical alphabet.

How can such a small mistake—the equivalent of changing the spelling of Smith to Smyth—have such an impact? Each three-letter "word" of a gene "sentence" spells out the instructions for producing 1 of 20 amino acids, compounds that in turn link to form proteins. A change in just one letter can result in the substitution of one amino acid for another. The new amino acid will be larger, smaller, stiffer or more elastic than the correct one. In ways radical and subtle, it will affect the shape of the protein and its activity. For if a cell is like a factory, then a protein is a cog in a machine that may have as many as 50 components. "If one of them develops a kink in its structure," says Harris, "then the machine doesn't fit together as well."

Kinks in proteins that form the nuclear matrix—a dynamic scaffold to which DNA is attached—may be particularly diabolical. The reason cancer cells typically have a swollen and misshapen nucleus, believes Johns Hopkins molecular biologist Donald Coffey, is that the proteins that form the nuclear matrix are misaligned in some fashion. Inside the matrix, notes Coffey, 50,000 to 100,000 loops of DNA are coiled like a Slinky, but the length of the loops, and where they begin and end, varies from tissue to tissue. The genes closest to the matrix are those that a particular cell intends to have turned on. Genes meant to stay inactive are much farther away. The conclusion is inescapable: a mutation in a gene that changes the architecture of the nuclear matrix could wreak havoc by turning the wrong genes on or off.



ROBERT HOLMGREN FOR TIME; BACKGROUND: LOS ALAMOS NATIONAL LABORATORY

IMMORTALITY These glowing telomeres on chromosome tips act as molecular clocks. Calvin Harley has found how cancer cells stop the ticktock.

YEARNINGS FOR IMMORTALITY Normal cells do not live forever. Under certain circumstances, cells are actually programmed to die. One of the most fascinating features of early development, for example, is the explosive proliferation of certain types of cells, followed by mass suicide. Human embryos start with paddles for hands; it is cell death that gives them fingers. Neurons also expire by the billions as the brain refines its circuitry during development. In adults, the cell-death program serves as a stern disciplinarian. Cells that become irreparably damaged are expected to fall on their swords for the greater good of the organism. "For an animal to live," says Dr. Samuel Broder, director of the National Cancer Institute, "it must contain within its cells the knowledge that they have to die. But the cancer cell divides at all cost. It's forgotten how to die."

The tumor-suppressor gene p53 is often described as "the guardian of the genome" because it keeps watch over DNA during cell division. When damage occurs, p53 commands other genes to bring cell division to a halt. If repairs are made, then p53 allows the cell cycle to continue. But in some cases, if the damage is too serious to be patched, p53 activates other genes that cause the cell to self-destruct. Mutations in p53, which have been detected in more than 50% of all human cancers, are thus extremely dangerous. In laboratory cultures, some cancer cells that possess mutant versions of p53 do not die when challenged by antitumor agents, while those that have normal p53 genes go belly-up.

Healthy cells apparently have a precise system for ensuring their mortality; short strips of DNA known as telomeres seem to provide a molecular clock. When a cell is young, it has more than a thousand telomeres strung along the ends of chromosomes like beads in a necklace. Each time a cell divides, 10 to 20 telomeres are lost, and the necklace grows shorter. Eventually, after many cell divisions, the necklace becomes so short that the cell fails an internal health check designed to keep old, possibly damaged cells from reproducing. Result: cell division stops, the cell begins to age rapidly, and eventually it dies. Cancer cells, in contrast, have learned to stop the ticking of the telomere clock. According to research published last week in the *Proceedings of the National Academy of Sciences* by Calvin Harley and colleagues at McMaster University in Hamilton, Ontario, malignant cells foil the clock by producing an enzyme—telomerase—that protects the length of the telomere chains. In essence, telomerase makes the cancer cell immortal.

A CALL FOR BLOOD Perhaps the most critical stage in the life of a tumor comes after it expands to about a million cells. At this point, it is "much smaller than a BB," says Dr. Judah Folkman of Harvard Medical School. This tiny mass—known as a carcinoma in situ, literally cancer in place—is malignant, but not yet dangerous. Why? Because the cells at the center of the tumor are too far from the bloodstream to obtain essential nutrients, they are less vigorous. Like a society with zero population growth, a carcinoma in situ adds about as many new cells as it loses old ones.

Months, years, even decades may pass. Then an ominous transition occurs. Some cells in the tumor begin secreting chemicals that attract endothelial cells—the key components of blood vessels. These cells form capillaries that grow into the tumor. They also pump out molecular messengers called growth factors that stimulate the tumor to divide more quickly.

What triggers blood-vessel formation, or angiogenesis, as the process is known? A major factor, scientists believe, is a sudden drop in the cancer cell's production of thrombospondin, a protein that inhibits the growth of new blood vessels. In the normal adult, angiogenesis is not only a rare event, but one cells strive to prevent, save for special circumstances like wound healing. For blood vessels invading joints can cause arthritis, and those invading the retina of the eye can cause blindness. To prevent such damage, cells keep blood vessels at bay by pumping out thrombospondin. At a recent scientific conference, Noel Bouck, a molecular biologist from Northwestern University Medical School, stunned her colleagues by presenting preliminary data suggesting that thrombospondin production may be regulated by that ubiquitous gene, p53.

PULLING UP STAKES Angiogenesis is the harbinger of metastasis. The same vessels that feed the tumor also provide it with av-

SHELLY KATZ—SYGMA FOR TIME

"It was like a shot for measles or mumps. I do not expect any side effects, except to feel better."

JACK SWEPSTON, 48. Pancreatic Cancer. On March 31 this Dallas dentist traveled to the National Cancer Institute in Bethesda, Maryland, to receive a new type of anticancer vaccine. Prepared by a team of researchers, including Drs. David Carbone and John Minna of the University of Texas Southwestern Medical Center, the vaccine was a synthetic version of a mutant protein fragment found in Swepston's tumor. The hope is that the immune system will learn to recognize this target and destroy the cells that make it. "I haven't felt a significant improvement yet," he says, "but the doctors are tremendously excited."

enues of escape. Not all the myriad cells shed by tumors survive the turbulent voyage through the bloodstream, notes experimental oncologist Ann Chambers of the London Regional Cancer Centre in Ontario. But those that do eventually slip through blood-vessel walls with ease. Using a video camera attached to a microscopic lens, Chambers has watched in wonder as melanoma and breast-cancer cells, injected into mice, become lodged in capillary walls, then crawl out into the liver. Three days later, her camera resolves the spidery shapes of tiny metastatic growths. The lesson, Chambers believes, is depressingly clear. Cancer cells zip in and out of blood vessels so readily that, once angiogenesis occurs, they should be presumed to have already spread around the body.

Metastasis is an event of awesome complexity, one that requires multiple genes to cooperate as closely as musicians in an orchestra. Some of these genes code for chemical solvents that enable the advancing cell to dissolve surrounding tissue. Others order up the production of adhesion molecules that, like treads under a tank, move the cell forward. Why would genes do that? The answer, notes Patricia Steeg of the National Cancer Institute, is that while the genes important to metastasis are abnormally turned on, they are not necessarily abnormal themselves. A cancer cell, in many ways, is not that different from an embryonic cell on its way to becoming a patch of skin or a bundle of nerves. Both embryonic and cancer cells divide and form ill-defined clumps. Both get up and move around. Both migrate and populate new areas. But while an embryonic cell stops proliferating and matures into adult tissue, the cancer cells just keep dividing.

One reason for the difference may lie in a gene known as nm23, first identified by Steeg in 1988. It seems to help mature cells stop dividing and arrange themselves in an orderly fashion. Steeg's research suggests that in cancer cells this crucial gene often malfunctions. When she introduced a normal nm23 gene (nm stands for nonmetastatic) into highly malignant human breast cells, then injected these cells into mice, their tendency to form metastases dropped as much as 90%.

GUARDING THE MASTER SWITCH Until last week, p53, the subject of some 1,000 scientific papers in 1993 alone, was considered the most important cancer gene. The journal *Science* even named it Molecule of the Year. But now there is a new contender for notoriety—MTS1, as Alexander Kamb and his colleagues refer to the multiple tumor-suppressor gene they have just discovered. "Multiple" refers to the fact that defects in this gene can cause many kinds of cancer, including melanoma, lung, breast and brain tumors. In fact, functional copies of MTS1 may be missing in more than 50% of all human cancers.

What makes MTS1 so significant is its clear role in the cell-division cycle. A cell divides not at will but in response to specific signals, such as growth factors produced by white blood cells rushing to repair a wound. These signals are picked up by receptors on the membrane of the cell and passed along—like batons in a high-speed relay—through the interior, all the way to a master "on" switch positioned deep in the nucleus. Not surprisingly, many oncogenes, including one called ras, the first human cancer gene ever identified, are involved in this type of signaling pathway. But there are other molecules that determine whether the cell should heed these signals. And the small protein produced by

THE BIG KILLERS

Estimates in the U.S., 1994

Cancer		Deaths	New cases	Five-year survival rate	Risk Factors
Lung		153,000	172,000	13%	Cigarette smoking; exposure to asbestos, chemicals, radiation, radon
Colon/Rectum		56,000	149,000	58%	Family history; high-fat, low-fiber diet
Female Breast		46,000	182,000	79%	Age; family history; no pregnancies; late menopause; early menarche
Prostate		38,000	200,000	77%	Age; family history; possibly fat intake
Pancreas		25,900	27,000	3%	Age; smoking; fat intake
Lymphoma	Hodgkin's Non-Hodgkin's	22,750	52,900	78% 52%	Reduced immune function; exposure to herbicides, solvents, vinyl chloride
Leukemia		19,100	28,600	38%	Genetic abnormalities; exposure to ionizing radiation, chemicals; viruses
Ovary		13,600	24,000	39%	Age; family history; genetic disorders; no pregnancies
Kidney		11,300	27,600	55%	Smoking
Bladder		10,600	51,200	79%	Smoking
Uterus	Cervical Endometrial	10,500	46,000	67% 83%	Intercourse at an early age; multiple sex partners; smoking Early menarche; late menopause; obesity
Oral		7,925	29,600	53%	Smoking; excessive use of alcohol
Skin Melanoma		6,900	32,000	84%	Sunburn; fair complexion; exposure to coal tar, pitch, creosote, arsenic, radium

Source: American Cancer Society

MTS1 appears to be among the most important inhibitors of cell division. Last year researchers at New York's Cold Spring Harbor Laboratory discovered that a protein they called p16 stifled an enzyme that is a growth promoter. Last week it became clear that p16 and the MTS1 protein are one and the same.

TARGETS FOR CANCER FIGHTERS Theoretically, any gene that goes awry in a cancer cell offers a way to attack the problem. But those that directly influence a cell's decision to divide are spurring particular interest. The protein made by the MTS1 gene seems exceptionally promising, for it has characteristics suggesting it may be easily fashioned into a drug, which then might be able to stop tumor cells in their tracks. "In terms of therapeutic potential," declares Kamb, "MTS1 may be the most important tumor-suppressor gene yet discovered."

Still, as pharmaceutical companies well know, many surprises can pop up on the way to developing a new drug, and other approaches to cancer therapy may win out in the end. Among the possibilities are anticancer vaccines designed to stimulate the immune system to combat tumors. Currently being tested in the U.S. and Canada is a vaccine that spurs an assault on the weirdly configured carbohydrates that protrude from tumor cells like spikes on a medieval ball and chain. At the meeting of the American Society for Cancer Research last week, Dr. David Berd of Thomas Jefferson University presented the most encouraging evidence to date that the vaccine strategy may work. Berd told of inoculating 47 melanoma patients with a vaccine made of their own tumor cells inactivated by radiation. Three years later, 60% remained tumor-free, compared with 20% in the unvaccinated control group. The approach works best, apparently, in patients who have tumors small enough to be surgically removed but whose disease shows signs of spread.

The discovery announced last week that cancer cells rely on the enzyme telomerase to stay alive opens up a different attack strategy. The leader of that research team, Calvin Harley, has taken a leave from McMaster University to work at Geron Corp. in Menlo Park, California. The company is trying to craft a drug that will block the action of telomerase. "The cancer cell," explains Harley, "is already very old. If we can inhibit telomerase, we might cause the tumor to die after a few doublings." Even better, the fact that cancer cells produce telomerase and that normal cells (save for sperm) don't, says Harley, "gives us hope that we may be able to develop a drug without serious side effects."

The formation of blood vessels in a tumor through angiogenesis is another promising target for an anticancer drug—

JOHN MCGRAIL FOR TIME

"They will have surgical options not available to me. For that reason I decided they would be tested. I'm a real advocate for early detection."

ANN FAGAN, 37, Colorectal Cancer Ten years ago, when Ann Fagan, a paralegal from Conyngham, Pennsylvania, was found to have cancer, she underwent an ileostomy, a procedure that constructs an opening for the bowels through the abdominal wall. Last year tests revealed that her daughters Katie (left), 13, and Sarah, 11, had inherited a genetic defect that puts them at high risk for the same type of cancer. But this diagnosis has a silver lining, since the girls will be able to have surgery before rather than after cancer develops. Cancer susceptibilities that come from inherited mutations may account for 20% of all cases.

because the process is so rare in normal cells. Clinical trials have begun on several compounds that interfere with angiogenesis. One such compound comes from a fungus that was accidentally discovered in 1989 when it contaminated cultures of endothelial cells in Judah Folkman's Harvard laboratory, dramatically curtailing their growth. This drug, says Folkman, is aimed not at curing cancer but at prolonging the period of time colonies of tumor cells missed by conventional therapy remain in place without spreading. "Suppose we prolong this period of dormancy for 10 years, and then another 10 years," muses Folkman. "Why, now we're beginning to compete with the normal life span."

Indeed, what seems most significant about all the new therapies, what joins them together, is not their power, for this has yet to be proved. Rather, it is the seismic shift in strategy they collectively represent. Increasingly, researchers speak not of slaughtering the cancer cell but of tricking it into dying naturally, perhaps of old age, as other cells do. They also talk of reining in the cancer cell, even rehabilitating it, a task that demands the development of less toxic drugs that can be tolerated over a lifetime. The model for cancer therapy of the future already exists. "After all, we don't cure diseases like diabetes and hypertension," says Dr. Lance Liotta, the National Cancer Institute's leading metastasis expert. "We control them. Why can't we look at cancer that way?"

By this reasoning, even metastatic cancer may eventually be brought to heel. Squeezed into a tiny cubicle day after day at the National Cancer Institute, Patricia Steeg stares at colonies of aggressive breast-cancer cells that have shut down the protective nm23 gene. Soon she will squirt over these colonies newly identified antitumor compounds. Among them she hopes to find one, maybe more, that interferes with metastatic growth. A total of 14 of these compounds are already sitting in a freezer in her lab—white crystals that cluster like snowflakes in the bottom of test tubes. If these fail to have an effect, Steeg has a list of more than 30 others that might. Like many cancer researchers, she conveys, through her own personal enthusiasm, a sense that an immense psychological barrier has been breached. No, Steeg has not yet found a drug that cures cancer or even controls it. But, she exclaims, "I'm beginning to like the odds." ■