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SCIENCE

A Catalog of Cancer Genes That's Done, or Just a Start

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Carl Zimmer

MATTER

Cancer is a disease of genes gone wrong. When certain genes mutate, they make cells behave in odd ways. The cells divide swiftly, they hide from the immune system that could kill them and they gain the nourishment they need to develop into tumors.

Scientists started identifying these cancer genes in the 1970s and their list slowly grew over the years. By studying them, scientists came to understand how different types of cancer develop and in some cases they were even able to develop gene-targeting drugs. Last May, for example, the Food and Drug Administration approved a drug known as Tarceva as a first-line treatment for lung cancer in which a gene called EGFR has mutated.

The National Institutes of Health, hoping to speed up the identification of cancer genes, started an ambitious project in 2005 called the Cancer Genome

Atlas. They analyzed 500 samples from each of over 20 types of cancer and found a wealth of new genes. The data have helped scientists discover more of the tricks cancer cells use to thrive at our expense.

"The Cancer Genome Atlas has been a spectacular success, there's no doubt about that," said Bruce Stillman, the president of Cold Spring Harbor Laboratory.

But now, as the Atlas project is coming to an end, researchers at the Broad Institute of M.I.T. and Harvard have published a study in the journal Nature that has scientists debating where cancer research should go next. They estimated that scientists would need to examine about 100,000 cancer samples —10 times as many as the $375 million Cancer Genome Atlas has gathered — to find most of the genes involved in 50 cancer types.

"We now know what it would take to get a complete catalog," said Eric S. Lander, the founding director of the Broad Institute and a co-author of the new study. "And we now know we're not close to done. We have a lot left to learn."

Traditionally, scientists have identified cancer genes by comparing healthy cells with cancerous ones. If they find a statistically unusually high number of cells with mutations in a particular gene, they can then examine it to see if it really does help drive cancer — or if it is just carrying a harmless mutation.

Dr. Lander and his colleagues suspected this method could miss some genes. While some cancer genes affect most cells of a given type of cancer, other genes are only involved in a fraction of them. (EGFR, the gene treated with Tarceva, is mutated in only about 10 percent of cases of nonsmall cell lung cancer.) Small samples of cancer cells might not contain the less common mutations.

The Broad researchers suspected that they could catch some of these missing genes by looking at several cancer types at once, because some genes are not limited to a single type of cancer.

For their new study, the scientists examined cancer samples from the Cancer Genome Atlas, as well as cancer samples from the Broad's own collection. All told, they analyzed 4,742 samples from 21 types of cancer.

The new study detected many of the genes that other scientists have previously linked to those 21 types of cancer. But they also found new genes that

had been overlooked before. All told, they identified 33 genes that they consider strong candidates for playing a role in cancer — a potential increase of the catalog of cancer genes of 25 percent.

"This was eye-opening to me," said Dr. Lander.

Dr. Lander and his colleagues began to wonder how many genes could be found if scientists looked at more cancer samples. Was the cancer catalog almost finished, or only just begun?

"We were able to ask for the first time, 'Are we there yet?'" said Dr. Lander.

They extrapolated from their own results to gauge how many more samples scientists would need to look at to find most cancer genes involved in at least 2 percent of cancers of a given type.

To find most cancer genes involved in the 50 most common types of cancer, the researchers estimated that they would have to analyze 100,000 samples. In other words, the atlas has gotten us a tenth of the way to the finish line.

Dr. Harold Varmus, the director of the National Cancer Institute, said the study has raised valuable questions. "The paper provides some models about what we might think about doing next," he said. He said the agency is now considering testing Dr. Lander's hypothesis on a few types of cancer by gathering more samples.

Dr. Lander and his colleagues argue for finishing off the cancer gene catalog. "Completing the genomic analysis of this disease should be a biomedical imperative," they wrote in their new paper.

In an interview, Dr. Lander said knowing most genes involved in cancer would be a powerful weapon against the disease. "How could we think of beating cancer in the long term without having the whole catalog?" he said. "It would be crazy not to have the information."

But Dr. Stillman of Cold Spring Harbor Laboratory said completing the atlas has to be weighed against other needs. "Whether we need to know every cancer gene, I'd like to see an argument for how that's going to help the advancement of new therapy," he said.

For many researchers, the question comes down to whether extending the atlas project would be the best use of existing research funds. "There's no

question that it would be valuable. The question is whether it's worth it," said Dr. Bert Vogelstein, a Howard Hughes Medical Institute Investigator at Johns Hopkins University.

Some scientists say it might make more sense to study common cancer genes that have already been identified, instead of searching for relatively rare genes that might not turn out to be helpful in fighting cancer.

Also in question is who would pay for advancing the cancer catalog project. "We still don't know how much money we're going to have this year," said Dr. Varmus of the National Cancer Institute's budget. "We're not going to set off tomorrow and do 100,000 complete genomes."

Dr. Lander argued that the project could be done for a reasonable cost, and might also be supported by philanthropic organizations or international partners. In any case, he said, he welcomed a debate about when science will finish the cancer gene catalog.

"If people say, 'I would rather not know that for five years, or 10 years,' that's a reasonable argument," said Dr. Lander. "But I would rather know that sooner."

Correction: February 6, 2014

Because of an editing error, an earlier version of this article misstated a finding of the new study. The researchers estimated that scientists would need to examine about 100,000 cancer samples — not genes — to find most of the genes involved in 50 cancer types.

The New York Times

November 26, 2013

In Israel, a Push to Screen for Cancer Gene Leaves Many Conflicted

By RONI CARYN RABIN

KFAR SABA, Israel — Ever since she tested positive for a defective gene that causes breast cancer, Tamar Modiano has harbored a mother's fear: that she had passed it on to her two daughters. Ms. Modiano had her breasts removed at 47 to prevent the disease and said that the day she found out her older daughter tested negative was one of the happiest of her life.

Now she wants her younger daughter, Hadas, 24, to be tested so she can start a family early if she is positive and then have a double mastectomy too. Ms. Modiano's elder daughter, Suzi Gattegno, 29, disagrees.

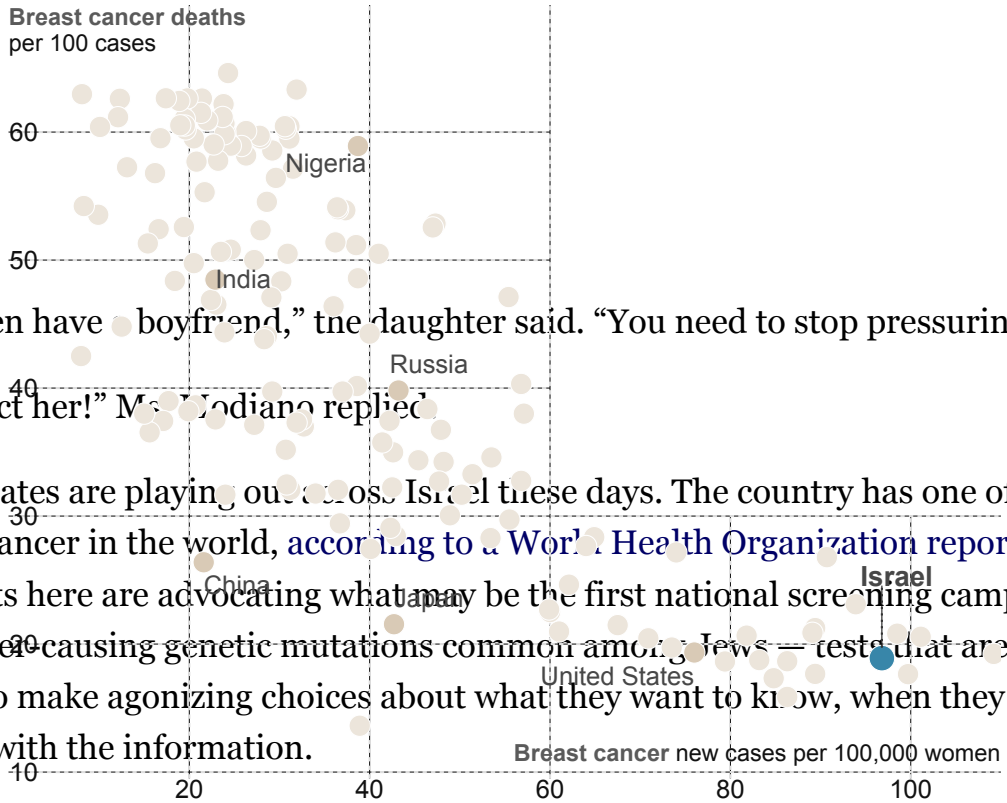
"You're keeping her from living her life," Ms. Gattegno told her mother. "You want to marry her off early."

"If she's a carrier, she should marry early," her mother countered.

Breast Cancer
Around the Globe

Israel has one of the highest rates of breast cancer in the world. Mortality is very low, in part because of intense screening.

INTERACTIVE GRAPHIC



“She doesn’t even have a boyfriend,” the daughter said. “You need to stop pressuring her.”

“I want to protect her!” Ms. Modiano replied.

Such family debates are playing out across Israel these days. The country has one of the highest rates of breast cancer in the world, according to a World Health Organization report. And some leading scientists here are advocating what may be the first national screening campaign to test women for cancer-causing genetic mutations common among Jews — tests that are already forcing young women to make agonizing choices about what they want to know, when they want to know it and what to do with the information.

The so-called Jewish breast cancer genes have preoccupied women here for years, but after the actress Angelina Jolie revealed in May that she had undergone a double mastectomy because she had tested positive for such a mutation, coverage here exploded, with radio and TV talk shows featuring Israeli women grappling with similar decisions.

Jews of Ashkenazi, or central and eastern European, backgrounds, who make up about half the Jews in Israel and the vast majority of those in the United States, are much more likely to carry mutations that increase the risks for both breast and ovarian cancers, according to the National Cancer Institute.

A number of influential geneticists and cancer doctors from various medical centers here say that the Israeli Health Ministry should pay for free voluntary genetic testing of all Ashkenazi women over the age of 25. About a million women would be covered, at a cost of less than $100 per test. Jews of Iraqi descent, whose families also often carry a harmful mutation, might also be screened.

The goal of a proposed universal screening program would be to identify an estimated 30,000 Israeli women who have the mutations. So far, with sporadic testing, about 6,000 of them have been found, many only after a cancer diagnosis, said Dr. Ephrat Levy-Lahad, the coordinator of the Israel Genetics Consortium.

“That’s our target population,” said Dr. Oded Olsha, a breast surgeon at Shaare Zedek Medical

Center in Jerusalem. “If we can find them, we can save their lives.”

Women who tested positive for mutations in the BRCA1 and BRCA2 genes, which suppress tumors, would be strongly encouraged to complete child bearing by their late 30s so they could have their ovaries removed by age 40. Risk-reducing mastectomies would also be offered.

The profoundly controversial idea of broad-based screening has already set off debate in Israel among advocates for women and those in the medical and scientific fields. Critics say it may lead to social stigma and a rash of unnecessary operations, and also burden some women with information they may not want or know how to use.

The choice is not a simple one. Removing the breasts and ovaries sharply reduces the risk of cancer, but mastectomies are disfiguring and women often experience scarring and numbness after breast reconstruction. Loss of the ovaries plunges women into menopause, potentially leading to hot flashes, a reduced sex drive and heightened risks of heart disease and bone loss.

But already demand for genetic testing is very high here — there are yearlong waiting lists — and national health insurance generally covers it as long as a woman is referred by her doctor or a genetic counselor.

While poor countries struggle to provide even basic cancer care to women, wealthier societies like Israel and the United States are increasingly using sophisticated technologies to identify those at greatest risk in an effort to thwart the disease before it gets started. Several American Jewish organizations have recently undertaken a campaign to raise awareness about the genetic susceptibility to breast and ovarian cancer among Ashkenazi Jews.

The cancer divide here in Israel is more ethnic than economic. Will only Ashkenazi Jews be routinely tested? Though they are much more likely to carry one of the common harmful mutations in the BRCA1 and BRCA2 genes, Israel is a melting pot of both Arab citizens and Jews from all over the world, and only half of the country’s six million Jews are of Ashkenazi ancestry.

Under the proposal being put forward by some Israeli geneticists, it is likely that Israeli Arab citizens and Jews of Sephardic ancestry — whose families originate in North Africa and the Middle East — would not routinely be included among those screened for BRCA mutations, a point of contention in a country where a social and ethnic rift already divides Sephardic and Ashkenazi Jews.

Families of Iraqi origin, like Ms. Modiano’s, may be covered because of their higher genetic risks.

She always knew there was cancer in her father's family. Three of his sisters died of breast cancer at young ages.

But she was tested for cancer-causing mutations only three years ago after finding out her relatives were being screened. The result stunned her.

"I thought about what it meant for me, and then I thought, 'What about my daughters?' " Ms. Modiano said recently, shuddering slightly. "I was petrified. I still am."

Within three months, Ms. Modiano had a risk-reducing double mastectomy and an operation to remove her ovaries. But the decisions facing her daughters, both in their 20s, were far more complicated. Neither was married, and each had a 50 percent chance of carrying the mutation.

Ms. Gattegno, who was in nursing school at the time, decided to be tested.

"I told my boyfriend that if I turned out to be a carrier, I would quit school for a while and we'd have kids right away," she said. "And then I'd have a prophylactic mastectomy."

Difficult Questions

At the Shaare Zedek Medical Center in Jerusalem, Dr. Levy-Lahad, who started one of the first genetic testing programs in Israel, is among the main champions of universal screening for Ashkenazi women. She has worked closely with the American scientist who identified the BRCA1 gene, Mary-Claire King.

"If you're only testing women after they've been affected, you've lost the game," Dr. Levy-Lahad said. "Genetic testing is about prevention."

She pointed to the risks. One in 40 Ashkenazi women carry a harmful genetic mutation, compared to less than one in 100 women generally.

Women with these mutations are four to five times more likely to develop aggressive breast cancers, according to the National Cancer Institute. The disease often comes at an early age and in both breasts, said Dr. Gad Rennert, the director of Israel's National Cancer Control Center.

The potential for preventing ovarian cancer, a rarer but more lethal disease, is even greater. The common harmful mutations found in Ashkenazis are implicated in about 30 percent of ovarian cancers in Israeli women — and 40 percent or more of cases in women under 60, Dr. Rennert said.

Practical and ethical questions abound. Should men — who are just as likely to pass the mutations to their children and who are themselves at increased risk for some cancers — also be tested? Will ultra-Orthodox Jews participate in screening, knowing a positive test could hurt their family's chances of making a good marriage match?

Identifying people as carriers can change their perceptions of themselves and the way they envision their futures, said Dr. Gail P. Jarvik, the head of the division of medical genetics at University of Washington Medical Center in Seattle.

Even though the testing would be voluntary, women could feel pressured to participate, said Barbara A. Koenig, a professor of medical anthropology and bioethics at the University of California, San Francisco. "When you institute mass screening, you're making a collective decision that this is a good thing."

There are also lingering scientific questions. While much is known about the three common Ashkenazi BRCA1 and BRCA2 mutations, the risk they confer varies. Some families may have other genetic factors that modify their risk, which explains why some carriers never develop cancer while others die in their 20s.

Women identified as mutation carriers are showered with resources for early detection and prevention. These women's risk for developing breast cancer ranges from 45 to 65 percent or higher, depending on family history, and their risk for ovarian cancer can be as high as 39 percent.

Routine mammography screening for most Israeli women starts at 50, but carriers are eligible for frequent clinical breast exams and expensive magnetic resonance imaging of the breast, all covered by national health insurance. They are also eligible for regular blood tests and vaginal ultrasounds to screen for ovarian cancer.

Cultural Obstacles

Many Israeli women who have the harmful mutations complain that male doctors display sexist attitudes about the importance of breasts and are loath to do mastectomies on healthy women.

Dr. Moshe Inbar, an outspoken oncologist in Tel Aviv who opposes preventive mastectomies, has said that a woman cannot have an orgasm after her breasts are removed, an assertion not supported by evidence.

"Would you like to live without your breasts?" Dr. Inbar, the director of the oncology division at Tel

Aviv Sourasky Medical Center, asked. “I try to dissuade women from doing this. Surgery is not something that should be done on patient demand; it should be done when indicated.”

While more than a third of American women carrying the harmful genetic mutations choose preventive mastectomies, only 4 percent of Israeli women do, according to a 2008 International Journal of Cancer study that compared risk-reducing procedures for samples of BRCA1 and BRCA2 mutation carriers in Canada, the United States, Israel and six European countries.

By contrast, well over half the carriers in all countries but Poland had their ovaries removed, a procedure that also reduces breast cancer risk.

But there are signs that attitudes are beginning to change here, as women take to the Internet to research their options, challenge the medical profession and shop for doctors.

Tamar Horesh, 35, a computer programmer from central Israel, has vivid memories of her mother’s painful death from ovarian cancer at 51.

When Ms. Horesh tested positive for a BRCA1 mutation, she said her husband supported her decision to surgically remove her ovaries and breasts. They had three young children to raise.

Finding a doctor to do it was another matter.

“The first doctor I went to said I was insane, and he said, ‘If you have brain cancer, are you going to chop off your head?’ ” said Ms. Horesh. “The second doctor said that he noticed I had a small chest, and he thought I just wanted an excuse to have my breasts enlarged.”

A third doctor told her what many women hear, “Come back when you have cancer,” and “Nobody dies of breast cancer nowadays.”

In fact, some 900 Israeli women die of breast cancer each year, according to the Israel Cancer Association.

Ms. Horesh eventually got referrals from Bracha, a group founded to raise awareness by Lisa Cohen, who has a BRCA mutation.

Ms. Cohen’s mother died of cancer at 49, and then her sister, who had four young children, died at 36. “I felt like I was going to be next in line,” said Ms. Cohen, a divorced mother of three who was determined to stay alive for her children.

A Personal Decision

Hadas Modiano, a university student in Jerusalem, is waiting a couple of years before she seriously considers being tested as her mother insists. But her mother's example has given her strength.

"I think I'm not as scared as I might have been because I saw what my mother went through," she said. "It was hard, but she has managed and overcome."

But for many women, the choices are harrowing. A Tel Aviv lawyer, 43, who asked that her name not be used to protect her privacy, was devastated when she found out at 26 that she had one of the bad mutations.

The lawyer, who was only 4 when her mother died of breast cancer, said she was among the first to line up for the genetic test when it became available in Israel in the 1990s.

"You may think you're prepared for this information, but you aren't," she said. "My blood went cold when I found out." Afterward, she said she realized, "The only solutions are so radical — amputating parts of your body."

When she first met the man who became her husband, she told him that she could never marry or have children. He convinced her otherwise. She goes for frequent scans and checkups but postponed having a mastectomy so she could breast-feed their children.

She chose to become pregnant through in vitro fertilization so female embryos that did not carry harmful mutations could be selected in the lab.

"Finally, there was something positive to do with the information," she said.

Preventive surgeries are not always successful. Tali Shalev had what was supposed to be a preventive double mastectomy, but pathologists found a cancerous lesion in the removed breast tissue. "I'm an example of someone who did everything possible," said Ms. Shalev, 40, who has three children.

The dilemmas of genetic testing are compounded in the ultra-Orthodox community, where the emphasis on modesty often dampens open discussion.

Still, Tziporah, 38, a Canadian-born Orthodox mother of seven who now lives in Israel, talks openly about her experience because she wants to reach other religious women. Tziporah, who goes by her nickname, Tzippy, asked that her last name not be used to protect the privacy of her

extended family members, who also may carry the gene. Her mother died of breast cancer at 42, when she was 5, and when Tzippy was pregnant with her last child a few years ago, she tested positive for a BRCA1 mutation.

She sought advice from several rabbis about whether she should go forward with risk-reducing surgeries. They reassured her that preserving life is one of the supreme values of Judaism.

So three years ago, after her youngest child was born, she had her breasts and ovaries removed. The operations were grueling, but she said she wanted to make sure her children would not suffer the same loss she had. And she said she felt she had a mission to encourage other women to be tested.

“You know why God did this to me?” she said. “Because I’ve got a really big mouth.”

So she is spreading the word within the Orthodox community that genetic screening can save lives.

“Women don’t have to be dying on their kids,” she said.

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Why Everyone Seems to Have Cancer

By GEORGE JOHNSON

EVERY New Year when the government publishes its Report to the Nation on the Status of Cancer, it is followed by a familiar lament. We are losing the war against cancer.

Half a century ago, the story goes, a person was far more likely to die from heart disease. Now cancer is on the verge of overtaking it as the No. 1 cause of death.

Troubling as this sounds, the comparison is unfair. Cancer is, by far, the harder problem — a condition deeply ingrained in the nature of evolution and multicellular life. Given that obstacle, cancer researchers are fighting and even winning smaller battles: reducing the death toll from childhood cancers and preventing — and sometimes curing — cancers that strike people in their prime. But when it comes to diseases of the elderly, there can be no decisive victory. This is, in the end, a zero-sum game.

The rhetoric about the war on cancer implies that with enough money and determination, science might reduce cancer mortality as dramatically as it has with other leading killers — one more notch in medicine's belt. But what, then, would we die from? Heart disease and cancer are primarily diseases of aging. Fewer people succumbing to one means more people living long enough to die from the other.

The newest cancer report, which came out in mid-December, put the best possible face on things. If one accounts for the advancing age of the population — with the graying of the baby boomers, death itself is on the rise — cancer mortality has actually been decreasing bit by bit in recent decades. But the decline has been modest compared with other threats.

A graph from the Centers for Disease Control and Prevention tells the story. There are two lines representing the age-adjusted mortality rate from heart disease and from cancer. In 1958 when the diagram begins, the line for heart disease is decisively on top. But it plunges by 68 percent while cancer declines so slowly — by only about 10 percent — that the slope appears far less significant.

Measuring from 1990, when tobacco had finished the worst of its damage and cancer deaths were

peaking, the difference is somewhat less pronounced: a decline of 44 percent for heart disease and 20 percent for cancer. But as the collision course continues, cancer seems insistent on becoming the one left standing — death's final resort. (The wild card in the equation is death from complications of Alzheimer's disease, which has been advancing year after year.)

Though not exactly consoling, the fact that we have reached this standoff is a kind of success. A century ago average life expectancy at birth was in the low to mid-50s. Now it is almost 79, and if you make it to 65 you're likely to live into your mid-80s. The median age of cancer death is 72. We live long enough for it to get us.

The diseases that once killed earlier in life — bubonic plague, smallpox, influenza, tuberculosis — were easier obstacles. For each there was a single infectious agent, a precise cause that could be confronted. Even AIDS is being managed more and more as a chronic condition.

Progress against heart disease has been slower. But the toll has been steadily reduced, or pushed further into the future, with diet, exercise and medicines that help control blood pressure and cholesterol. When difficulties do arise they can often be treated as mechanical problems — clogged piping, worn-out valves — for which there may be a temporary fix.

Because of these interventions, people between 55 and 84 are increasingly more likely to die from cancer than from heart disease. For those who live beyond that age, the tables reverse, with heart disease gaining the upper hand. But year by year, as more failing hearts can be repaired or replaced, cancer has been slowly closing the gap.

For the oldest among us, the two killers are fighting to a draw. But there are reasons to believe that cancer will remain the most resistant. It is not so much a disease as a phenomenon, the result of a basic evolutionary compromise. As a body lives and grows, its cells are constantly dividing, copying their DNA — this vast genetic library — and bequeathing it to the daughter cells. They in turn pass it to their own progeny: copies of copies of copies. Along the way, errors inevitably occur. Some are caused by carcinogens but most are random misprints.

Over the eons, cells have developed complex mechanisms that identify and correct many of the glitches. But the process is not perfect, nor can it ever be. Mutations are the engine of evolution. Without them we never would have evolved. The trade-off is that every so often a certain combination will give an individual cell too much power. It begins to evolve independently of the rest of the body. Like a new species thriving in an ecosystem, it grows into a cancerous tumor. For that there can be no easy fix.

These microscopic rebellions have been happening for at least half a billion years, since the advent of complex multicellular life — collectives of cells that must work together, holding back, as best each can, the natural tendency to proliferate. Those that do not — the cancer cells — are doing, in a Darwinian sense, what they are supposed to do: mutating, evolving and increasing in fitness compared with their neighbors, the better behaved cells of the body. And these are left at a competitive disadvantage, shackled by a compulsion to obey the rules.

As people age their cells amass more potentially cancerous mutations. Given a long enough life, cancer will eventually kill you — unless you die first of something else. That would be true even in a world free from carcinogens and equipped with the most powerful medical technology.

Faced with this inevitability, there have been encouraging reductions in the death toll from childhood cancer, with mortality falling by more than half since 1975. For older people, some early-stage cancers — those that have not learned to colonize other parts of the body — can be cured with a combination of chemicals, radiation therapy and surgery. Others can be held in check for years, sometimes indefinitely. But the most virulent cancers have evolved such wily subterfuges (a survival instinct of their own) that they usually prevail. Progress is often measured in a few extra months of life.

OVER all, the most encouraging gains are coming from prevention. Worldwide, some 15 to 20 percent of cancers are believed to be caused by infectious agents. With improvements in refrigeration and public sanitation, stomach cancer, which is linked to Helicobacter pylori bacteria, has been significantly reduced, especially in more developed parts of the world. Vaccines against human papilloma virus have the potential of nearly eliminating cervical cancer.

Where antismoking campaigns are successful, lung cancer, which has accounted for almost 30 percent of cancer deaths in the United States, is steadily diminishing. More progress can be made with improvements in screening and by reducing the incidence of obesity, a metabolic imbalance that, along with diabetes, gives cancer an edge.

Surprisingly, only a small percentage of cancers have been traced to the thousands of synthetic chemicals that industry has added to the environment. As regulations are further tightened, cancer rates are being reduced a little more.

Most of the progress has been in richer countries. With enough political will the effort can be taken to poorer parts of the world. In the United States, racial disparities in cancer rates must be addressed. But there is a long way to go. For most cancers the only identifiable cause is entropy,

the random genetic mutations that are an inevitable part of multicellular life.

Advances in the science will continue. For some cancers, new immune system therapies that bolster the body's own defenses have shown glints of promise. Genomic scans determining a cancer's precise genetic signature, nano robots that repair and reverse cellular damage — there are always new possibilities to explore.

Maybe someday some of us will live to be 200. But barring an elixir for immortality, a body will come to a point where it has outwitted every peril life has thrown at it. And for each added year, more mutations will have accumulated. If the heart holds out, then waiting at the end will be cancer.

George Johnson is a former reporter and editor at The New York Times and the author of "The Cancer Chronicles."

The New York Times

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December 9, 2012

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY

PHILIPSBURG, Pa. — Emma Whitehead has been bounding around the house lately, practicing somersaults and rugby-style tumbles that make her parents wince.

It is hard to believe, but last spring Emma, then 6, was near death from leukemia. She had relapsed twice after chemotherapy, and doctors had run out of options.

Desperate to save her, her parents sought an experimental treatment at the Children's Hospital of Philadelphia, one that had never before been tried in a child, or in anyone with the type of leukemia Emma had. The experiment, in April, used a disabled form of the virus that causes AIDS to reprogram Emma's immune system genetically to kill cancer cells.

The treatment very nearly killed her. But she emerged from it cancer-free, and about seven months later is still in complete remission. She is the first child and one of the first humans ever in whom new techniques have achieved a long-sought goal — giving a patient's own immune system the lasting ability to fight cancer.

Emma had been ill with acute lymphoblastic leukemia since 2010, when she was 5, said her parents, Kari and Tom. She is their only child.

She is among just a dozen patients with advanced leukemia to have received the experimental treatment, which was developed at the University of Pennsylvania. Similar approaches are also being tried at other centers, including the National Cancer Institute and Memorial Sloan-Kettering Cancer Center in New York.

"Our goal is to have a cure, but we can't say that word," said Dr. Carl June, who leads the research team at the University of Pennsylvania. He hopes the new treatment will eventually replace bone-marrow transplantation, an even more arduous, risky and expensive procedure that is now the last hope when other treatments fail in leukemia and related diseases.

Three adults with chronic leukemia treated at the University of Pennsylvania have also had

complete remissions, with no signs of disease; two of them have been well for more than two years, said Dr. David Porter. Four adults improved but did not have full remissions, and one was treated too recently to evaluate. A child improved and then relapsed. In two adults, the treatment did not work at all. The Pennsylvania researchers were presenting their results on Sunday and Monday in Atlanta at a meeting of the American Society of Hematology.

Despite the mixed results, cancer experts not involved with the research say it has tremendous promise, because even in this early phase of testing it has worked in seemingly hopeless cases. “I think this is a major breakthrough,” said Dr. Ivan Borrello, a cancer expert and associate professor of medicine at the Johns Hopkins University School of Medicine.

Dr. John Wagner, the director of pediatric blood and marrow transplantation at the University of Minnesota, called the Pennsylvania results “phenomenal” and said they were “what we’ve all been working and hoping for but not seeing to this extent.”

A major drug company, Novartis, is betting on the Pennsylvania team and has committed $20 million to building a research center on the university’s campus to bring the treatment to market.

Hervé Hoppenot, the president of Novartis Oncology, called the research “fantastic” and said it had the potential — if the early results held up — to revolutionize the treatment of leukemia and related blood cancers. Researchers say the same approach, reprogramming the patient’s immune system, may also eventually be used against tumors like breast and prostate cancer.

To perform the treatment, doctors remove millions of the patient’s T-cells — a type of white blood cell — and insert new genes that enable the T-cells to kill cancer cells. The technique employs a disabled form of H.I.V. because it is very good at carrying genetic material into T-cells. The new genes program the T-cells to attack B-cells, a normal part of the immune system that turn malignant in leukemia.

The altered T-cells — called chimeric antigen receptor cells — are then dripped back into the patient’s veins, and if all goes well they multiply and start destroying the cancer.

The T-cells home in on a protein called CD-19 that is found on the surface of most B-cells, whether they are healthy or malignant.

A sign that the treatment is working is that the patient becomes terribly ill, with raging fevers and chills — a reaction that oncologists call “shake and bake,” Dr. June said. Its medical name is cytokine-release syndrome, or cytokine storm, referring to the natural chemicals that pour out of

cells in the immune system as they are being activated, causing fevers and other symptoms. The storm can also flood the lungs and cause perilous drops in blood pressure — effects that nearly killed Emma.

Steroids sometimes ease the reaction, but they did not help Emma. Her temperature hit 105. She wound up on a ventilator, unconscious and swollen almost beyond recognition, surrounded by friends and family who had come to say goodbye.

But at the 11th hour, a battery of blood tests gave the researchers a clue as to what might help save Emma: her level of one of the cytokines, interleukin-6 or IL-6, had shot up a thousandfold. Doctors had never seen such a spike before and thought it might be what was making her so sick.

Dr. June knew that a drug could lower IL-6 — his daughter takes it for rheumatoid arthritis. It had never been used for a crisis like Emma's, but there was little to lose. Her oncologist, Dr. Stephan A. Grupp, ordered the drug. The response, he said, was "amazing."

Within hours, Emma began to stabilize. She woke up a week later, on May 2, the day she turned 7; the intensive-care staff sang "Happy Birthday."

Since then, the research team has used the same drug, tocilizumab, in several other patients.

In patients with lasting remissions after the treatment, the altered T-cells persist in the bloodstream, though in smaller numbers than when they were fighting the disease. Some patients have had the cells for years.

Dr. Michel Sadelain, who conducts similar studies at the Sloan-Kettering Institute, said: "These T-cells are living drugs. With a pill, you take it, it's eliminated from your body and you have to take it again." But T-cells, he said, "could potentially be given only once, maybe only once or twice or three times."

The Pennsylvania researchers said they were surprised to find any big drug company interested in their work, because a new batch of T-cells must be created for each patient — a far cry from the familiar commercial strategy of developing products like Viagra or cholesterol medicines, in which millions of people take the same drug.

But Mr. Hoppenot said Novartis was taking a different path with cancer drugs, looking for treatments that would have a big, unmistakable impact on a small number of patients. Such home-run drugs can be approved more quickly and efficiently, he said, with smaller studies than are

needed for drugs with less obvious benefits.

“The economic model is totally acceptable,” Mr. Hoppenot said.

But such drugs tend to be extremely expensive. A prime example is the Novartis drug Gleevec, which won rapid approval in 2001 for use against certain types of leukemia and gastrointestinal tumors. It can cost more than $5,000 a month, depending on the dosage.

Dr. June said that producing engineered T-cells costs about $20,000 per patient — far less than the cost of a bone-marrow transplant. Scaling up the procedure should make it even less expensive, he said, but he added, “Our costs do not include any profit margin, facility depreciation costs or other clinical care costs, and other research costs.”

The research is still in its early stages, and many questions remain. The researchers are not entirely sure why the treatment works, or why it sometimes fails. One patient had a remission after being treated only twice, and even then the reaction was so delayed that it took the researchers by surprise. For the patients who had no response whatsoever, the team suspects a flawed batch of T-cells. The child who had a temporary remission apparently relapsed because not all of her leukemic cells had the marker that was targeted by the altered T-cells.

It is not clear whether a patient’s body needs the altered T-cells forever. The cells do have a drawback: they destroy healthy B-cells as well as cancerous ones, leaving patients vulnerable to certain types of infections, so Emma and the other patients need regular treatments with immune globulins to prevent illness.

So far, her parents say, Emma seems to have taken it all in stride. She went back to school this year with her second-grade classmates, and though her grades are high and she reads about 50 books a month, she insists impishly that her favorite subjects are lunch and recess.

“It’s time for her to be a kid again and get her childhood back,” Mr. Whitehead said.

NOTE: Read Chapter on Cancer & the Cell Cycle For Background FIRST 1

The Genetic Basis of Cancer

An accumulation of genetic defects can apparently cause normal cells to become cancerous and cancerous cells to become increasingly dangerous

by Webster K. Cavenee and Raymond L. White

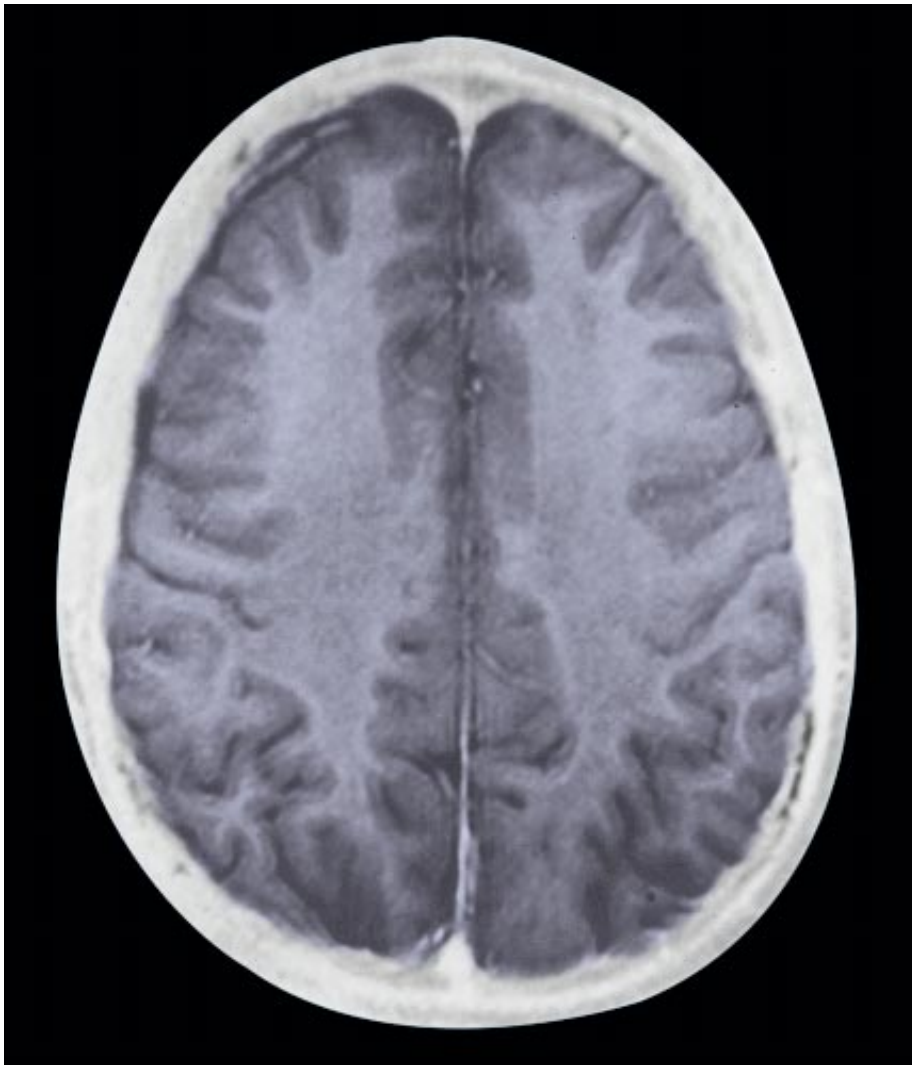
Patients stricken with cancer feel as if they have been invaded by an alien force. Yet malignancies arise from our own tissue. In fact, the weight of evidence today indicates that cancers generally derive from a single cell that is changed dramatically by a series of genetic alterations.

A healthy cell has a well-defined shape and fits neatly within the ordered array of cells surrounding it. It responds to the dictates of its environment, giving rise to daughter cells solely when the balance of stimulatory and inhibitory signals from the outside favors cell division. But the process of replication, or growth, carries the constant hazard of genetic mutations: random changes that can impair the regulatory circuits of a cell. If a single mutation occurs, the newly damaged cell, which may look normal and be slightly less responsive to external messages, may occasionally undergo unscheduled cell division.

Eventually, an accumulation of genetic damage can cause a daughter cell to become quite deaf to external messages and to display the signs of malignancy. In particular, it loses its distinctive shape and boundaries, ceases to respond to growth-inhibiting signals and gains the ability to replicate uncontrollably. The resulting mass, in turn, can compress and damage healthy tissue in its vicinity. What is worse, it can invade the barriers that separate one organ from another and can metastasize, establishing new colonies at distant sites.

Studies carried out over the past 20 years have begun to identify many of the genes that take part in this progression from normalcy to cancer. The ongoing research is confirming and extending early proposals that cancer develops primarily because cells suffer irreversible damage to particular classes of genes. It is also creating opportunities for improved diagnosis and therapy.

The emerging view of tumor progression reflects a convergence of several lines of research, the oldest of which still involves painstakingly looking at cells through a microscope. By 1914, for instance, the German cytologist Theodor Boveri had concluded from such



WEBSTER K. CAVENEE and RAYMOND L. WHITE collaborated at the University of Utah in the early 1980s. Cavenee is director of the Ludwig Institute for Cancer Research at the San Diego branch. He is also professor of medicine and member of the Center for Molecular Genetics at the University of California, San Diego. Before accepting his current posts, he had faculty appointments at the University of Cincinnati and McGill University. White, who has been on the faculty of the University of Utah since 1980, is director of the Huntsman Cancer Institute and chairman of the department of oncological sciences. This is his second article for *Scientific American.*

observations that malignant cells had abnormal chromosomes and that any event leading to such aberrancy would cause cancer.

Microscopic observations became considerably more specific after 1970, when new staining techniques, together with improved equipment, made it possible to distinguish each of the 23 pairs of chromosomes that collectively contain all the genes forming the blueprint for a human being. (All human cells, except for sperm and eggs, carry two sets of chromosomes—one inherited from the mother and one from the father.) Each chromosome takes up the stain in specific regions and thus becomes marked by a characteristic series of light and dark bands, a kind of bar code identifying the individual chromosome.

By comparing stained chromosomes from normal cells with those from tumors, investigators noted many different signs of genetic disarray in cancers. The chromosomes of tumors were often broken, with some of the pieces joined to other chromosomes. Individual chromosomes were present in multiple copies rather than the normal two. Whole chromosomes, or sometimes internal segments, seemed to have disappeared entirely. Unfortunately, until the 1980s researchers generally lacked the tools they needed to determine whether the chromosomal rearrangements were among the causes of cancer or were a by-product of its development.

Two Hits

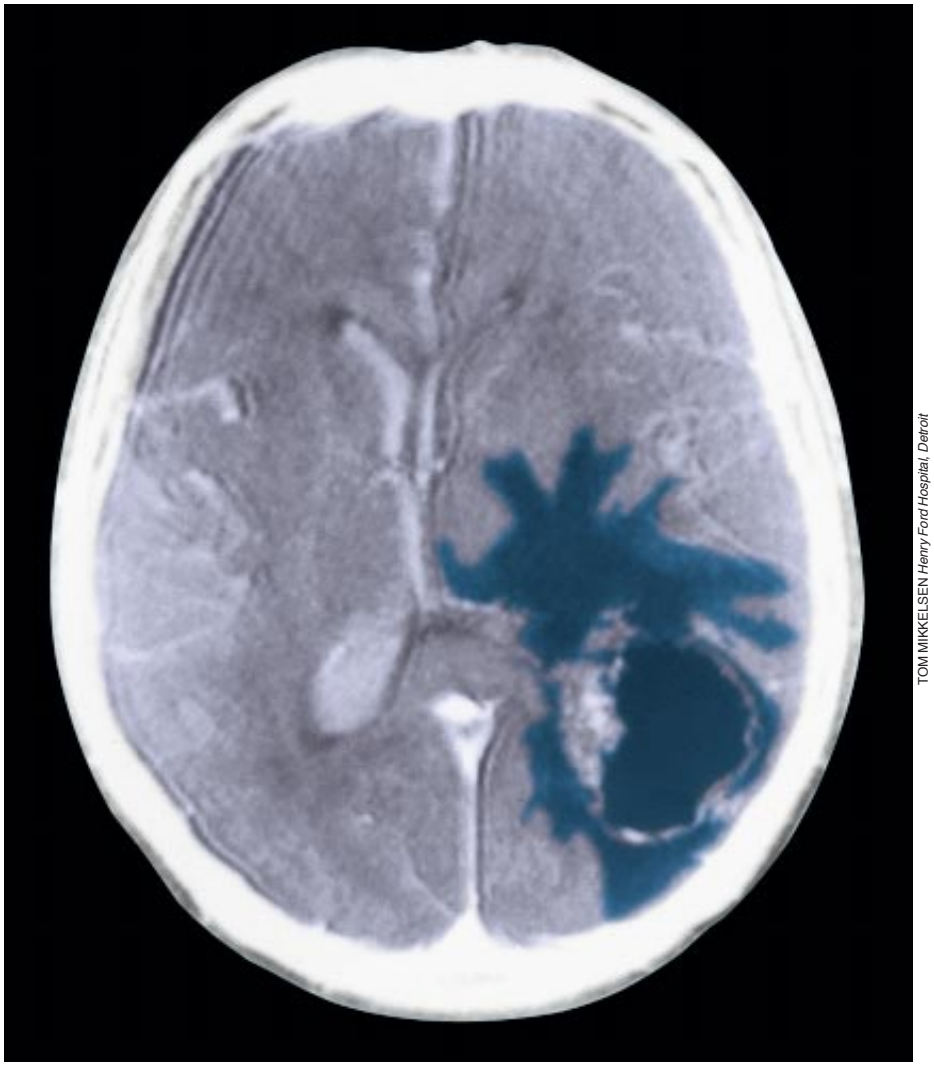
Quite different evidence that genes had a role to play came from observations that some extended families suffered an unusually high incidence of certain cancers. When particular diseases "run" in families in predictable patterns, an inherited defect is usually at fault.

Yet the discovery that some cancers could apparently be inherited also raised perplexing questions. A genetic defect passed to a child through the sperm or egg should appear in every cell of the body. Why, then, did people with inherited disease typically acquire only one or a few cancers and only at discrete sites? Further, did the existence of familial cancers necessarily mean that sporadic (nonfamilial) disease, which is much more common, also had a genetic basis? Or did sporadic cancers arise by completely different processes than inherited ones?

A proposal put forward in 1971 by Alfred G. Knudson, Jr., now at the Fox Chase Cancer Center in Philadelphia, seemed to offer an answer to both questions, although it took about a decade for his ideas to gain broad acceptance. Knudson had been puzzling over the cause of retinoblastoma, a rare childhood disorder in which malignant tumors develop in the retina before the age of six. He noted that sometimes the disease occurred in both eyes, but most of the time it affected only one eye. Moreover, children who were affected bilaterally often had close relatives afflicted with retinoblastoma.

A statistical analysis comparing the age at onset for each form of the disease showed that the bilateral type was usually diagnosed at an earlier age than was the unilateral type. Also, the shape of the age distribution curves suggested to Knudson that retinoblastoma resulted from two cellular defects arising at separate times. In bilateral disease the first defect was probably inherited and present in all cells of the body from the moment of conception. In unilateral disease the first defect probably arose during development or later and perhaps exclusively in retinal cells. In both cases, however, a tumor formed only if the first defect in a retinal cell was later accompanied by a second, independent one. Knudson's two-hit theory, as it is frequently called, turns out to be essentially correct for all cancers, not just retinoblastoma, although more than just two hits are often required.

The need for two hits—now known to constitute damage to genes—explains why patients in cancer-prone families are not riddled with tumors throughout their bodies: inheritance of just one genetic defect predisposes a person to



TOM MIKKELSEN *Henry Ford Hospital, Detroit*

CANCER OF THE BRAIN progressed in just three months from being invisible on a scan (*left*) to covering a large area of one hemisphere (*blue area, right*). The patient, whose initial complaint was an uncontrollable twitching in one eye, died two months after the second image was made. Recent evidence indicates that brain tumors and other malignancies arise when multiple genetic mutations combine to free a single cell from normal restraints on proliferation, invasiveness and movement.

cancer but does not cause it directly; a second event is required. Knudson's intuition that the causes of sporadic and familial cases can involve the same biochemical abnormalities has also been confirmed. But even back in the 1970s his insights provided justification for thinking that research aimed at discovering genetic and other cellular aberrations in rare familial cancers could shed light on the processes leading to sporadic malignancies.

Oncogenes Take Center Stage

As various researchers focused on the genetics of familial malignancies, other workers convinced that genes were at the root of cancer were taking a rather different approach to finding cancer-related genes. It had been known for many years that viruses can cause tumors in animals. That link had spurred a great deal of research aimed at identifying the cancer-causing genes carried by the viruses and at finding the host genes that were affected. Those efforts revealed, surprisingly, that the genes implicated in malignant diseases were often altered forms of human genes that the viruses had picked up during their travels. Other times the viruses activated host genes that were usually quiescent.

The normal versions of the pirated and activated genes—now called proto-oncogenes—carry codes specifying the composition of proteins that encourage cells to replicate. These growth-promoting genes come in many varieties. Some specify the amino acid sequences of receptors that protrude from the cell surface and bind to molecules known as growth factors. When bound by such factors, receptors issue an intracellular signal that ultimately causes cells to replicate. Others of the genes code for proteins that lie inside the cell and govern the propagation of the intracellular growth signal. Still others encode proteins that control cell division.

Discovery that the viral genes had human counterparts introduced the intriguing possibility that human cancers—including the majority not caused by viruses—might stem from mutations that convert useful proto-oncogenes into carcinogenic forms, or oncogenes. Consistent with this notion, studies indicated that alteration of just one copy, or allele, of these proto-oncogenes was enough to transform—render cancerous—some types of cells growing in culture. Such dominant mutations cause cells to overproduce a normal protein or to make an aberrant form that is overactive. In either case, the result is that stimulatory signals increase within the cell even when no such signals come from the outside.

Later studies supported a role for oncogenes—and also complicated matters. Notably, in 1982 and 1983, investigators in France and the U.S. conducted studies similar to the original cell-culture experiments, but with an important difference. Because normal cells would not grow indefinitely in a culture dish, those earlier studies had relied on rodent cells that were unusual in their ability to proliferate for a long time in culture. To eliminate this possibly confounding influence, François Cuzin of the University of Nice, Robert A. Weinberg of the Massachusetts Institute of Technology and H. Earl Ruley, then at Cold Spring Harbor Laboratory in New York State, asked whether single oncogenes could also transform normal rodent cells.

They found that mutations in at least two proto-oncogenes had to be present and that only certain combinations of mutations led to malignancy. These results suggested that individual oncogenes, though potentially quite powerful, were not able to cause tumors by themselves. A major effort was then launched to see whether human tumors carried oncogenic alterations of the types and combinations that were able to transform cells in culture.

For a while it seemed that oncogenes might explain most cases of cancer. This view was strengthened by discovery of more than a dozen of them in human tumors. The results were ultimately disappointing, however; a mere 20 percent of human tumors turned out to carry the expected alterations singly, and none of them had the pairs of cooperative alterations found in cultured cells. At the time, it also appeared that the inherited mutations responsible for predisposing people to familial cancers were not oncogenes. These were all strong hints that the full story was yet to be told.

Enter Tumor Suppressor Genes

Even before those hints attracted much attention, the two of us were beginning to suspect that damage to a different kind of gene might play a part in cancers. Such genes came to be known as tumor suppressors because many of them code for proteins that inhibit cell replication. In contrast to the mutations that activate oncogenes, mutations of these genes, we believed, would be recessive: they would affect cell function only when both alleles were damaged or lost. In testing this idea, we relied on new technology we had developed for the more general purpose of following the inheritance of genes and chromosomes through extended families [see "Chromosome Mapping with DNA Markers," by Ray White and Jean-Marc Lalouel; SCIENTIFIC AMERICAN, February 1988].

In the early 1980s, while collaborating at the University of Utah, we realized that our technique—which involved tracking genetic markers (identifiable segments of DNA) in tissues—could be used to determine whether segments of chromosomes carried by normal cells were missing in a tumor. For instance, if a selected region of a chromosome was deleted in a tumor, we could spot that loss by observing that a marker known to travel with that region was also missing.

Our experiments were focused by earlier studies of Jorge J. Yunis of the University of Minnesota and Uta Francke of Yale University. That research indicated a gene on chromosome 13 might be involved in retinoblastoma. With our DNA-marker technology, we were able to demonstrate in 1983 that large segments of chromosome 13 were missing in cells taken from sporadic as well as inherited retinoblastomas. This new evidence strongly supported the idea that the two hits hypothesized by Knudson could consist of the physical or functional loss of one allele of a gene followed by elimination of or damage to the normal copy. The missing DNA on chromosome 13, now known as the *RB* (retinoblastoma) gene, was isolated by Stephen H. Friend of Weinberg's laboratory in 1986 [see "Finding the Anti-Oncogene," by Robert A. Weinberg; SCIENTIFIC AMERICAN, September 1988].

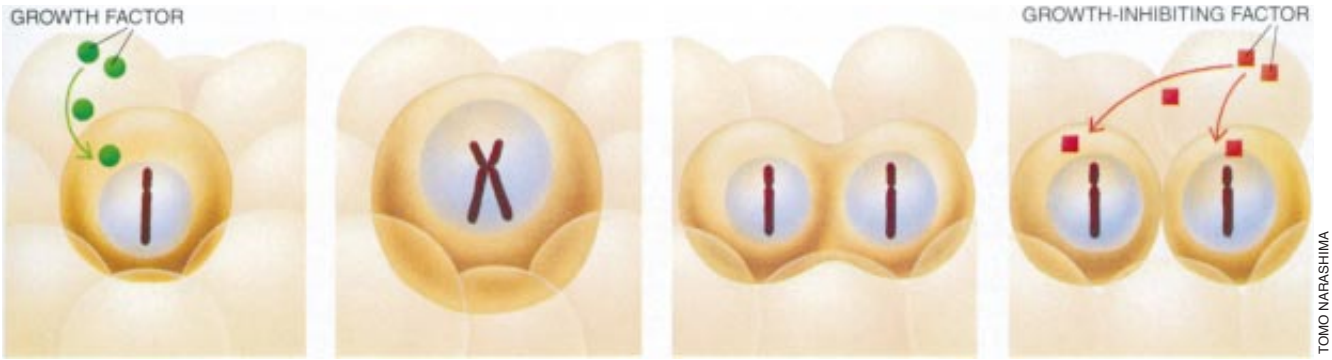
Subsequent studies have shown that recessive loss of the *RB* gene occurs in other cancers as well. What is more, inactivation or loss of DNA has now been shown to be a major feature in the genesis of every solid cancer examined so far. Breast cancer, prostate cancer, lung cancer, bladder cancer, pancreatic cancer and many others are marked by the disruption or elimination of multiple tumor suppressor genes.

By the late 1980s, then, there was good evidence that mutations in both proto-oncogenes and tumor suppressors could participate in causing cancer. It seemed reasonable to guess that some kinds of cancer resulted from a combination of such mutations. But did the mutations collect in the same cell or did some affect one cell, and others, different cells? A model of tumor progression proposed in the 1950s by Leslie Foulds of the Chester Beatty Research Institute in London and expanded in the 1970s by Peter C. Nowell of the University of Pennsylvania suggested that if both kinds of mutations were in-

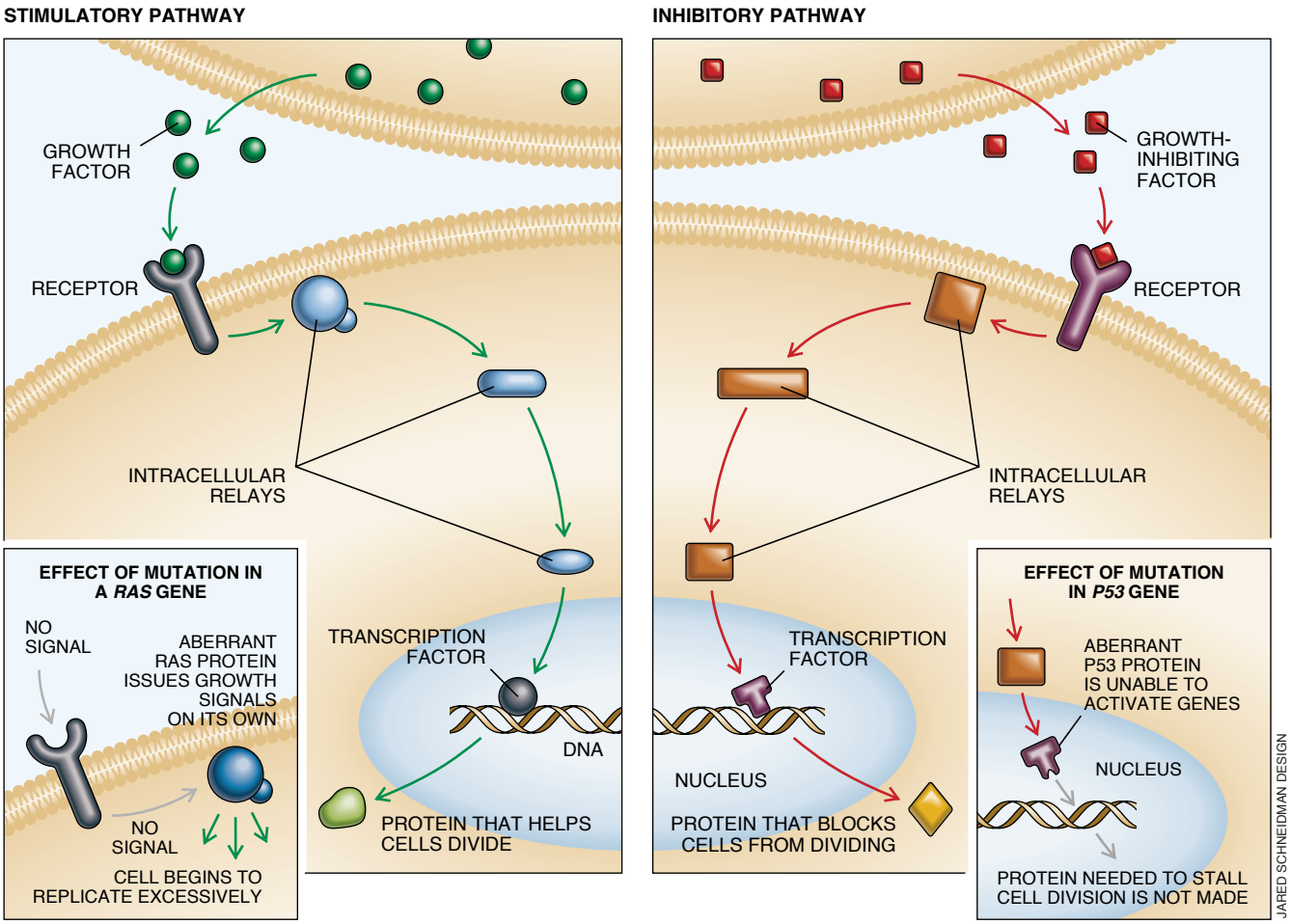
volved, they would accumulate in one cell and its direct descendants.

In this scheme, cancers are thought to arise and become more dangerous through a process known as clonal evolution. First, a single cell undergoes a genetic mutation that enables it to divide under conditions that cause normal cells to stop replicating. Because the inappropriately dividing cells copy their DNA and give identical sets to their offspring, the next generation of cells carries the same changes and shows the same inappropriate growth. Later, one of these cells or their descendants undergoes a mutation that further enhances its ability to escape normal regulation, perhaps allowing it to pass through surrounding tissue and enter the bloodstream. This mutation, too, is passed to daughter cells. Repetition of the process enables one cell to accumulate the mutations it needs to metastasize and colonize other organs.

If the theory were correct, it would mean the majority of cells in a tumor would carry the same defects. That being the case, therapy capable of counteracting one or more of those defects would be effective against all, or a great



TOMO NARASHIMA



JARED SCHNEIDMAN DESIGN

NORMAL CELL REPRODUCES ITSELF (*sequence at top*) in response to stimulation by external growth factors (*green*); it stops dividing in response to inhibitory factors (*red, far right*). For either reaction to occur, messages from the factors must be relayed deep into the target cell (*large panels*). Many cancer-causing genes are abnormal versions of ones that code for proteins in stimulatory pathways (*left panel*). The altered genes, called oncogenes, cause stimulatory proteins to be overproduced or overactive. In one example, mutation of a particular *ras* gene can lead to synthesis of a hyperactive ras protein (*inset at left*). Many other cancer-related genes code for proteins in inhibitory pathways (*right panel*) and are often called tumor suppressors. Damage to these genes can promote cancer if the defects prevent inhibitory proteins from being made or functioning properly—as often occurs when the *p53* gene is mutated (*inset at right*).

majority, of the cancer cells—a feature that is essential for eradicating any malignancy. For this reason and others, we set out to see if we could find evidence for the clonal evolution of tumors. One of us (White) focused primarily on colon cancer, and the other of us (Cavenee) on brain tumors. As part of this work, we had to identify many of the genes involved in these cancers.

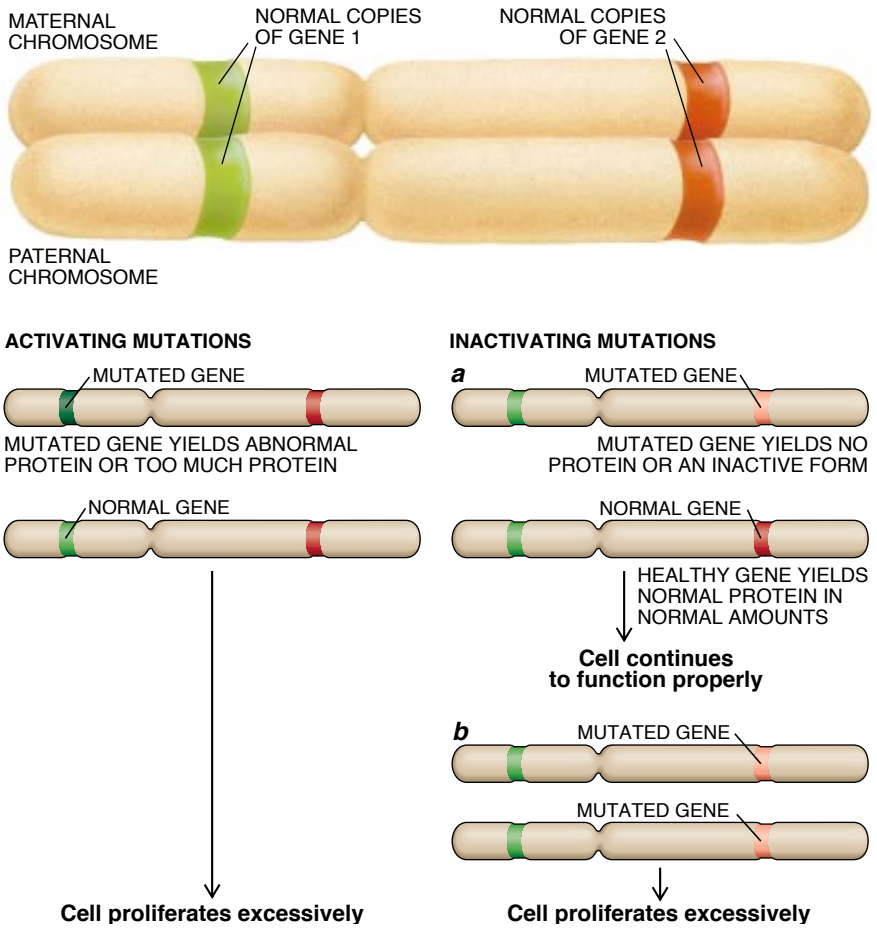
The Genetics of Colon Cancer

White turned to colon cancer in part because it usually emerges from a well-defined precursor—the colon polyp. If a cancer developed in a clonal fashion, mutations arising in an early stage of tumor development would be expected to be present in later stages, and each successive stage would be marked by additional mutations. To test this expectation experimentally, it is necessary to collect samples from the successive stages and compare their genes. In colon disease, samples are fairly easy to obtain. As a polyp, which is initially microscopic, becomes larger and more irregular, it becomes readily accessible to the gastroenterologist (who removes it for therapeutic purposes) and thus to the experimentalist.

Colon cancer also held appeal for our purpose because families that were genetically prone to a rare disease called familial adenomatous polyposis had been identified and were available for study. In affected individuals the colon becomes carpeted with hundreds or thousands of polyps, one or more of which is likely to become cancerous in midlife. Clearly, an inherited defect in some gene—called *APC* (for adenomatous polyposis coli)—was necessary for polyp formation and, in turn, for the development of colon cancer in such patients. It also seemed possible that appearance of a defect in the *APC* gene was one of the earliest steps, if not the first step, leading to many cases of sporadic colon cancer. If that gene could be isolated, these ideas could be tested, and investigators would have at least one of the genes needed for evaluating whether colon cancer developed in a clonal manner.

In 1987 Mark Leppert in White's laboratory at Utah and Walter F. Bodmer and his colleagues at the Imperial Cancer Research Fund in London separately demonstrated, through use of the marker technology described earlier, that the *APC* gene resided near the middle of the long arm of chromosome 5. Intensive work, often collaborative, by White's laboratory and those of two other investigators—Yusuke Nakamura of the Cancer Institute in Tokyo and Bert Vogelstein of Johns Hopkins University—eventually revealed the precise location of the gene. The research also identified several inherited *APC* mutations that appeared in sporadic as well as familial colon tumors. This work thus defined a first step in the evolution of colon cancer. It also provided additional confirmation of the speculation that the same genes are often mutated in both inherited and sporadic tumors.

The groups found, too, that all the cancer-related mutations in the *APC* gene led to production of an incomplete protein. Evidently, cells could operate relatively normally if they retained one normal *APC* allele and thus made some amount of the full APC protein. But if both alleles became damaged, a needed brake on replication disappeared. The precise function of the *APC* gene is unclear, but now that the gene is in hand, its normal responsibilities and its role in cancer should soon be defined.

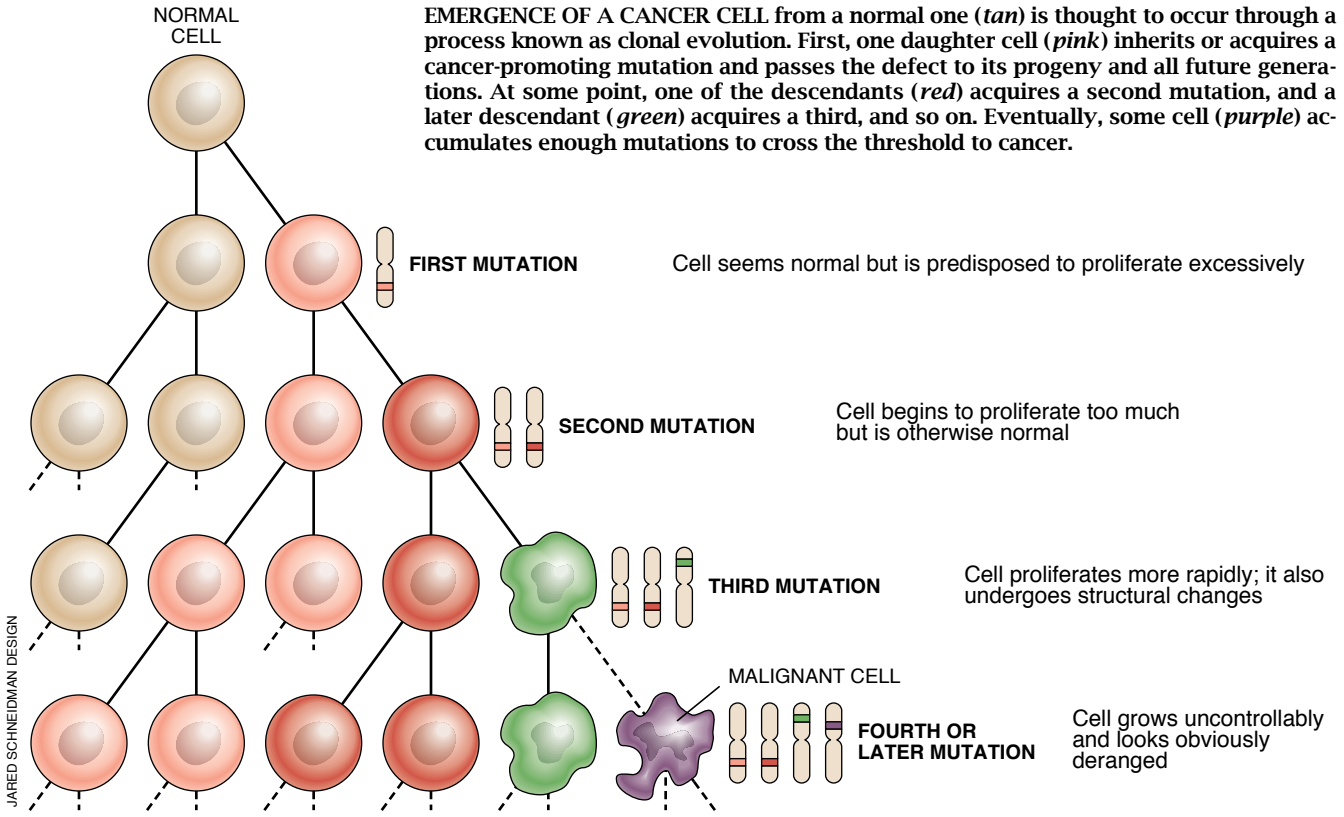


GENES ARE INHERITED IN MATCHING PAIRS—one from the mother and one from the father (*top*). Sometimes mutation of a single copy pushes a cell toward cancer (*left*)—such as when it leads to production of a protein that activates excessive cell division. (Oncogenic mutations fall into that category.) Other times both copies must be altered—such as when a gene coding for a protein that stalls cell division is inactivated (*right*). If only one copy of such a gene is affected (*a*), the other copy can still generate the needed protein. But if both copies are hobbled (*b*), an important brake on tumor development is lost.

Multiple Defects

The steps that follow immediately after the *APC* gene is inactivated are still obscure. In many cases, however, later mutation in a single allele of a particular proto-oncogene seems to push a polyp toward malignancy. This gene, as Manuel Perucho observed when he was at Cold Spring Harbor Laboratory, is one of several *ras* genes. The protein normally made under the direction of this gene sits under the cell membrane and relays stimulatory messages from growth factor receptors to other molecules in the cytoplasm. The mutant version does not wait for signals from the outside but issues its own autonomous growth signals.

Vogelstein and his group have shown that large polyps and colon cancers often carry only mutated copies of two additional tumor suppressor genes. One



EMERGENCE OF A CANCER CELL from a normal one (*tan*) is thought to occur through a process known as clonal evolution. First, one daughter cell (*pink*) inherits or acquires a cancer-promoting mutation and passes the defect to its progeny and all future generations. At some point, one of the descendants (*red*) acquires a second mutation, and a later descendant (*green*) acquires a third, and so on. Eventually, some cell (*purple*) accumulates enough mutations to cross the threshold to cancer.

is *p53,* which resides on chromosome 17 and is now known to be involved in many different cancers. The normal protein product of this gene functions in several biochemical pathways, including those enabling a cell to repair damage to DNA. The other is a gene—probably *DCC* (for deleted in colorectal cancer)—that resides on chromosome 18. *DCC* codes for a protein that appears on the cell surface and helps colon cells stick to one another.

The discovery that genetic changes in the *APC* gene occur early and persist, whereas other changes appear only in later stages, fits well with the theory of clonal evolution. But that conclusion was initially statistical and based on examining tissues removed from many different patients. That approach could not demonstrate conclusively that mutations appearing in one generation of cells are passed to later generations of those same cells. Another strategy, however, provided more convincing results.

Sometimes the polyp from which a cancer has emerged can be identified at the edge of a cancer. By comparing the DNA in a polyp with that in its adjacent cancer, Vogelstein showed that every mutational hit found in a polyp also appeared in the corresponding cancer, as would be expected if the tumor formed by clonal evolution. Further, the cancer invariably included mutations that were not found in the polyp, as would also be expected if the added mutations accounted for the increased aggressiveness of a cancer. For instance, some polyps carried a *ras* mutation without a *p53* defect, but the cancers growing from the polyps had both mutations. As yet, there is no strong evidence that mutation of *ras, p53* and *DCC* genes must happen in any particular order for a polyp to become cancerous, although the *ras* mutation seems to come first fairly often.

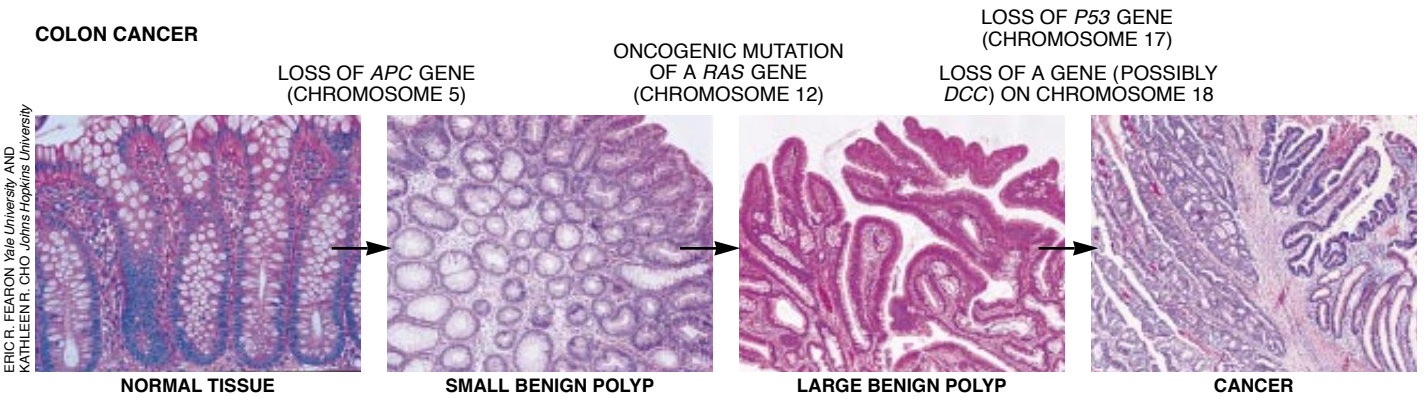
Brain Tumors Reveal Their Secrets

In spite of these encouraging findings, study of colon cancer has a major analytical limitation. To truly demonstrate that a given clone of cells is undergoing progressive changes in its genes, one needs to examine the same tumor over time. In the case of colon cancer, tumors are almost always removed at the earliest stage of detection. Such practice makes good clinical sense, but it prevents sequential observations. This consideration led Cavenee to seek out a disease in which removal of a tumor is sometimes followed by the reappearance of the tumor in a more aggressive form at the same site. In 1987, while he was at the Ludwig Institute for Cancer Research at McGill University, he and his co-workers settled on cancers known as astrocytomas—the most common tumors that originate in the brain.

Cancer of the brain is defined somewhat differently than it is in other tissues. In that organ, cells do not need to invade connective tissue or metastasize in order to be lethal; sadly, proliferation at a site critical to survival can sometimes be enough to kill a patient. Hence, most masses in the brain are called cancers. Cavenee's group examined progression of astrocytomas from their less malignant to more malignant stages, as determined by the size and shape of the tumors and by the structure of their constituent cells.

When the investigators began this work in 1987, they did not have the blueprint of genetic change that was emerging for colon cancer. They therefore began by laying the groundwork for future studies of individual patients. They obtained tumors from many different patients, grouped them according to stages, or grades, of advancing disease, and compared the genetic derangements found in each stage.

Over the next four years they made good headway. They learned, for instance, that tumors of every grade had inactivating alterations in chromosome 17, in a gene they had not yet identified. Moreover, the proportion of tumors displaying the mutation in the lowest stage was equal to that in all other stages; this pattern is a sign that the mutation came early and was retained. If a mutation generally occurred later in disease,

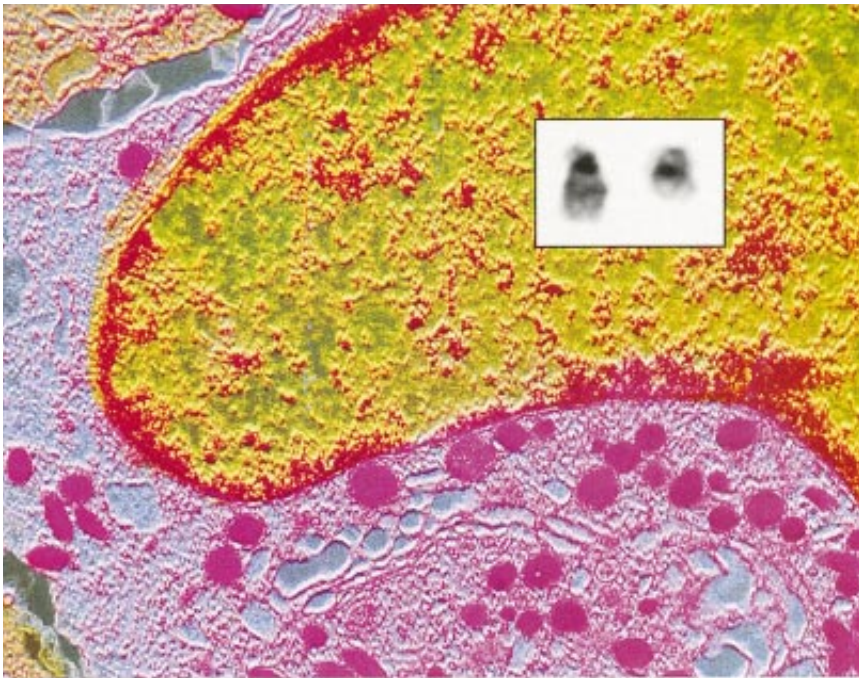


ERIC R. FEARON *Yale University* AND KATHLEEN R. CHO *Johns Hopkins University*

GENETIC CHANGES indicated at the top are among those thought to participate frequently in the development of colon cancer (*left*) or in the progression of a common brain cancer (astrocytoma) from its mildest to its most aggressive

the frequency would rise in the later stages. By the end of the 1980s Vogelstein's laboratory established that mutations in the *p53* gene, on chromosome 17, were among the most common alterations in human cancer. Subsequent analysis of Cavenee's tissue samples confirmed his growing suspicion that the chromosome 17 mutation was actually a defect in the *p53* gene.

Aware that a particular region of chromosome 9 was deleted in other kinds of brain tumors, C. David James on Cavenee's team, in conjunction with V. Peter Collins of the Ludwig Institute in Stockholm, examined this chromosome as well. Middle- and late-stage astrocytomas, but not early ones, often showed a loss in both copies of this chromosome. Thus, the deletion probably encouraged progression to middle-stage tumors from a lesser stage. The lost region contains a cluster of genes that code for proteins known as interferons. Such proteins can draw the attention of the immune system to diseased cells, and so elimination of their genes presumably helps cancer cells evade immune destruction. The missing region may additionally include two newly discovered genes, called *multiple tumor suppressors 1* and *2,* whose protein products are involved in regulating cell division. Disappearance of any of these genes could potentially contribute to a variety of cancers.



PETER C. NOWELL *University of Pennsylvania*

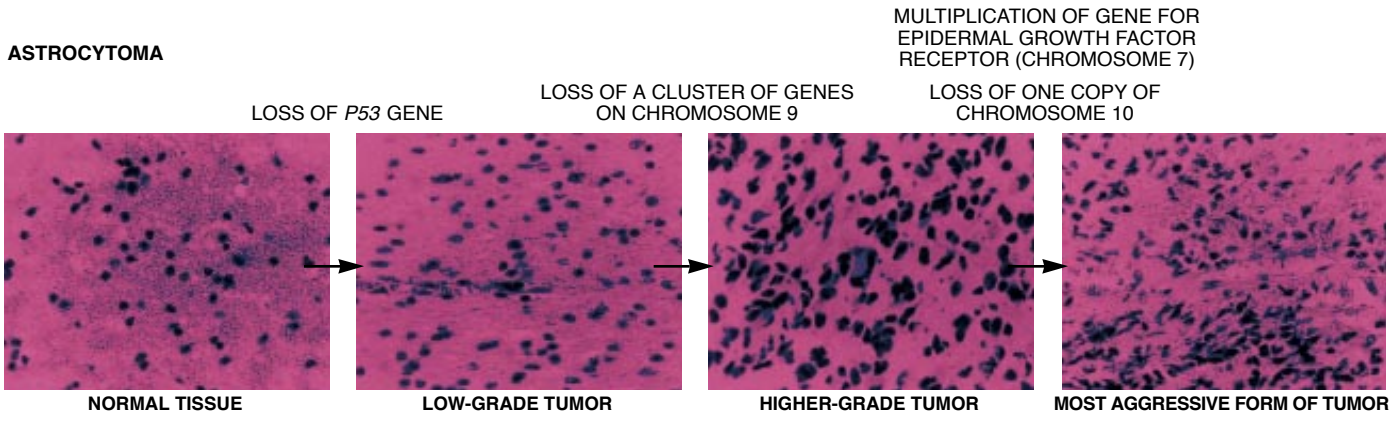
PHILADELPHIA CHROMOSOME (*at right in inset*) was the first chromosomal abnormality ever linked to a specific cancer. In the 1960s Peter C. Nowell of the University of Pennsylvania observed that the appearance of an unusually small chromosome in white blood cells was a hallmark of leukemia. It is now known that the aberrant structure forms when a normal version of chromosome 22 (*at left in inset*) swaps genetic material with another chromosome, in the process giving up more than it receives. Unfortunately, the DNA gained by chromosome 22 combines with a preexisting gene to form a hybrid oncogene.

The tissue studies also extended reports by Axel Ullrich of Genentech, Michael D. Waterfield of the Ludwig Institute in London and Joseph Schlessinger of the Weizmann Institute of Science in Israel that chromosomes in astrocytomas often carry more than one copy of the gene specifying the receptor for epidermal growth factor. Because each copy can be used to make the protein, cells will carry extra receptors on their surface. That abundance, in turn, can cause cells to overreact to the presence of the growth factor. This alteration seems to participate in bringing tumors from a middle to a late stage of disease.

Finally, Cavenee's group found that virtually all the end-stage tumors examined were missing one copy of chromosome 10 and that the loss was rare in earlier stages. This pattern says the loss is probably involved in advancement to the most virulent stage. Regrettably, though, we do not yet know which gene or genes on the lost chromosome are most important to the progression.

These results suggested by 1991 that formation of brain tumors involves, at a minimum, inactivation of the *p53* gene, loss of a gene on chromosome 9, oncogenic amplification of the gene for the epidermal growth factor receptor and, at a very late stage, loss of at least one copy of chromosome 10. But stronger proof that astrocytomas are caused by the accumulation of these, and possibly other, defects in cells required examining genetic changes in the cancer of single individuals over time.

At about that time Tom Mikkelsen joined Cavenee's laboratory and took on the challenge of comparing the genetic makeup of original astrocytomas with that of later recurrences arising at the same sites. This task was impossible earlier not only because the genes involved were not known but also be-



form (*right*). Other genes not listed here play roles as well. Unless otherwise indicated, the term "gene loss" indicates that both copies of a tumor suppressor gene have been damaged or deleted. The images show magnified slices of tissue.

cause matched pairs of tumors are hard to obtain. A patient seen initially at one institution may be cared for elsewhere when the cancer returns. Also, physicians do not remove tumors that reappear if it is thought that surgery is unlikely to extend survival. Luckily, however, two distinguished clinicians—Mark L. Rosenblum of the University of California at San Francisco and Karl Schwechheimer of Albert Ludwigs University in Freiberg, Germany—had come forward with collections of frozen tissue that included a few matched sets.

To Cavenee's satisfaction and delight, the genetic analysis of these tissues—done in collaboration with David Sidransky in Vogelstein's group—fulfilled the predictions of the theory of clonal evolution. The initial tumors possessed fewer mutations than did the recurrences. These alterations included one or more of the genetic hits (such as damage to chromosome 17) that had been identified in the low-grade tumors analyzed previously. And, most significant, the corresponding high-grade versions possessed each alteration found in the primary tumor as well as additional defects (of the kinds identified in the earlier studies). For reasons that are not obvious, progression of astrocytomas seems to follow a more defined sequence of genetic changes than is apparent in colon cancer.

Next on the Agenda

The collected results we have described offer strong support for the idea that cancer develops and becomes more dangerous primarily because cells in a single lineage accumulate defects in genes that normally regulate cell proliferation. Changes in other kinds of genes, many of which have not yet been identified, presumably facilitate the ability of tumors to grow, invade local tissue and establish distant metastases. Hormones and other factors in the environment around the genetically altered cells almost certainly enhance their genetically defined deregulation.

Questions remain. Why do cell types differ in the mix of mutations they require in order to become cancerous? And how is it possible for five or more mutations to accumulate in cells? After all, the probability is actually quite small that any given cell bearing a permanent mutation in a cancer-related gene will independently gain another mutation in such a gene.

Newly discovered genetic aberrations found in a second form of inherited colon tumors (hereditary nonpolyposis colon cancer) may offer a partial answer to the last question. The affected genes specify proteins responsible for identifying and repairing mistakes made when DNA in a replicating cell is copied. If these repair genes themselves are damaged, the number of mutations passed to daughter cells will go up dramatically. The daughter cells may then deliver DNA carrying still more mutations to their progeny. Defects in repair genes may thus play a role in making late-stage tumors highly aggressive. They may even account for the astonishingly fast rate at which some tumors arise and become killers.

Mutations in certain genes can also be especially devastating if the mutations have multiple effects. As a case in point, damage to the *p53* gene can apparently do more than release a brake on proliferation. Certain mutations seem to reduce the ability of cells to limit blood vessel formation. As extra vessels grow in a tumor, they help to nourish the mass and to serve as conduits through which malignant cells can spread to distant sites. In parallel, the abnormal proteins yielded by the altered gene may aid tumor cells in resisting the destructive effects of radiation.

As investigators gain clarity on the specific groups of genetic changes that lead to and exacerbate particular forms of cancer, their insights should point the way to practical benefits for patients. When the mutations follow in a fairly set sequence, their identification in a patient's tumor should be of value for clarifying the stage of disease and thus for tailoring therapy to the individual's needs. In addition, knowledge of the genes that are mutated in a primary tumor may make it possible to detect recurrences of some cancers earlier than is now possible—by spotting mutations that have occurred in tissues not yet displaying detectable masses.

Expanded understanding of the genetic bases of cancer can also be expected to lead to the introduction of drugs that will counteract the effects of selected mutations and thereby slow tumor development or halt it altogether. Some evidence suggests it may not be necessary to correct the effects of every mutation; doing so for one or two genes may well prove to be sufficient for taming renegade cells.

The process by which normal cells become cancerous and grow ever more dangerous is undoubtedly even more complicated than has been discovered so far. But continued investigation of the genetic changes underlying specific cancers seems a rational way to tease apart many of those complexities—and to gain new leads for treatment.

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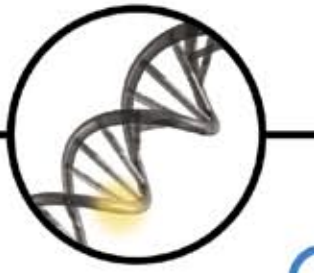
3

MAPPING THE CANCER GENOME



Pinpointing the genes involved in cancer will help chart a new course across the complex landscape of human malignancies

By Francis S. Collins and Anna D. Barker

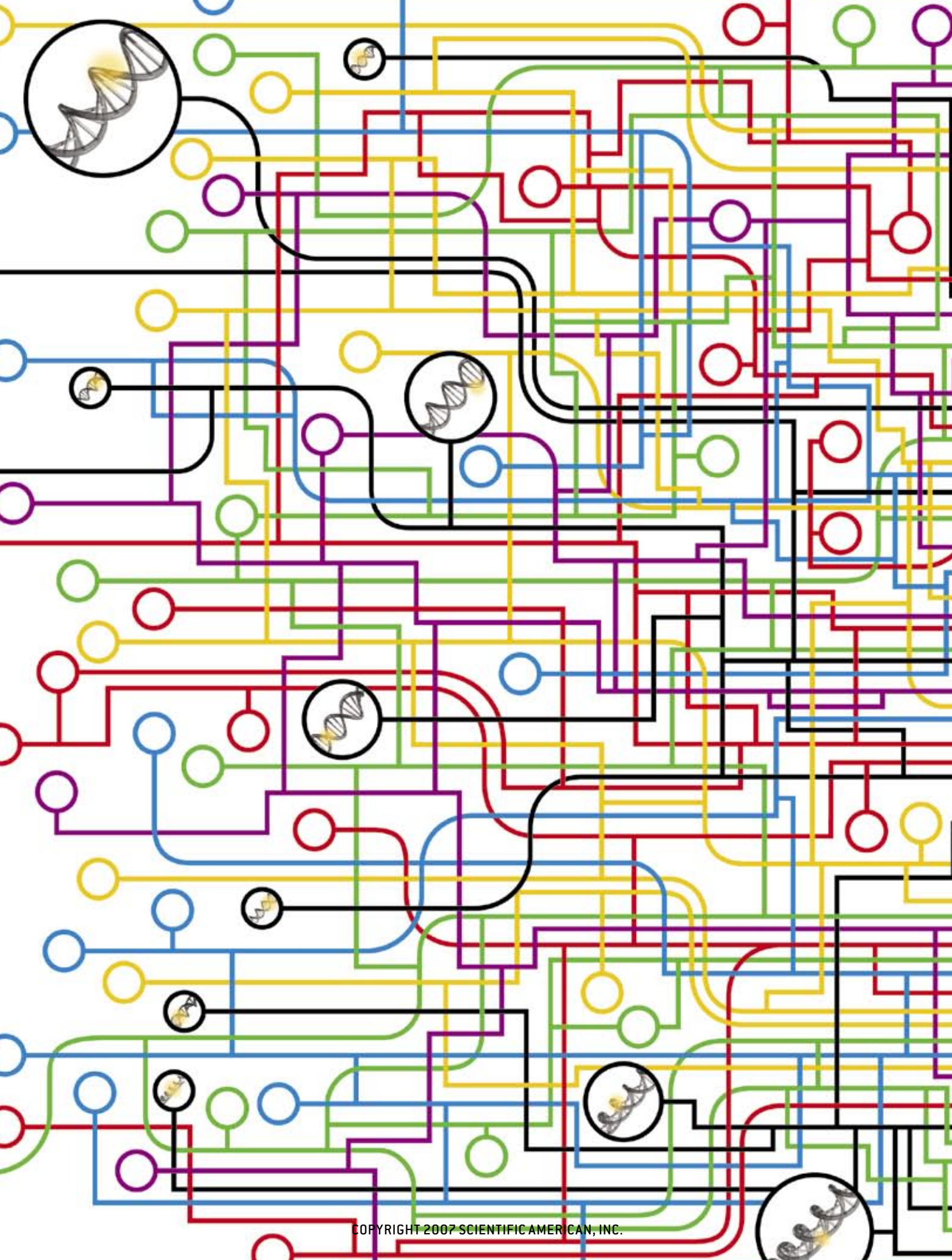
"If we wish to learn more about cancer, we must now concentrate on the cellular genome." Nobel laureate Renato Dulbecco penned those words more than 20 years ago in one of the earliest public calls for what would become the Human Genome Project. "We are at a turning point," Dulbecco, a pioneering cancer researcher, declared in 1986 in the journal *Science*. Discoveries in preceding years had made clear that much of the deranged behavior of cancer cells stemmed from damage to their genes and alterations in their functioning. "We have two options," he wrote. "Either try to discover the genes important in malignancy by a piecemeal approach, or … sequence the whole genome."

Dulbecco and others in the scientific community grasped that sequencing the human genome, though a monumental achievement itself, would mark just the first step of the quest to fully understand the biology of cancer. With the complete sequence of nucleotide bases in normal human DNA in hand, scientists would then need to classify the wide array of human genes according to their function—which in turn could reveal their roles in cancer. Over the span of two decades Dulbecco's vision has moved from pipe dream to reality. Less than three years after the Human Genome Project's completion, the National Institutes of Health has officially launched the pilot stage of an effort to create a comprehensive catalogue of the genomic changes involved in cancer: The Cancer Genome Atlas (TCGA).

The main reason to pursue this next ambitious venture in large-scale biology with great urgency is cancer's terrible toll on humankind. Every day more than 1,500 Americans die from cancer—about one person every minute. As the U.S. population ages, this rate is expected to rise significantly in the years ahead unless investigators find ways to accelerate the identification of new vulnerabilities within cancerous cells and develop novel strategies for attacking those targets.

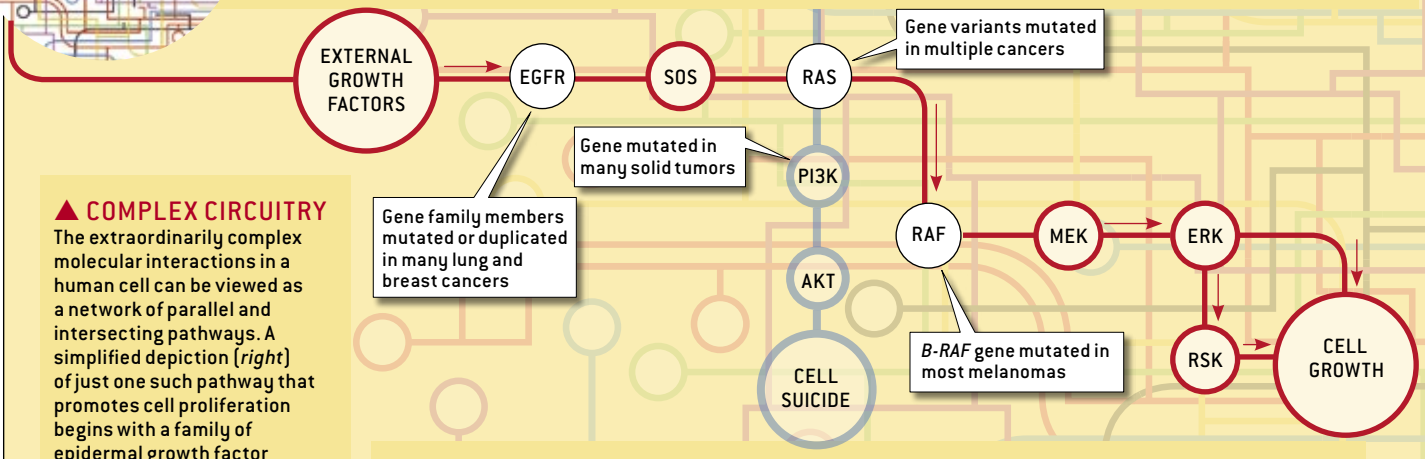
Still, however noble the intent, it takes more than a desire to ease human suffering to justify a research enterprise of this magnitude. When applied to the 50 most common types of cancer, this effort could ultimately prove to be the equivalent of more than 10,000 Human Genome Projects in terms of the sheer volume of DNA to be sequenced. The dream must therefore be matched with an ambitious but realistic assessment of the emerging scientific opportunities for waging a smarter war against cancer.

SLIM FILMS



MANY PATHWAYS TO MALIGNANCY

Gene malfunctions underlie the ability of cancer cells to escape normal constraints on a cell's behavior. Because genes give rise to proteins that serve as cellular building blocks, signals and regulators of other genes, a mutation that disables one gene, or causes it to be overactive, can have multiple deranging effects on the cell (*below*). Nevertheless, cells usually need to accrete several cancer-promoting, or oncogenic, mutations in separate genes to acquire the hallmark properties of malignancy (*box at right*). Identifying all the genes whose alteration can produce those traits should one day reveal which mutations are the true drivers of specific types of cancer—even of a specific patient's malignancy—and therefore the most effective ways to intervene in the disease.



▲ COMPLEX CIRCUITRY

The extraordinarily complex molecular interactions in a human cell can be viewed as a network of parallel and intersecting pathways. A simplified depiction (*right*) of just one such pathway that promotes cell proliferation begins with a family of epidermal growth factor receptors (EGFR) in the cell membrane. Their stimulation by growth factors outside the cell transmits signals to additional proteins and genes, ultimately prompting the cell to "grow" by dividing.

▲ ONCOGENIC MUTATIONS

In a significant portion of lung and breast tumors, members of the *EGFR* gene family are mutated or duplicated, which boosts the number or function of the receptors they encode, overstimulating this growth pathway. Damage to downstream genes can have similar results. Changes in the *B-RAF* gene, seen in some 70 percent of melanomas, also promote hyperactive cell proliferation. Versions of the *RAS* gene are mutated in many cancer types, which can affect cell growth as well as intersecting pathways—for example, interfering with a suicide program that normally destroys damaged cells.

A Disease of Genes

THE IDEA THAT ALTERATIONS to the cellular genome lie at the heart of all forms of cancer is not new. Since the first identification in 1981 of a cancer-promoting version of a human gene, known as an oncogene, scientists have increasingly come to understand that cancer is caused primarily by mutations in specific genes. The damage can be incurred through exposure to toxins or radiation, by faulty DNA repair processes or by errors that occur when DNA is copied prior to cell division. In relatively rare cases, a cancer-predisposing mutation is carried within a gene variant inherited from one's ancestors.

Whatever their origin, these mutations disrupt biological pathways in ways that result in the uncontrolled cell replication, or growth, that is characteristic of cancer as well as other hallmarks of malignancy, such as the ability to invade neighboring tissues and to spread to sites throughout the body. Some mutations may disable genes that normally protect against abnormal cell behavior, whereas others increase the activity of disruptive genes. Most cells must acquire at least several of these alterations before they become transformed into cancer cells—a process that can take years.

Over the past two decades many individual research groups have used groundbreaking molecular biology techniques to search for mutations in genes that are likely candidates for wreaking havoc on normal patterns of cell growth and behavior. This approach has identified about 350 cancer-related genes and yielded many significant insights into this diabolical disease. A database of these changes, called the catalogue of somatic mutations in cancer, or COSMIC, is maintained by Michael Stratton's group at the Wellcome Trust Sanger Institute in Cambridge, England. But no one imagines that it is the complete list.

So does it make sense to continue exploring the genomic basis of cancer at cottage-industry scale when we now possess the means to vastly increase the scope and speed of discovery? In recent years a number of ideas, tools and technologies have emerged and, more important, converged in a manner that

Overview/*Cancer Connections*

- Changes in the structure or activity of genes underlie the malignant behavior of cancer cells.
- Identification of genes involved in certain cancers is already advancing diagnosis and treatment.
- The Cancer Genome Atlas is a monumental initiative to eventually identify all the genetic alterations in different forms of cancer so that gene changes driving the disease can be targeted directly.

LUCY READING-IKKANDA; ACKNOWLEDGMENT: SPECIAL THANKS TO JEFFREY SETTLEMAN OF THE CENTER FOR CANCER RESEARCH AT MASSACHUSETTS GENERAL HOSPITAL AND DAPHNE W. BELL OF THE NHGRI CANCER GENETICS BRANCH FOR THEIR ADVICE ON THE PATHWAY ILLUSTRATION

Hallmarks of Cancer

The six abnormal capabilities listed below together give tumors their lethal power to overrun their native tissue and spread through the body.

Self-sufficiency in growth signaling
Cancer cells amplify external growth cues or generate their own.

Insensitivity to antigrowth signals
Cancer cells become deaf to quiescence cues from surrounding tissue.

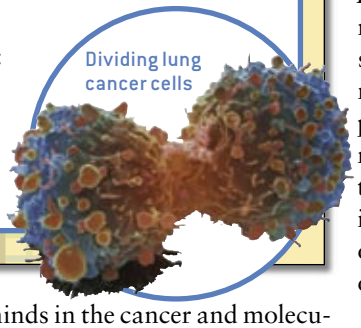
Evasion of cell suicide
Mechanisms that should trigger or carry out a self-destruct program in damaged cells are disabled or overridden.

Limitless replicative potential
Cancer cells evade intrinsic limits on the number of times a normal cell can divide.

Sustained blood vessel growth
Tumors emit signals promoting the development of new blood vessels to deliver oxygen and nutrients.

Invasiveness and motility
Cancer cells defy multiple signals and forces that hold a cell in place and prevent it from traveling to—and thriving in—other tissues.

Adapted from "The Hallmarks of Cancer," by Douglas Hanahan and Robert A. Weinberg, in Cell, *Vol. 100; January 7, 2000.*


Dividing lung cancer cells

has convinced many leading minds in the cancer and molecular biology communities that it is time for a systematic, collaborative and comprehensive exploration of the genomics of cancer.

The Human Genome Project laid a solid foundation for TCGA by creating a standardized reference sequence of the three billion DNA base pairs in the genome of normal human tissues. Now another initiative is needed to compare the DNA sequences and other physical characteristics of the genomes of normal cells with those of cancerous cells, to identify the major genetic changes that drive the hallmark features of cancer [*see box above*]. The importance of international partnerships in large-scale biology to pool resources and speed scientific discovery was also demonstrated by the Human Genome Project, and TCGA is exploring similar collaborations.

Finally, the Human Genome Project spurred significant advances in the technologies used to sequence and analyze genomes. At the start of that project in 1990, for example, the cost of DNA sequencing was more than $10 per "finished" nucleotide base. Today the cost is less than a penny per base and is expected to drop still further with the emergence of innovative sequencing methods [see "Genomes for All," by George M. Church; Scientific American, January 2006]. Because of these and other technological developments, the large-scale approach embodied in TCGA—unthinkable even a few years ago—has emerged as perhaps the most efficient and cost-effective way to identify the wide array of genomic factors involved in cancer.

Proofs of Concept

PILES OF DATA are, of course, not worth much without evidence that comprehensive knowledge of cancer's molecular origins can actually make a difference in the care of people. Several recent developments have provided proofs of concept that identifying specific genetic changes in cancer cells can indeed point to better ways to diagnose, treat and prevent the disease. They offer encouraging glimpses of what is to come and also demonstrate why the steps toward those rewards are complex, time-consuming and expensive.

In 2001, when the Wellcome Trust Sanger Institute began its own effort to use genomic technologies to explore cancer, the project's immediate goal was to optimize robotics and information management systems in test runs that involved sequencing 20 genes in 378 cancer samples. But the group hit pay dirt a year later when they found that a gene called *B-RAF* was mutated in about 70 percent of the malignant melanoma cases they examined. A variety of researchers swiftly set their sights on this potential new therapeutic target in the most deadly form of skin cancer. They tested multiple approaches—from classic chemical drugs to small interfering ribonucleic acids—in cell lines and in mice, to see if these interventions could block or reduce the activity of *B-RAF* or inhibit a protein called MEK that is overproduced as a result of *B-RAF* mutations. Just five years later the most promising of these therapies are being tested in clinical trials.

Other research groups have already zeroed in on genetic mutations linked to certain types of breast cancer, colon cancer, leukemia, lymphoma and additional cancers to develop molecular diagnostics, as well as prognostic tests that can point to an agent in the current arsenal of chemotherapies to which a particular patient is most likely to respond. Cancer genomics has also helped to directly shape the development and use of some of the newest treatments.

The drug Gleevec, for example, was designed to inhibit an enzyme produced by a mutant fused version of two genes, called *BCR-ABL*, that causes chronic myelogenous leukemia. Gleevec is proving dramatically effective against that disease and showing value in the treatment of more genetically complex malignancies, such as gastrointestinal stromal tumor and several other relatively rare cancers that involve similar

THE AUTHORS

FRANCIS S. COLLINS and *ANNA D. BARKER* are leaders of The Cancer Genome Atlas initiative in their positions as, respectively, director of the National Human Genome Research Institute and deputy director for Advanced Technologies and Strategic Partnerships of the National Cancer Institute. Collins led the Human Genome Project to its completion of the human DNA sequence, and Barker has headed drug development and biotechnology research efforts in the public and private sectors, with a particular focus on fighting cancer.

STEVE GSCHMEISSNER *Photo Researchers, Inc.*

Genes and Cancer

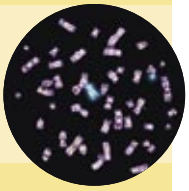
A connection between genetic abnormalities and the aberrant features of cancer cells was first suggested more than 100 years ago by German biologist Theodor Boveri and others. But over the past few decades evidence that gene alterations directly cause the deranged behavior of cancer cells began accumulating. Calls arose by 1986 to sequence the normal human genome to study malignant gene changes comprehensively. The Human Genome Project was completed in 2003. The Cancer Genome Atlas project will start cataloguing the gene mutations found in three types of human cancer this year.

1890–1914
Studies of abnormal chromosome distribution during cell division suggest a role in malignancy.

Theodor Boveri ▶

1950s–1960s
Multiple discoveries reveal that tumor viruses can cause cancer by injecting their genes into cells.

1960
First genetic defect associated with a specific cancer—an abnormality known as the Philadelphia chromosome—is discovered in chronic myelogenous leukemia (CML) cells.



1976
Scientists discover that *src,* a nonviral gene found in animal cells, can cause cancer.

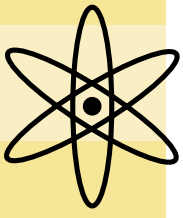
1979
P53, later found to be the most frequently mutated gene in human cancer, is discovered.

1981
H-RAS is the first human oncogene (a gene whose alteration is cancer-promoting) to be discovered.

1983
Altered methylation of DNA, suspected to affect gene activation, found in cancer cells.

1986
Renato Dulbecco, writing in *Science,* calls for sequencing the human genome to advance cancer research.

1986
U.S. Department of Energy considers sequencing the human genome to further study of radiation effects.



1986
First tumor suppressor gene, *RB1,* is identified.

1987
Fused gene *BCR-ABL* in the Philadelphia chromosome is found to cause CML.

1990
Model of multistep tumor genesis clarifies the role of accumulated gene changes in cellular transformation to malignancy.

1990
Human Genome Project begins.

enzymes. Herceptin, an agent that targets a cellular signal–receiving protein called *HER2,* is successful against breast cancers with an abnormal multiplication of the *HER2* gene that causes overproduction of the receptor protein.

Strategies for selecting treatments based on specific gene mutations in a patient's cancer are also being tested in studies of the drugs Iressa and Tarceva for lung cancer, as well as Avastin for lung, colon and other cancers. The performance of these new gene-based diagnostics, prognostics and therapeutics is certainly good news, although the list of such interventions remains far shorter than it would be if researchers in academia and the private sector had ready access to the entire atlas of genomic changes that occur in cancer.

A recent study led by investigators at Johns Hopkins University illustrates both the power of large-scale genomics applied to the discovery of cancer genes and the tremendous undertaking a comprehensive cancer genome atlas will be. The group sequenced about 13,000 genes in tumor tissues taken from 11 colorectal cancer patients and 11 breast cancer patients and reported finding potentially significant mutations in nearly 200 different genes. Interestingly, only about a dozen genes had previously been linked to these two types of cancer, and most scientists had generally expected to find just a few more.

Among the major challenges encountered by researchers sequencing cancer cell genomes is the difficulty of distinguishing meaningless mutations in the tumor samples from those that are cancer-related. Somewhat surprisingly, early sequencing studies have also found very little overlap among the genetic mutations present in different types of cancer and even substantial variation in the pattern of genetic mutations among tumor samples from patients with the same type of cancer. Such findings underscore the idea that many different possible combinations of mutations can transform a normal cell into a cancer cell. Therefore, even among patients with cancers of the same body organ or tissue, the genetic profile of each individual's tumor can differ greatly.

To grasp the full scope of what TCGA hopes to achieve, one must consider the complexities identified in such early efforts and imagine extending the work to more than 100 types of cancer. It is enough to give even veterans of the Human Genome Project and seasoned cancer biologists pause. Yet TCGA participants and other scientific pioneers from around the world are forging ahead, because we are convinced that amid the intricacies of the cancer genome may lie the greatest promise for saving the lives of patients.

Although researchers will probably take many years to complete a comprehensive catalogue of all the genomic mutations that cause normal cells to become malignant, findings with the potential to revolutionize cancer treatment are likely to appear well before this compendium is finished, as the proofs of concept have shown. As each new type of cancer is studied and added to TCGA, investigators will gain another rich new set of genomic targets and profiles that can be used to develop more tailored therapies.

PHOTO RESEARCHERS, INC. (*Boveri*); DEPARTMENT OF CLINICAL CYTOGENETICS, ADDENBROOKE'S HOSPITAL *Photo Researchers, Inc.* (*Philadelphia chromosome*); STEVE GSCHMEISSNER *Photo Researchers, Inc.* (*tumor cell*); MARK J. WINTER *Photo Researchers, Inc.* (*Gleevec molecule*); CECIL H. FOX *Photo Researchers, Inc.* (*Biospecimen Core Resource*); AFFYMETRIX (*Cancer Genome Characterization Centers*); NATIONAL HUMAN GENOME RESEARCH INSTITUTE (*Genome Sequencing Centers*); © CDC/PHIL *Corbis* (*Data Coordinating Center*)

Compiling a Colossal Atlas

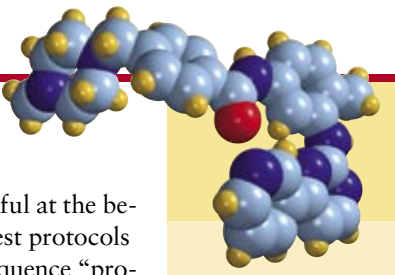
A PHASED-IN STRATEGY that proved successful at the beginning of the Human Genome Project was to test protocols and technology before scaling up to full DNA sequence "production." Similarly, TCGA is beginning with a pilot project to develop and test the scientific framework needed to ultimately map all the genomic abnormalities involved in cancer.

In 2006 the National Cancer Institute and National Human Genome Research Institute selected the scientific teams and facilities that will participate in this pilot project, along with the cancer types they will begin examining. Over the next three years these two institutes will devote $100 million to compiling an atlas of genomic changes in three tumor types: glioblastomas of the brain, lung cancer and ovarian cancer. These particular cancers were chosen for several reasons, including their value in gauging the feasibility of scaling up this project to a much larger number of cancer types. Indeed, only if this pilot phase achieves its goals will the NIH move forward with a full-fledged project to develop a complete cancer atlas.

The three malignancies that we selected for the pilot collectively account for more than 210,000 cancer cases in the U.S. every year and caused an estimated 191,000 deaths in this country in 2006 alone. Moreover, tumor specimen collections meeting the project's strict scientific, technical and ethical requirements exist for these cancer types. Last September our institutes announced the selection of three biorepositories to provide such specimens, along with new tumor samples as needed, and normal tissue from the same patients for comparison. Those facilities will deliver materials to a central Biospecimen Core Resource, one of four major structural components in TCGA's pilot project.

Cancer Genome Characterization Centers, Genome Sequencing Centers and a Data Coordinating Center constitute the project's other three main elements [*see illustration at right*], and all these groups will collaborate and exchange data openly. Specifically, the seven Cancer Genome Characterization Centers will use a variety of technologies to examine the activity levels of genes within tumor samples and to uncover and catalogue so-called large-scale genomic changes that contribute to the development and progression of cancer. Such alterations include chromosome rearrangements, changes in gene copy numbers and epigenetic changes, which are chemical modifications of the DNA strand that can turn gene activity on or off without actually altering the DNA sequence.

Genes and other chromosomal areas of interest identified by the Cancer Genome Characterization Centers will become targets for sequencing by the three Genome Sequencing Centers. In addition, families of genes suspected to be important in cancer, such as those encoding enzymes involved in cell-cycle control known as tyrosine kinases and phosphatases, will be sequenced to identify genetic mutations or other small-scale changes in their DNA code. At present, we estimate that some 2,000 genes—in each of perhaps 1,500 tumor samples—will be sequenced during this pilot project. The exact numbers will, of course, depend on the samples obtained and what is discovered



◀ Gleevec model

1993
Preclinical testing starts on drug that would become Gleevec, the first therapy developed to target a known gene-based cause of a cancer.

1999
Gene-activity profiles are first shown to distinguish between cancer types and to predict chemotherapy response.

2001
Gleevec earns FDA approval.

2002
Wellcome Trust Sanger Institute tumor genome survey discovers a mutation in *B-RAF* gene common to 70 percent of melanomas.

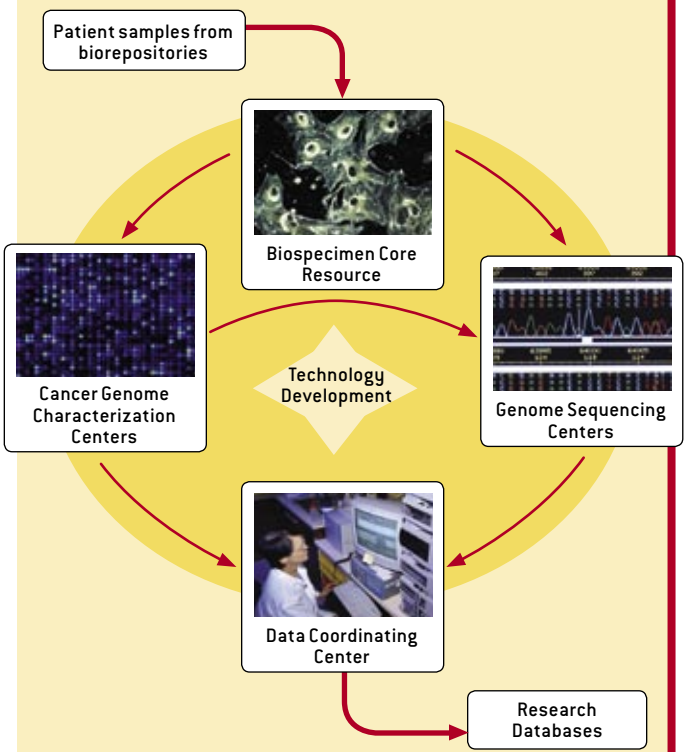
2003
Human Genome Project is completed.

2005
The Cancer Genome Atlas (TCGA) pilot project is announced by the National Institutes of Health.

2006
TCGA names pilot project participants and three cancer types for sequencing and genetic analysis.

2007–2010
TCGA will collect and analyze tumor samples obtained from designated biorepository institutions treating patients with cancer. The project's four primary components—a Biospecimen Core Resource, seven Cancer Genome Characterization Centers, three Genome Sequencing Centers and a Data Coordinating Center—will cooperate to test methods and technologies and to generate and manage data that will be made available to the wider research community.

How Will It Work?



about them by the Cancer Genome Characterization Centers.

Both the sequencing and genome characterization groups, many of which were participants in the Human Genome Project, can expect to encounter a far greater level of complexity than that in the DNA of normal cells. Once cells become cancerous, they are prone to an even greater rate of mutation as their self-control and repair mechanisms fail. The genomic makeup of individual cells can therefore vary dramatically within a single tumor, and the integrated teams will need to develop robust methods for efficiently distinguishing the "signal" of a potentially biologically significant mutation from the "noise" of the high background rate of mutations seen in many tumors. Furthermore, tumors almost always harbor some nonmalignant cells, which can dilute the sample. If the tumor DNA to be sequenced is too heterogeneous, some important mutations may be missed.

Following the lead of the Human Genome Project and other recent medical genomics efforts, all these data will be made swiftly and freely available to the worldwide research community. To further enhance its usefulness to both basic and clinical researchers and, ultimately, health care professionals, TCGA will link its sequence data and genome analyses with

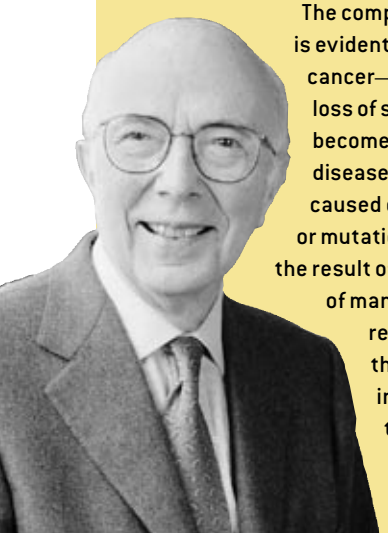
From Genome to Cancer—Why the Time Is Right

By Renato Dulbecco

When in 1986 I suggested a new project directed at identifying all human genes, one of my overriding goals was to find those genes involved in cancer development—a feat I hoped would lead to new tools for cancer research and, ultimately, to new therapies. That original human genome project has now been carried out and has demonstrated its usefulness for the discovery of genes involved in many diseases, including cancer. Moreover, the genome sequencing effort has been extended to other organisms—from bacteria to chimpanzees—and is showing the unity of life by revealing how many genes distant species share in common.

In the course of this work, new technologies have also provided a much more detailed understanding of the complicated processes by which genes give rise to a variety of functional molecules. An important outcome of this research is the realization that genes do not act alone but are participants in extensive networks of activity within cells. Any change in the functioning of one gene can therefore be accompanied by changes in the workings of multiple genes and proteins involved in the cells' self-maintenance.

Cancer results from the stepwise loss of cellular self-control.



The complexity of this system in normal cells is evident in what we already know about cancer—that it results from the stepwise loss of such cellular self-control, which becomes more and more complete as the disease progresses. That progression is caused only in part by physical alterations, or mutations, in specific genes; mostly it is the result of consequent changes in the activity of many other genes involved in cell regulation. Single genes may therefore be responsible in the initiation of cancer and so potential therapeutic targets. To reach the more advanced stages of these cancers (such as the acute phase of myeloid leukemia or the metastatic phase of other cancers), however, the participation of many other genes is required. Most of them are still unknown.

An exception is the recently observed phenomenon of oncogene addiction in certain tumor cells: despite the presence of numerous mutations to the cellular genome, turning off the activity of one so-called oncogene causes the cells to commit suicide via a mechanism known as apoptosis. But how generally this phenomenon occurs is also unknown. To approach these questions, it will be necessary to have a complete catalogue of the structural and functional alterations of genes and other cellular components that cause the loss of regulation in cancer cells. This process, in turn, will require a complete determination of their connections into networks by computational means—a task for the future.

On the way to this goal, however, many other unanswered questions can be explored by the research community. A possible role for stem cells in cancer, for example, is supported by similarities in the behavior of stem cells and cancer cells: both have an unlimited ability to divide; both are very sensitive to the cellular environment, or niche, in which they grow; and many of the genes known to be active in stem cells are also activated in cancer cells.

The advent of genomics has provided welcome insight into the mechanisms by which normal cells become cancerous, but our picture is still incomplete. The time has come to obtain a truly comprehensive catalogue of the genes involved in cancer, bringing to bear all the power of the new tools of genomics and molecular biology to the problem. The Cancer Genome Atlas project aims to do just that.

Renato Dulbecco is president emeritus of the Salk Institute for Biological Studies and co-recipient of the 1975 Nobel Prize in Physiology or Medicine for discoveries related to the interaction of tumor viruses and the genetic material of the cell.

SALK INSTITUTE FOR BIOLOGICAL STUDIES

information about observable characteristics of the original tumors and the clinical outcomes of the sample donors. Developing the bioinformatic tools to gather, integrate and analyze those massive amounts of data, while safeguarding the confidentiality of patient information, is therefore another hurdle that must be cleared to turn our vision into reality.

Uncharted Territory

THE ROAD AHEAD is fraught with scientific, technological and policy challenges—some of which are known and others as yet unknown. Among the uncertainties to be resolved: Will new sequencing technologies deliver on their early promise in time to make this effort economically feasible? How quickly can we improve and expand our toolbox for systematically detecting epigenetic changes and other large-scale genomic alterations involved in cancer, especially those associated with metastasis? How can we harness the power of computational biology to create data portals that prove useful to basic biologists, clinical researchers and, eventually, health care professionals on the front lines? How can we balance intellectual-property rights in a way that promotes both basic research and the development of therapies? When will Congress finally pass genetic nondiscrimination legislation so that knowledge gained through TCGA will have the maximum positive influence on Americans' health? The list goes on.

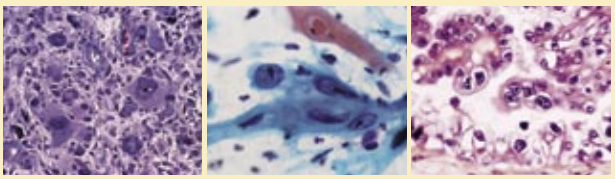
To avoid raising false expectations, we also must be clear about the questions this project will not attempt to answer. Although it will serve as a resource for a broad range of biological exploration, TCGA is only a foundation for the future of cancer research and certainly not the entire house. And we face the sobering issue of time—something that is in short supply for many cancer patients and their families. As we survey the considerable empty spaces that exist in our current map of genomic knowledge about cancer, the prospect of filling those gaps is both exhilarating and daunting. Scientists and the public need to know up front that this unprecedented foray into molecular cartography is going to take years of hard work and creative problem solving by thousands of researchers from many different disciplines.

Where all this work will lead can only be dimly glimpsed today. In this sense, our position is similar to that of the early 19th-century explorers Meriwether Lewis and William Clark. As they ventured up the Missouri River into the largely uncharted Northwest Territory in 1804, their orders from President Thomas Jefferson were to "take observations of latitude and longitude at all remarkable points.... Your observations are to be taken with great pains and accuracy; to be entered distinctly and intelligibly for others, as well as yourself."

Although Lewis and Clark did not find the much-longed-for water route across the continent, their detailed maps proved valuable to their fledgling nation in myriad ways that Jefferson could never have imagined. For the sake of all those whose lives have and will be touched by cancer, we can only hope our 21st-century expedition into cancer biology exceeds even Renato Dulbecco's grandest dreams. SA

Targeting Gene Changes in Cancer

TCGA pilot project teams will examine the DNA of some 1,500 tumor samples from patients with cancers of the lung, ovaries or brain (glioblastoma), looking for genetic changes. Approximately 2,000 suspect genes in each sample will be sequenced to identify specific mutations. The list of target genes will be tailored to each cancer type and largely determined by what the Cancer Genome Characterization Centers find in the samples, although candidates will also be drawn from categories of genes already associated with cancer.



From left to right: Glioblastoma, lung cancer, ovarian cancer

GENE CATEGORIES	EXAMPLES
Genes identified by TCGA Cancer Genome Characterization Centers as having aberrant structure or activity in a significant number of tumor samples	In some brain tumor cell lines, a gene encoding the intracellular protein NF-KAPPA B is much more active than in normal brain tissue
Well-known oncogenes (genes whose overactivity or alteration is cancer-promoting)	• Growth factor receptor genes: *HER2* (breast and lung cancers), *EGFR* (lung and colon cancers) • Signaling protein genes: *BCR-ABL* (chronic myelogenous leukemia), *RAS* (many cancers), *B-RAF* (skin cancers) • Regulators of cell death: *BCL-3* (lymphoma)
Well-known tumor suppressors (genes that protect cells from malignant transformation, unless disabled by mutation)	• Controllers of cell division: *RB1* (retinoblastoma) • DNA repairers: *HNPCC* (colon cancer, endometrial cancer) • Promoters of programmed cell suicide: *P53* (lung, colon, breast and brain tumors)
Genes related to known oncogenes and tumor suppressor genes by similarity or pathway membership	The oncogenes *HER2* and *EGFR* are part of the epidermal growth factor receptor signaling pathway, which contains at least half a dozen other genes suspected of playing key roles in cancer development and progression

MORE TO EXPLORE

The New Era in Cancer Research. Harold Varmus in *Science,* Vol. 312, pages 1162–1165; May 26, 2006.

The Consensus Coding Sequences of Human Breast and Colorectal Cancers. Tobias Sjöblom et al. in *Science,* Vol. 314, pages 268–274; October 13, 2006. (Published online September 7, 2006.)

The Cancer Genome Atlas: **http://cancergenome.nih.gov**

CNRI *Photo Researchers, Inc.* (*glioblastoma* and *ovarian cancer*); JONATHAN ASHTON *Photo Researchers, Inc.* (*lung cancer*)

The New York Times | http://nyti.ms/1byTWFo

SCIENCE

A Catalog of Cancer Genes That's Done, or Just a Start

FEB. 6, 2014

Carl Zimmer

MATTER

Cancer is a disease of genes gone wrong. When certain genes mutate, they make cells behave in odd ways. The cells divide swiftly, they hide from the immune system that could kill them and they gain the nourishment they need to develop into tumors.

Scientists started identifying these cancer genes in the 1970s and their list slowly grew over the years. By studying them, scientists came to understand how different types of cancer develop and in some cases they were even able to develop gene-targeting drugs. Last May, for example, the Food and Drug Administration approved a drug known as Tarceva as a first-line treatment for lung cancer in which a gene called EGFR has mutated.

The National Institutes of Health, hoping to speed up the identification of cancer genes, started an ambitious project in 2005 called the Cancer Genome

Atlas. They analyzed 500 samples from each of over 20 types of cancer and found a wealth of new genes. The data have helped scientists discover more of the tricks cancer cells use to thrive at our expense.

"The Cancer Genome Atlas has been a spectacular success, there's no doubt about that," said Bruce Stillman, the president of Cold Spring Harbor Laboratory.

But now, as the Atlas project is coming to an end, researchers at the Broad Institute of M.I.T. and Harvard have published a study in the journal Nature that has scientists debating where cancer research should go next. They estimated that scientists would need to examine about 100,000 cancer samples —10 times as many as the $375 million Cancer Genome Atlas has gathered — to find most of the genes involved in 50 cancer types.

"We now know what it would take to get a complete catalog," said Eric S. Lander, the founding director of the Broad Institute and a co-author of the new study. "And we now know we're not close to done. We have a lot left to learn."

Traditionally, scientists have identified cancer genes by comparing healthy cells with cancerous ones. If they find a statistically unusually high number of cells with mutations in a particular gene, they can then examine it to see if it really does help drive cancer — or if it is just carrying a harmless mutation.

Dr. Lander and his colleagues suspected this method could miss some genes. While some cancer genes affect most cells of a given type of cancer, other genes are only involved in a fraction of them. (EGFR, the gene treated with Tarceva, is mutated in only about 10 percent of cases of nonsmall cell lung cancer.) Small samples of cancer cells might not contain the less common mutations.

The Broad researchers suspected that they could catch some of these missing genes by looking at several cancer types at once, because some genes are not limited to a single type of cancer.

For their new study, the scientists examined cancer samples from the Cancer Genome Atlas, as well as cancer samples from the Broad's own collection. All told, they analyzed 4,742 samples from 21 types of cancer.

The new study detected many of the genes that other scientists have previously linked to those 21 types of cancer. But they also found new genes that

had been overlooked before. All told, they identified 33 genes that they consider strong candidates for playing a role in cancer — a potential increase of the catalog of cancer genes of 25 percent.

"This was eye-opening to me," said Dr. Lander.

Dr. Lander and his colleagues began to wonder how many genes could be found if scientists looked at more cancer samples. Was the cancer catalog almost finished, or only just begun?

"We were able to ask for the first time, 'Are we there yet?'" said Dr. Lander.

They extrapolated from their own results to gauge how many more samples scientists would need to look at to find most cancer genes involved in at least 2 percent of cancers of a given type.

To find most cancer genes involved in the 50 most common types of cancer, the researchers estimated that they would have to analyze 100,000 samples. In other words, the atlas has gotten us a tenth of the way to the finish line.

Dr. Harold Varmus, the director of the National Cancer Institute, said the study has raised valuable questions. "The paper provides some models about what we might think about doing next," he said. He said the agency is now considering testing Dr. Lander's hypothesis on a few types of cancer by gathering more samples.

Dr. Lander and his colleagues argue for finishing off the cancer gene catalog. "Completing the genomic analysis of this disease should be a biomedical imperative," they wrote in their new paper.

In an interview, Dr. Lander said knowing most genes involved in cancer would be a powerful weapon against the disease. "How could we think of beating cancer in the long term without having the whole catalog?" he said. "It would be crazy not to have the information."

But Dr. Stillman of Cold Spring Harbor Laboratory said completing the atlas has to be weighed against other needs. "Whether we need to know every cancer gene, I'd like to see an argument for how that's going to help the advancement of new therapy," he said.

For many researchers, the question comes down to whether extending the atlas project would be the best use of existing research funds. "There's no

question that it would be valuable. The question is whether it's worth it," said Dr. Bert Vogelstein, a Howard Hughes Medical Institute Investigator at Johns Hopkins University.

Some scientists say it might make more sense to study common cancer genes that have already been identified, instead of searching for relatively rare genes that might not turn out to be helpful in fighting cancer.

Also in question is who would pay for advancing the cancer catalog project. "We still don't know how much money we're going to have this year," said Dr. Varmus of the National Cancer Institute's budget. "We're not going to set off tomorrow and do 100,000 complete genomes."

Dr. Lander argued that the project could be done for a reasonable cost, and might also be supported by philanthropic organizations or international partners. In any case, he said, he welcomed a debate about when science will finish the cancer gene catalog.

"If people say, 'I would rather not know that for five years, or 10 years,' that's a reasonable argument," said Dr. Lander. "But I would rather know that sooner."

Correction: February 6, 2014

Because of an editing error, an earlier version of this article misstated a finding of the new study. The researchers estimated that scientists would need to examine about 100,000 cancer samples — not genes — to find most of the genes involved in 50 cancer types.

The New York Times

November 26, 2013

In Israel, a Push to Screen for Cancer Gene Leaves Many Conflicted

By RONI CARYN RABIN

KFAR SABA, Israel — Ever since she tested positive for a defective gene that causes breast cancer, Tamar Modiano has harbored a mother's fear: that she had passed it on to her two daughters. Ms. Modiano had her breasts removed at 47 to prevent the disease and said that the day she found out her older daughter tested negative was one of the happiest of her life.

Now she wants her younger daughter, Hadas, 24, to be tested so she can start a family early if she is positive and then have a double mastectomy too. Ms. Modiano's elder daughter, Suzi Gattegno, 29, disagrees.

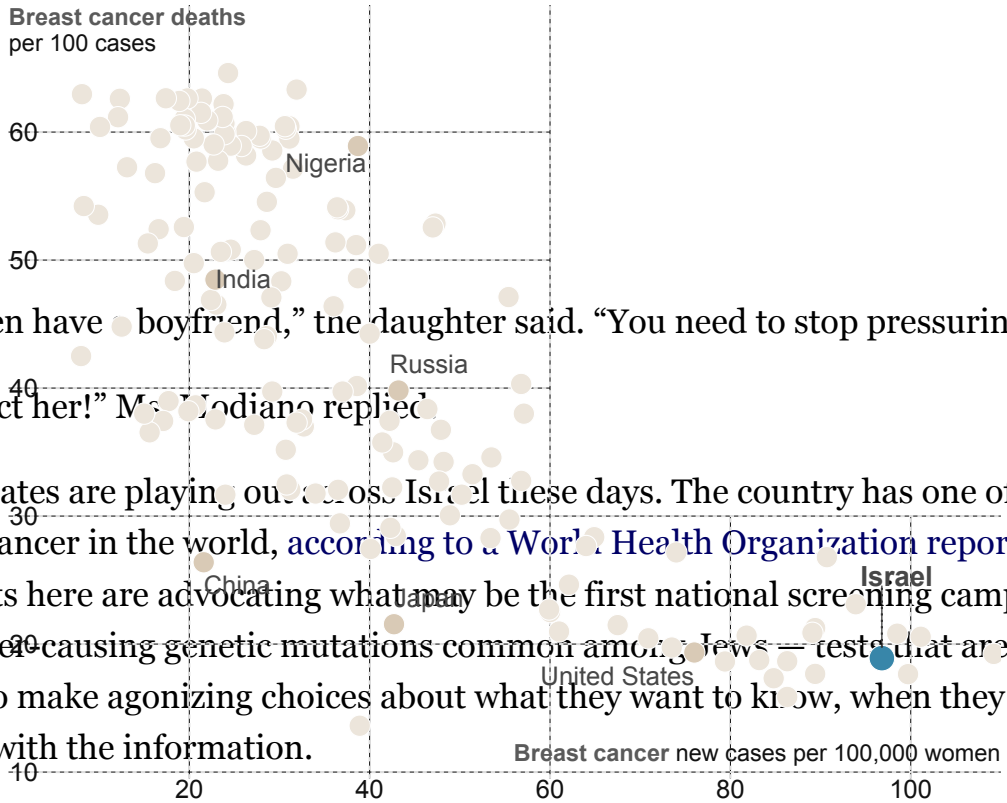
"You're keeping her from living her life," Ms. Gattegno told her mother. "You want to marry her off early."

"If she's a carrier, she should marry early," her mother countered.

Breast Cancer
Around the Globe

Israel has one of the highest rates of breast cancer in the world. Mortality is very low, in part because of intense screening.

INTERACTIVE GRAPHIC



“She doesn’t even have a boyfriend,” the daughter said. “You need to stop pressuring her.”

“I want to protect her!” Ms. Modiano replied.

Such family debates are playing out across Israel these days. The country has one of the highest rates of breast cancer in the world, according to a World Health Organization report. And some leading scientists here are advocating what may be the first national screening campaign to test women for cancer-causing genetic mutations common among Jews — tests that are already forcing young women to make agonizing choices about what they want to know, when they want to know it and what to do with the information.

The so-called Jewish breast cancer genes have preoccupied women here for years, but after the actress Angelina Jolie revealed in May that she had undergone a double mastectomy because she had tested positive for such a mutation, coverage here exploded, with radio and TV talk shows featuring Israeli women grappling with similar decisions.

Jews of Ashkenazi, or central and eastern European, backgrounds, who make up about half the Jews in Israel and the vast majority of those in the United States, are much more likely to carry mutations that increase the risks for both breast and ovarian cancers, according to the National Cancer Institute.

A number of influential geneticists and cancer doctors from various medical centers here say that the Israeli Health Ministry should pay for free voluntary genetic testing of all Ashkenazi women over the age of 25. About a million women would be covered, at a cost of less than $100 per test. Jews of Iraqi descent, whose families also often carry a harmful mutation, might also be screened.

The goal of a proposed universal screening program would be to identify an estimated 30,000 Israeli women who have the mutations. So far, with sporadic testing, about 6,000 of them have been found, many only after a cancer diagnosis, said Dr. Ephrat Levy-Lahad, the coordinator of the Israel Genetics Consortium.

“That’s our target population,” said Dr. Oded Olsha, a breast surgeon at Shaare Zedek Medical

Center in Jerusalem. “If we can find them, we can save their lives.”

Women who tested positive for mutations in the BRCA1 and BRCA2 genes, which suppress tumors, would be strongly encouraged to complete child bearing by their late 30s so they could have their ovaries removed by age 40. Risk-reducing mastectomies would also be offered.

The profoundly controversial idea of broad-based screening has already set off debate in Israel among advocates for women and those in the medical and scientific fields. Critics say it may lead to social stigma and a rash of unnecessary operations, and also burden some women with information they may not want or know how to use.

The choice is not a simple one. Removing the breasts and ovaries sharply reduces the risk of cancer, but mastectomies are disfiguring and women often experience scarring and numbness after breast reconstruction. Loss of the ovaries plunges women into menopause, potentially leading to hot flashes, a reduced sex drive and heightened risks of heart disease and bone loss.

But already demand for genetic testing is very high here — there are yearlong waiting lists — and national health insurance generally covers it as long as a woman is referred by her doctor or a genetic counselor.

While poor countries struggle to provide even basic cancer care to women, wealthier societies like Israel and the United States are increasingly using sophisticated technologies to identify those at greatest risk in an effort to thwart the disease before it gets started. Several American Jewish organizations have recently undertaken a campaign to raise awareness about the genetic susceptibility to breast and ovarian cancer among Ashkenazi Jews.

The cancer divide here in Israel is more ethnic than economic. Will only Ashkenazi Jews be routinely tested? Though they are much more likely to carry one of the common harmful mutations in the BRCA1 and BRCA2 genes, Israel is a melting pot of both Arab citizens and Jews from all over the world, and only half of the country’s six million Jews are of Ashkenazi ancestry.

Under the proposal being put forward by some Israeli geneticists, it is likely that Israeli Arab citizens and Jews of Sephardic ancestry — whose families originate in North Africa and the Middle East — would not routinely be included among those screened for BRCA mutations, a point of contention in a country where a social and ethnic rift already divides Sephardic and Ashkenazi Jews.

Families of Iraqi origin, like Ms. Modiano’s, may be covered because of their higher genetic risks.

She always knew there was cancer in her father's family. Three of his sisters died of breast cancer at young ages.

But she was tested for cancer-causing mutations only three years ago after finding out her relatives were being screened. The result stunned her.

"I thought about what it meant for me, and then I thought, 'What about my daughters?' " Ms. Modiano said recently, shuddering slightly. "I was petrified. I still am."

Within three months, Ms. Modiano had a risk-reducing double mastectomy and an operation to remove her ovaries. But the decisions facing her daughters, both in their 20s, were far more complicated. Neither was married, and each had a 50 percent chance of carrying the mutation.

Ms. Gattegno, who was in nursing school at the time, decided to be tested.

"I told my boyfriend that if I turned out to be a carrier, I would quit school for a while and we'd have kids right away," she said. "And then I'd have a prophylactic mastectomy."

Difficult Questions

At the Shaare Zedek Medical Center in Jerusalem, Dr. Levy-Lahad, who started one of the first genetic testing programs in Israel, is among the main champions of universal screening for Ashkenazi women. She has worked closely with the American scientist who identified the BRCA1 gene, Mary-Claire King.

"If you're only testing women after they've been affected, you've lost the game," Dr. Levy-Lahad said. "Genetic testing is about prevention."

She pointed to the risks. One in 40 Ashkenazi women carry a harmful genetic mutation, compared to less than one in 100 women generally.

Women with these mutations are four to five times more likely to develop aggressive breast cancers, according to the National Cancer Institute. The disease often comes at an early age and in both breasts, said Dr. Gad Rennert, the director of Israel's National Cancer Control Center.

The potential for preventing ovarian cancer, a rarer but more lethal disease, is even greater. The common harmful mutations found in Ashkenazis are implicated in about 30 percent of ovarian cancers in Israeli women — and 40 percent or more of cases in women under 60, Dr. Rennert said.

Practical and ethical questions abound. Should men — who are just as likely to pass the mutations to their children and who are themselves at increased risk for some cancers — also be tested? Will ultra-Orthodox Jews participate in screening, knowing a positive test could hurt their family's chances of making a good marriage match?

Identifying people as carriers can change their perceptions of themselves and the way they envision their futures, said Dr. Gail P. Jarvik, the head of the division of medical genetics at University of Washington Medical Center in Seattle.

Even though the testing would be voluntary, women could feel pressured to participate, said Barbara A. Koenig, a professor of medical anthropology and bioethics at the University of California, San Francisco. "When you institute mass screening, you're making a collective decision that this is a good thing."

There are also lingering scientific questions. While much is known about the three common Ashkenazi BRCA1 and BRCA2 mutations, the risk they confer varies. Some families may have other genetic factors that modify their risk, which explains why some carriers never develop cancer while others die in their 20s.

Women identified as mutation carriers are showered with resources for early detection and prevention. These women's risk for developing breast cancer ranges from 45 to 65 percent or higher, depending on family history, and their risk for ovarian cancer can be as high as 39 percent.

Routine mammography screening for most Israeli women starts at 50, but carriers are eligible for frequent clinical breast exams and expensive magnetic resonance imaging of the breast, all covered by national health insurance. They are also eligible for regular blood tests and vaginal ultrasounds to screen for ovarian cancer.

Cultural Obstacles

Many Israeli women who have the harmful mutations complain that male doctors display sexist attitudes about the importance of breasts and are loath to do mastectomies on healthy women.

Dr. Moshe Inbar, an outspoken oncologist in Tel Aviv who opposes preventive mastectomies, has said that a woman cannot have an orgasm after her breasts are removed, an assertion not supported by evidence.

"Would you like to live without your breasts?" Dr. Inbar, the director of the oncology division at Tel

Aviv Sourasky Medical Center, asked. “I try to dissuade women from doing this. Surgery is not something that should be done on patient demand; it should be done when indicated.”

While more than a third of American women carrying the harmful genetic mutations choose preventive mastectomies, only 4 percent of Israeli women do, according to a 2008 International Journal of Cancer study that compared risk-reducing procedures for samples of BRCA1 and BRCA2 mutation carriers in Canada, the United States, Israel and six European countries.

By contrast, well over half the carriers in all countries but Poland had their ovaries removed, a procedure that also reduces breast cancer risk.

But there are signs that attitudes are beginning to change here, as women take to the Internet to research their options, challenge the medical profession and shop for doctors.

Tamar Horesh, 35, a computer programmer from central Israel, has vivid memories of her mother’s painful death from ovarian cancer at 51.

When Ms. Horesh tested positive for a BRCA1 mutation, she said her husband supported her decision to surgically remove her ovaries and breasts. They had three young children to raise.

Finding a doctor to do it was another matter.

“The first doctor I went to said I was insane, and he said, ‘If you have brain cancer, are you going to chop off your head?’ ” said Ms. Horesh. “The second doctor said that he noticed I had a small chest, and he thought I just wanted an excuse to have my breasts enlarged.”

A third doctor told her what many women hear, “Come back when you have cancer,” and “Nobody dies of breast cancer nowadays.”

In fact, some 900 Israeli women die of breast cancer each year, according to the Israel Cancer Association.

Ms. Horesh eventually got referrals from Bracha, a group founded to raise awareness by Lisa Cohen, who has a BRCA mutation.

Ms. Cohen’s mother died of cancer at 49, and then her sister, who had four young children, died at 36. “I felt like I was going to be next in line,” said Ms. Cohen, a divorced mother of three who was determined to stay alive for her children.

A Personal Decision

Hadas Modiano, a university student in Jerusalem, is waiting a couple of years before she seriously considers being tested as her mother insists. But her mother's example has given her strength.

"I think I'm not as scared as I might have been because I saw what my mother went through," she said. "It was hard, but she has managed and overcome."

But for many women, the choices are harrowing. A Tel Aviv lawyer, 43, who asked that her name not be used to protect her privacy, was devastated when she found out at 26 that she had one of the bad mutations.

The lawyer, who was only 4 when her mother died of breast cancer, said she was among the first to line up for the genetic test when it became available in Israel in the 1990s.

"You may think you're prepared for this information, but you aren't," she said. "My blood went cold when I found out." Afterward, she said she realized, "The only solutions are so radical — amputating parts of your body."

When she first met the man who became her husband, she told him that she could never marry or have children. He convinced her otherwise. She goes for frequent scans and checkups but postponed having a mastectomy so she could breast-feed their children.

She chose to become pregnant through in vitro fertilization so female embryos that did not carry harmful mutations could be selected in the lab.

"Finally, there was something positive to do with the information," she said.

Preventive surgeries are not always successful. Tali Shalev had what was supposed to be a preventive double mastectomy, but pathologists found a cancerous lesion in the removed breast tissue. "I'm an example of someone who did everything possible," said Ms. Shalev, 40, who has three children.

The dilemmas of genetic testing are compounded in the ultra-Orthodox community, where the emphasis on modesty often dampens open discussion.

Still, Tziporah, 38, a Canadian-born Orthodox mother of seven who now lives in Israel, talks openly about her experience because she wants to reach other religious women. Tziporah, who goes by her nickname, Tzippy, asked that her last name not be used to protect the privacy of her

extended family members, who also may carry the gene. Her mother died of breast cancer at 42, when she was 5, and when Tzippy was pregnant with her last child a few years ago, she tested positive for a BRCA1 mutation.

She sought advice from several rabbis about whether she should go forward with risk-reducing surgeries. They reassured her that preserving life is one of the supreme values of Judaism.

So three years ago, after her youngest child was born, she had her breasts and ovaries removed. The operations were grueling, but she said she wanted to make sure her children would not suffer the same loss she had. And she said she felt she had a mission to encourage other women to be tested.

“You know why God did this to me?” she said. “Because I’ve got a really big mouth.”

So she is spreading the word within the Orthodox community that genetic screening can save lives.

“Women don’t have to be dying on their kids,” she said.

The New York Times

January 4, 2014

Why Everyone Seems to Have Cancer

By GEORGE JOHNSON

EVERY New Year when the government publishes its Report to the Nation on the Status of Cancer, it is followed by a familiar lament. We are losing the war against cancer.

Half a century ago, the story goes, a person was far more likely to die from heart disease. Now cancer is on the verge of overtaking it as the No. 1 cause of death.

Troubling as this sounds, the comparison is unfair. Cancer is, by far, the harder problem — a condition deeply ingrained in the nature of evolution and multicellular life. Given that obstacle, cancer researchers are fighting and even winning smaller battles: reducing the death toll from childhood cancers and preventing — and sometimes curing — cancers that strike people in their prime. But when it comes to diseases of the elderly, there can be no decisive victory. This is, in the end, a zero-sum game.

The rhetoric about the war on cancer implies that with enough money and determination, science might reduce cancer mortality as dramatically as it has with other leading killers — one more notch in medicine's belt. But what, then, would we die from? Heart disease and cancer are primarily diseases of aging. Fewer people succumbing to one means more people living long enough to die from the other.

The newest cancer report, which came out in mid-December, put the best possible face on things. If one accounts for the advancing age of the population — with the graying of the baby boomers, death itself is on the rise — cancer mortality has actually been decreasing bit by bit in recent decades. But the decline has been modest compared with other threats.

A graph from the Centers for Disease Control and Prevention tells the story. There are two lines representing the age-adjusted mortality rate from heart disease and from cancer. In 1958 when the diagram begins, the line for heart disease is decisively on top. But it plunges by 68 percent while cancer declines so slowly — by only about 10 percent — that the slope appears far less significant.

Measuring from 1990, when tobacco had finished the worst of its damage and cancer deaths were

peaking, the difference is somewhat less pronounced: a decline of 44 percent for heart disease and 20 percent for cancer. But as the collision course continues, cancer seems insistent on becoming the one left standing — death's final resort. (The wild card in the equation is death from complications of Alzheimer's disease, which has been advancing year after year.)

Though not exactly consoling, the fact that we have reached this standoff is a kind of success. A century ago average life expectancy at birth was in the low to mid-50s. Now it is almost 79, and if you make it to 65 you're likely to live into your mid-80s. The median age of cancer death is 72. We live long enough for it to get us.

The diseases that once killed earlier in life — bubonic plague, smallpox, influenza, tuberculosis — were easier obstacles. For each there was a single infectious agent, a precise cause that could be confronted. Even AIDS is being managed more and more as a chronic condition.

Progress against heart disease has been slower. But the toll has been steadily reduced, or pushed further into the future, with diet, exercise and medicines that help control blood pressure and cholesterol. When difficulties do arise they can often be treated as mechanical problems — clogged piping, worn-out valves — for which there may be a temporary fix.

Because of these interventions, people between 55 and 84 are increasingly more likely to die from cancer than from heart disease. For those who live beyond that age, the tables reverse, with heart disease gaining the upper hand. But year by year, as more failing hearts can be repaired or replaced, cancer has been slowly closing the gap.

For the oldest among us, the two killers are fighting to a draw. But there are reasons to believe that cancer will remain the most resistant. It is not so much a disease as a phenomenon, the result of a basic evolutionary compromise. As a body lives and grows, its cells are constantly dividing, copying their DNA — this vast genetic library — and bequeathing it to the daughter cells. They in turn pass it to their own progeny: copies of copies of copies. Along the way, errors inevitably occur. Some are caused by carcinogens but most are random misprints.

Over the eons, cells have developed complex mechanisms that identify and correct many of the glitches. But the process is not perfect, nor can it ever be. Mutations are the engine of evolution. Without them we never would have evolved. The trade-off is that every so often a certain combination will give an individual cell too much power. It begins to evolve independently of the rest of the body. Like a new species thriving in an ecosystem, it grows into a cancerous tumor. For that there can be no easy fix.

These microscopic rebellions have been happening for at least half a billion years, since the advent of complex multicellular life — collectives of cells that must work together, holding back, as best each can, the natural tendency to proliferate. Those that do not — the cancer cells — are doing, in a Darwinian sense, what they are supposed to do: mutating, evolving and increasing in fitness compared with their neighbors, the better behaved cells of the body. And these are left at a competitive disadvantage, shackled by a compulsion to obey the rules.

As people age their cells amass more potentially cancerous mutations. Given a long enough life, cancer will eventually kill you — unless you die first of something else. That would be true even in a world free from carcinogens and equipped with the most powerful medical technology.

Faced with this inevitability, there have been encouraging reductions in the death toll from childhood cancer, with mortality falling by more than half since 1975. For older people, some early-stage cancers — those that have not learned to colonize other parts of the body — can be cured with a combination of chemicals, radiation therapy and surgery. Others can be held in check for years, sometimes indefinitely. But the most virulent cancers have evolved such wily subterfuges (a survival instinct of their own) that they usually prevail. Progress is often measured in a few extra months of life.

OVER all, the most encouraging gains are coming from prevention. Worldwide, some 15 to 20 percent of cancers are believed to be caused by infectious agents. With improvements in refrigeration and public sanitation, stomach cancer, which is linked to Helicobacter pylori bacteria, has been significantly reduced, especially in more developed parts of the world. Vaccines against human papilloma virus have the potential of nearly eliminating cervical cancer.

Where antismoking campaigns are successful, lung cancer, which has accounted for almost 30 percent of cancer deaths in the United States, is steadily diminishing. More progress can be made with improvements in screening and by reducing the incidence of obesity, a metabolic imbalance that, along with diabetes, gives cancer an edge.

Surprisingly, only a small percentage of cancers have been traced to the thousands of synthetic chemicals that industry has added to the environment. As regulations are further tightened, cancer rates are being reduced a little more.

Most of the progress has been in richer countries. With enough political will the effort can be taken to poorer parts of the world. In the United States, racial disparities in cancer rates must be addressed. But there is a long way to go. For most cancers the only identifiable cause is entropy,

the random genetic mutations that are an inevitable part of multicellular life.

Advances in the science will continue. For some cancers, new immune system therapies that bolster the body's own defenses have shown glints of promise. Genomic scans determining a cancer's precise genetic signature, nano robots that repair and reverse cellular damage — there are always new possibilities to explore.

Maybe someday some of us will live to be 200. But barring an elixir for immortality, a body will come to a point where it has outwitted every peril life has thrown at it. And for each added year, more mutations will have accumulated. If the heart holds out, then waiting at the end will be cancer.

George Johnson is a former reporter and editor at The New York Times and the author of "The Cancer Chronicles."

The New York Times

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December 9, 2012

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY

PHILIPSBURG, Pa. — Emma Whitehead has been bounding around the house lately, practicing somersaults and rugby-style tumbles that make her parents wince.

It is hard to believe, but last spring Emma, then 6, was near death from leukemia. She had relapsed twice after chemotherapy, and doctors had run out of options.

Desperate to save her, her parents sought an experimental treatment at the Children's Hospital of Philadelphia, one that had never before been tried in a child, or in anyone with the type of leukemia Emma had. The experiment, in April, used a disabled form of the virus that causes AIDS to reprogram Emma's immune system genetically to kill cancer cells.

The treatment very nearly killed her. But she emerged from it cancer-free, and about seven months later is still in complete remission. She is the first child and one of the first humans ever in whom new techniques have achieved a long-sought goal — giving a patient's own immune system the lasting ability to fight cancer.

Emma had been ill with acute lymphoblastic leukemia since 2010, when she was 5, said her parents, Kari and Tom. She is their only child.

She is among just a dozen patients with advanced leukemia to have received the experimental treatment, which was developed at the University of Pennsylvania. Similar approaches are also being tried at other centers, including the National Cancer Institute and Memorial Sloan-Kettering Cancer Center in New York.

"Our goal is to have a cure, but we can't say that word," said Dr. Carl June, who leads the research team at the University of Pennsylvania. He hopes the new treatment will eventually replace bone-marrow transplantation, an even more arduous, risky and expensive procedure that is now the last hope when other treatments fail in leukemia and related diseases.

Three adults with chronic leukemia treated at the University of Pennsylvania have also had

complete remissions, with no signs of disease; two of them have been well for more than two years, said Dr. David Porter. Four adults improved but did not have full remissions, and one was treated too recently to evaluate. A child improved and then relapsed. In two adults, the treatment did not work at all. The Pennsylvania researchers were presenting their results on Sunday and Monday in Atlanta at a meeting of the American Society of Hematology.

Despite the mixed results, cancer experts not involved with the research say it has tremendous promise, because even in this early phase of testing it has worked in seemingly hopeless cases. “I think this is a major breakthrough,” said Dr. Ivan Borrello, a cancer expert and associate professor of medicine at the Johns Hopkins University School of Medicine.

Dr. John Wagner, the director of pediatric blood and marrow transplantation at the University of Minnesota, called the Pennsylvania results “phenomenal” and said they were “what we’ve all been working and hoping for but not seeing to this extent.”

A major drug company, Novartis, is betting on the Pennsylvania team and has committed $20 million to building a research center on the university’s campus to bring the treatment to market.

Hervé Hoppenot, the president of Novartis Oncology, called the research “fantastic” and said it had the potential — if the early results held up — to revolutionize the treatment of leukemia and related blood cancers. Researchers say the same approach, reprogramming the patient’s immune system, may also eventually be used against tumors like breast and prostate cancer.

To perform the treatment, doctors remove millions of the patient’s T-cells — a type of white blood cell — and insert new genes that enable the T-cells to kill cancer cells. The technique employs a disabled form of H.I.V. because it is very good at carrying genetic material into T-cells. The new genes program the T-cells to attack B-cells, a normal part of the immune system that turn malignant in leukemia.

The altered T-cells — called chimeric antigen receptor cells — are then dripped back into the patient’s veins, and if all goes well they multiply and start destroying the cancer.

The T-cells home in on a protein called CD-19 that is found on the surface of most B-cells, whether they are healthy or malignant.

A sign that the treatment is working is that the patient becomes terribly ill, with raging fevers and chills — a reaction that oncologists call “shake and bake,” Dr. June said. Its medical name is cytokine-release syndrome, or cytokine storm, referring to the natural chemicals that pour out of

cells in the immune system as they are being activated, causing fevers and other symptoms. The storm can also flood the lungs and cause perilous drops in blood pressure — effects that nearly killed Emma.

Steroids sometimes ease the reaction, but they did not help Emma. Her temperature hit 105. She wound up on a ventilator, unconscious and swollen almost beyond recognition, surrounded by friends and family who had come to say goodbye.

But at the 11th hour, a battery of blood tests gave the researchers a clue as to what might help save Emma: her level of one of the cytokines, interleukin-6 or IL-6, had shot up a thousandfold. Doctors had never seen such a spike before and thought it might be what was making her so sick.

Dr. June knew that a drug could lower IL-6 — his daughter takes it for rheumatoid arthritis. It had never been used for a crisis like Emma's, but there was little to lose. Her oncologist, Dr. Stephan A. Grupp, ordered the drug. The response, he said, was "amazing."

Within hours, Emma began to stabilize. She woke up a week later, on May 2, the day she turned 7; the intensive-care staff sang "Happy Birthday."

Since then, the research team has used the same drug, tocilizumab, in several other patients.

In patients with lasting remissions after the treatment, the altered T-cells persist in the bloodstream, though in smaller numbers than when they were fighting the disease. Some patients have had the cells for years.

Dr. Michel Sadelain, who conducts similar studies at the Sloan-Kettering Institute, said: "These T-cells are living drugs. With a pill, you take it, it's eliminated from your body and you have to take it again." But T-cells, he said, "could potentially be given only once, maybe only once or twice or three times."

The Pennsylvania researchers said they were surprised to find any big drug company interested in their work, because a new batch of T-cells must be created for each patient — a far cry from the familiar commercial strategy of developing products like Viagra or cholesterol medicines, in which millions of people take the same drug.

But Mr. Hoppenot said Novartis was taking a different path with cancer drugs, looking for treatments that would have a big, unmistakable impact on a small number of patients. Such home-run drugs can be approved more quickly and efficiently, he said, with smaller studies than are

needed for drugs with less obvious benefits.

“The economic model is totally acceptable,” Mr. Hoppenot said.

But such drugs tend to be extremely expensive. A prime example is the Novartis drug Gleevec, which won rapid approval in 2001 for use against certain types of leukemia and gastrointestinal tumors. It can cost more than $5,000 a month, depending on the dosage.

Dr. June said that producing engineered T-cells costs about $20,000 per patient — far less than the cost of a bone-marrow transplant. Scaling up the procedure should make it even less expensive, he said, but he added, “Our costs do not include any profit margin, facility depreciation costs or other clinical care costs, and other research costs.”

The research is still in its early stages, and many questions remain. The researchers are not entirely sure why the treatment works, or why it sometimes fails. One patient had a remission after being treated only twice, and even then the reaction was so delayed that it took the researchers by surprise. For the patients who had no response whatsoever, the team suspects a flawed batch of T-cells. The child who had a temporary remission apparently relapsed because not all of her leukemic cells had the marker that was targeted by the altered T-cells.

It is not clear whether a patient’s body needs the altered T-cells forever. The cells do have a drawback: they destroy healthy B-cells as well as cancerous ones, leaving patients vulnerable to certain types of infections, so Emma and the other patients need regular treatments with immune globulins to prevent illness.

So far, her parents say, Emma seems to have taken it all in stride. She went back to school this year with her second-grade classmates, and though her grades are high and she reads about 50 books a month, she insists impishly that her favorite subjects are lunch and recess.

“It’s time for her to be a kid again and get her childhood back,” Mr. Whitehead said.

The Genetic Basis of Cancer

An accumulation of genetic defects can apparently cause normal cells to become cancerous and cancerous cells to become increasingly dangerous

by Webster K. Cavenee and Raymond L. White

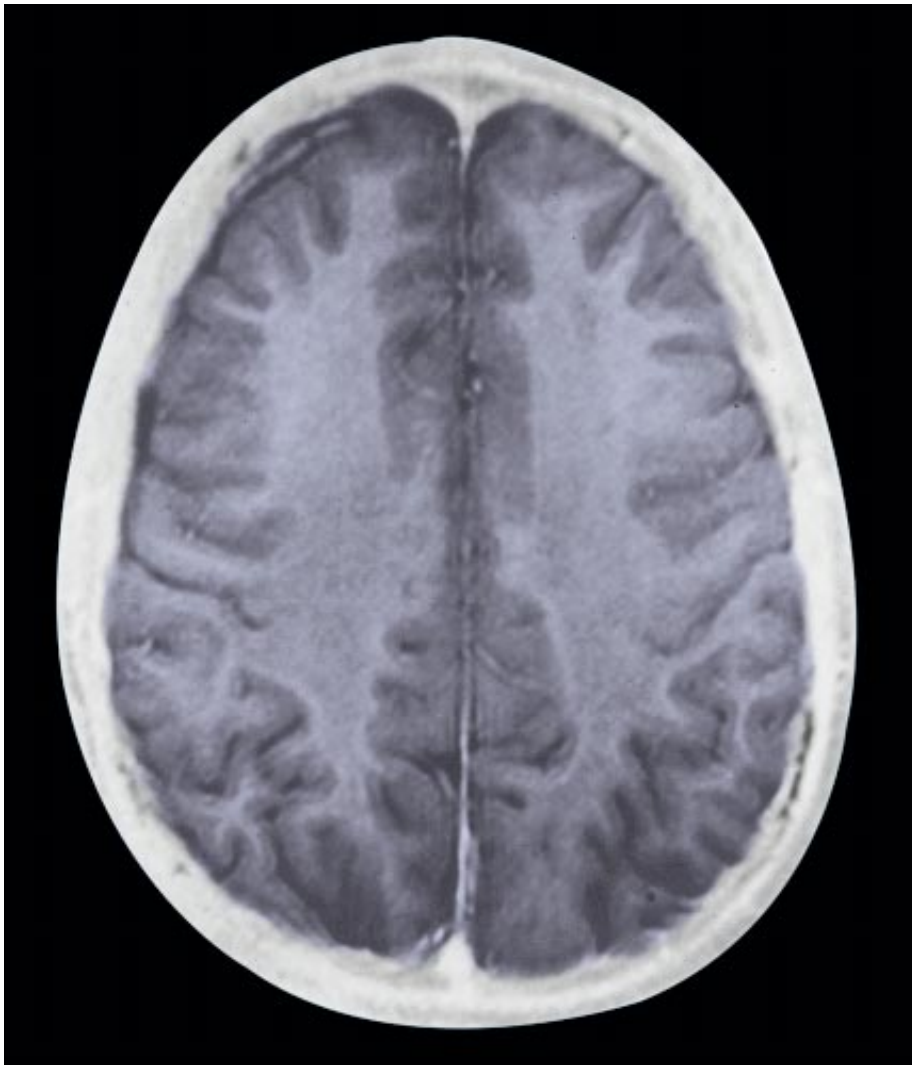
Patients stricken with cancer feel as if they have been invaded by an alien force. Yet malignancies arise from our own tissue. In fact, the weight of evidence today indicates that cancers generally derive from a single cell that is changed dramatically by a series of genetic alterations.

A healthy cell has a well-defined shape and fits neatly within the ordered array of cells surrounding it. It responds to the dictates of its environment, giving rise to daughter cells solely when the balance of stimulatory and inhibitory signals from the outside favors cell division. But the process of replication, or growth, carries the constant hazard of genetic mutations: random changes that can impair the regulatory circuits of a cell. If a single mutation occurs, the newly damaged cell, which may look normal and be slightly less responsive to external messages, may occasionally undergo unscheduled cell division.

Eventually, an accumulation of genetic damage can cause a daughter cell to become quite deaf to external messages and to display the signs of malignancy. In particular, it loses its distinctive shape and boundaries, ceases to respond to growth-inhibiting signals and gains the ability to replicate uncontrollably. The resulting mass, in turn, can compress and damage healthy tissue in its vicinity. What is worse, it can invade the barriers that separate one organ from another and can metastasize, establishing new colonies at distant sites.

Studies carried out over the past 20 years have begun to identify many of the genes that take part in this progression from normalcy to cancer. The ongoing research is confirming and extending early proposals that cancer develops primarily because cells suffer irreversible damage to particular classes of genes. It is also creating opportunities for improved diagnosis and therapy.

The emerging view of tumor progression reflects a convergence of several lines of research, the oldest of which still involves painstakingly looking at cells through a microscope. By 1914, for instance, the German cytologist Theodor Boveri had concluded from such



WEBSTER K. CAVENEE and RAYMOND L. WHITE collaborated at the University of Utah in the early 1980s. Cavenee is director of the Ludwig Institute for Cancer Research at the San Diego branch. He is also professor of medicine and member of the Center for Molecular Genetics at the University of California, San Diego. Before accepting his current posts, he had faculty appointments at the University of Cincinnati and McGill University. White, who has been on the faculty of the University of Utah since 1980, is director of the Huntsman Cancer Institute and chairman of the department of oncological sciences. This is his second article for *Scientific American.*

observations that malignant cells had abnormal chromosomes and that any event leading to such aberrancy would cause cancer.

Microscopic observations became considerably more specific after 1970, when new staining techniques, together with improved equipment, made it possible to distinguish each of the 23 pairs of chromosomes that collectively contain all the genes forming the blueprint for a human being. (All human cells, except for sperm and eggs, carry two sets of chromosomes—one inherited from the mother and one from the father.) Each chromosome takes up the stain in specific regions and thus becomes marked by a characteristic series of light and dark bands, a kind of bar code identifying the individual chromosome.

By comparing stained chromosomes from normal cells with those from tumors, investigators noted many different signs of genetic disarray in cancers. The chromosomes of tumors were often broken, with some of the pieces joined to other chromosomes. Individual chromosomes were present in multiple copies rather than the normal two. Whole chromosomes, or sometimes internal segments, seemed to have disappeared entirely. Unfortunately, until the 1980s researchers generally lacked the tools they needed to determine whether the chromosomal rearrangements were among the causes of cancer or were a by-product of its development.

Two Hits

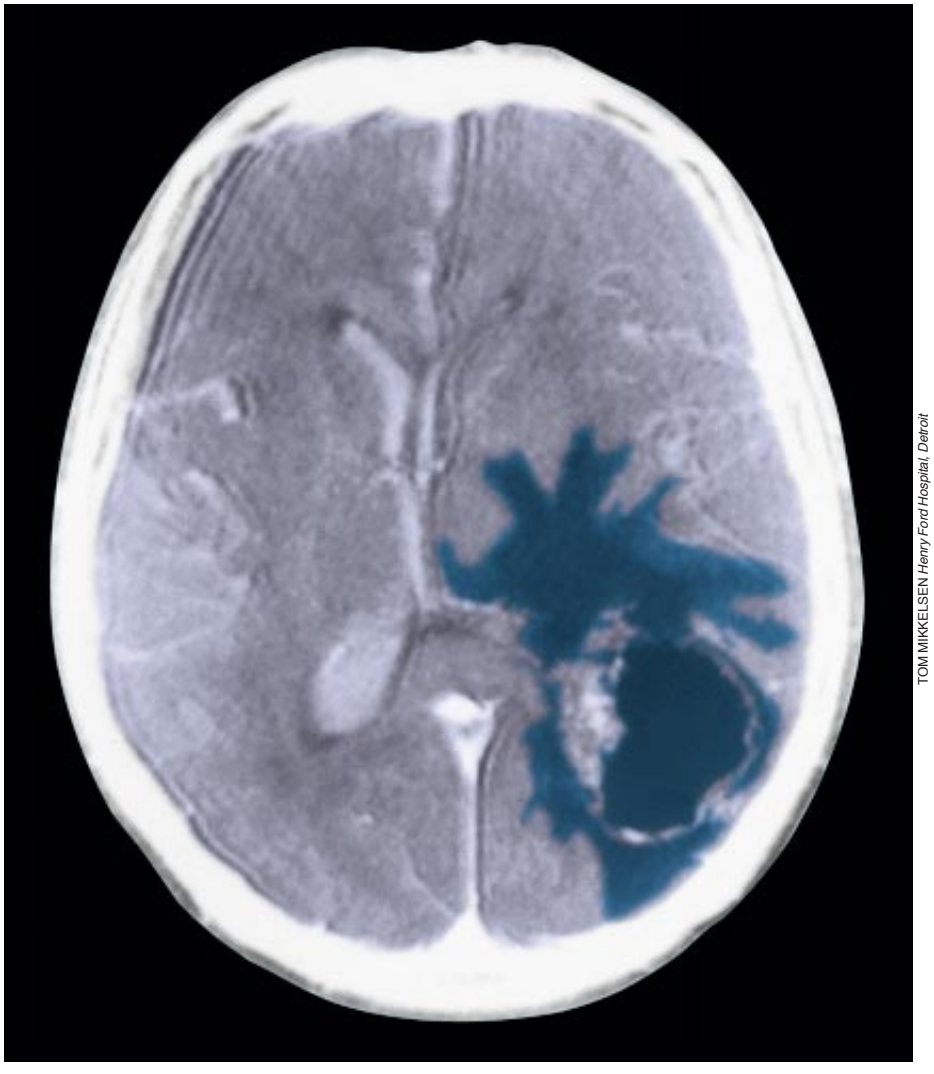
Quite different evidence that genes had a role to play came from observations that some extended families suffered an unusually high incidence of certain cancers. When particular diseases "run" in families in predictable patterns, an inherited defect is usually at fault.

Yet the discovery that some cancers could apparently be inherited also raised perplexing questions. A genetic defect passed to a child through the sperm or egg should appear in every cell of the body. Why, then, did people with inherited disease typically acquire only one or a few cancers and only at discrete sites? Further, did the existence of familial cancers necessarily mean that sporadic (nonfamilial) disease, which is much more common, also had a genetic basis? Or did sporadic cancers arise by completely different processes than inherited ones?

A proposal put forward in 1971 by Alfred G. Knudson, Jr., now at the Fox Chase Cancer Center in Philadelphia, seemed to offer an answer to both questions, although it took about a decade for his ideas to gain broad acceptance. Knudson had been puzzling over the cause of retinoblastoma, a rare childhood disorder in which malignant tumors develop in the retina before the age of six. He noted that sometimes the disease occurred in both eyes, but most of the time it affected only one eye. Moreover, children who were affected bilaterally often had close relatives afflicted with retinoblastoma.

A statistical analysis comparing the age at onset for each form of the disease showed that the bilateral type was usually diagnosed at an earlier age than was the unilateral type. Also, the shape of the age distribution curves suggested to Knudson that retinoblastoma resulted from two cellular defects arising at separate times. In bilateral disease the first defect was probably inherited and present in all cells of the body from the moment of conception. In unilateral disease the first defect probably arose during development or later and perhaps exclusively in retinal cells. In both cases, however, a tumor formed only if the first defect in a retinal cell was later accompanied by a second, independent one. Knudson's two-hit theory, as it is frequently called, turns out to be essentially correct for all cancers, not just retinoblastoma, although more than just two hits are often required.

The need for two hits—now known to constitute damage to genes—explains why patients in cancer-prone families are not riddled with tumors throughout their bodies: inheritance of just one genetic defect predisposes a person to



TOM MIKKELSEN *Henry Ford Hospital, Detroit*

CANCER OF THE BRAIN progressed in just three months from being invisible on a scan (*left*) to covering a large area of one hemisphere (*blue area, right*). The patient, whose initial complaint was an uncontrollable twitching in one eye, died two months after the second image was made. Recent evidence indicates that brain tumors and other malignancies arise when multiple genetic mutations combine to free a single cell from normal restraints on proliferation, invasiveness and movement.

cancer but does not cause it directly; a second event is required. Knudson's intuition that the causes of sporadic and familial cases can involve the same biochemical abnormalities has also been confirmed. But even back in the 1970s his insights provided justification for thinking that research aimed at discovering genetic and other cellular aberrations in rare familial cancers could shed light on the processes leading to sporadic malignancies.

Oncogenes Take Center Stage

As various researchers focused on the genetics of familial malignancies, other workers convinced that genes were at the root of cancer were taking a rather different approach to finding cancer-related genes. It had been known for many years that viruses can cause tumors in animals. That link had spurred a great deal of research aimed at identifying the cancer-causing genes carried by the viruses and at finding the host genes that were affected. Those efforts revealed, surprisingly, that the genes implicated in malignant diseases were often altered forms of human genes that the viruses had picked up during their travels. Other times the viruses activated host genes that were usually quiescent.

The normal versions of the pirated and activated genes—now called proto-oncogenes—carry codes specifying the composition of proteins that encourage cells to replicate. These growth-promoting genes come in many varieties. Some specify the amino acid sequences of receptors that protrude from the cell surface and bind to molecules known as growth factors. When bound by such factors, receptors issue an intracellular signal that ultimately causes cells to replicate. Others of the genes code for proteins that lie inside the cell and govern the propagation of the intracellular growth signal. Still others encode proteins that control cell division.

Discovery that the viral genes had human counterparts introduced the intriguing possibility that human cancers—including the majority not caused by viruses—might stem from mutations that convert useful proto-oncogenes into carcinogenic forms, or oncogenes. Consistent with this notion, studies indicated that alteration of just one copy, or allele, of these proto-oncogenes was enough to transform—render cancerous—some types of cells growing in culture. Such dominant mutations cause cells to overproduce a normal protein or to make an aberrant form that is overactive. In either case, the result is that stimulatory signals increase within the cell even when no such signals come from the outside.

Later studies supported a role for oncogenes—and also complicated matters. Notably, in 1982 and 1983, investigators in France and the U.S. conducted studies similar to the original cell-culture experiments, but with an important difference. Because normal cells would not grow indefinitely in a culture dish, those earlier studies had relied on rodent cells that were unusual in their ability to proliferate for a long time in culture. To eliminate this possibly confounding influence, François Cuzin of the University of Nice, Robert A. Weinberg of the Massachusetts Institute of Technology and H. Earl Ruley, then at Cold Spring Harbor Laboratory in New York State, asked whether single oncogenes could also transform normal rodent cells.

They found that mutations in at least two proto-oncogenes had to be present and that only certain combinations of mutations led to malignancy. These results suggested that individual oncogenes, though potentially quite powerful, were not able to cause tumors by themselves. A major effort was then launched to see whether human tumors carried oncogenic alterations of the types and combinations that were able to transform cells in culture.

For a while it seemed that oncogenes might explain most cases of cancer. This view was strengthened by discovery of more than a dozen of them in human tumors. The results were ultimately disappointing, however; a mere 20 percent of human tumors turned out to carry the expected alterations singly, and none of them had the pairs of cooperative alterations found in cultured cells. At the time, it also appeared that the inherited mutations responsible for predisposing people to familial cancers were not oncogenes. These were all strong hints that the full story was yet to be told.

Enter Tumor Suppressor Genes

Even before those hints attracted much attention, the two of us were beginning to suspect that damage to a different kind of gene might play a part in cancers. Such genes came to be known as tumor suppressors because many of them code for proteins that inhibit cell replication. In contrast to the mutations that activate oncogenes, mutations of these genes, we believed, would be recessive: they would affect cell function only when both alleles were damaged or lost. In testing this idea, we relied on new technology we had developed for the more general purpose of following the inheritance of genes and chromosomes through extended families [see "Chromosome Mapping with DNA Markers," by Ray White and Jean-Marc Lalouel; SCIENTIFIC AMERICAN, February 1988].

In the early 1980s, while collaborating at the University of Utah, we realized that our technique—which involved tracking genetic markers (identifiable segments of DNA) in tissues—could be used to determine whether segments of chromosomes carried by normal cells were missing in a tumor. For instance, if a selected region of a chromosome was deleted in a tumor, we could spot that loss by observing that a marker known to travel with that region was also missing.

Our experiments were focused by earlier studies of Jorge J. Yunis of the University of Minnesota and Uta Francke of Yale University. That research indicated a gene on chromosome 13 might be involved in retinoblastoma. With our DNA-marker technology, we were able to demonstrate in 1983 that large segments of chromosome 13 were missing in cells taken from sporadic as well as inherited retinoblastomas. This new evidence strongly supported the idea that the two hits hypothesized by Knudson could consist of the physical or functional loss of one allele of a gene followed by elimination of or damage to the normal copy. The missing DNA on chromosome 13, now known as the *RB* (retinoblastoma) gene, was isolated by Stephen H. Friend of Weinberg's laboratory in 1986 [see "Finding the Anti-Oncogene," by Robert A. Weinberg; SCIENTIFIC AMERICAN, September 1988].

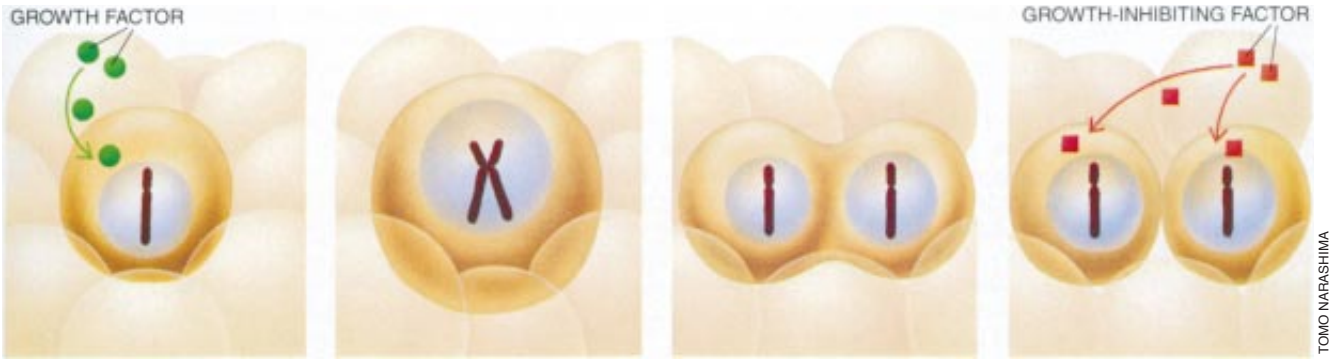
Subsequent studies have shown that recessive loss of the *RB* gene occurs in other cancers as well. What is more, inactivation or loss of DNA has now been shown to be a major feature in the genesis of every solid cancer examined so far. Breast cancer, prostate cancer, lung cancer, bladder cancer, pancreatic cancer and many others are marked by the disruption or elimination of multiple tumor suppressor genes.

By the late 1980s, then, there was good evidence that mutations in both proto-oncogenes and tumor suppressors could participate in causing cancer. It seemed reasonable to guess that some kinds of cancer resulted from a combination of such mutations. But did the mutations collect in the same cell or did some affect one cell, and others, different cells? A model of tumor progression proposed in the 1950s by Leslie Foulds of the Chester Beatty Research Institute in London and expanded in the 1970s by Peter C. Nowell of the University of Pennsylvania suggested that if both kinds of mutations were in-

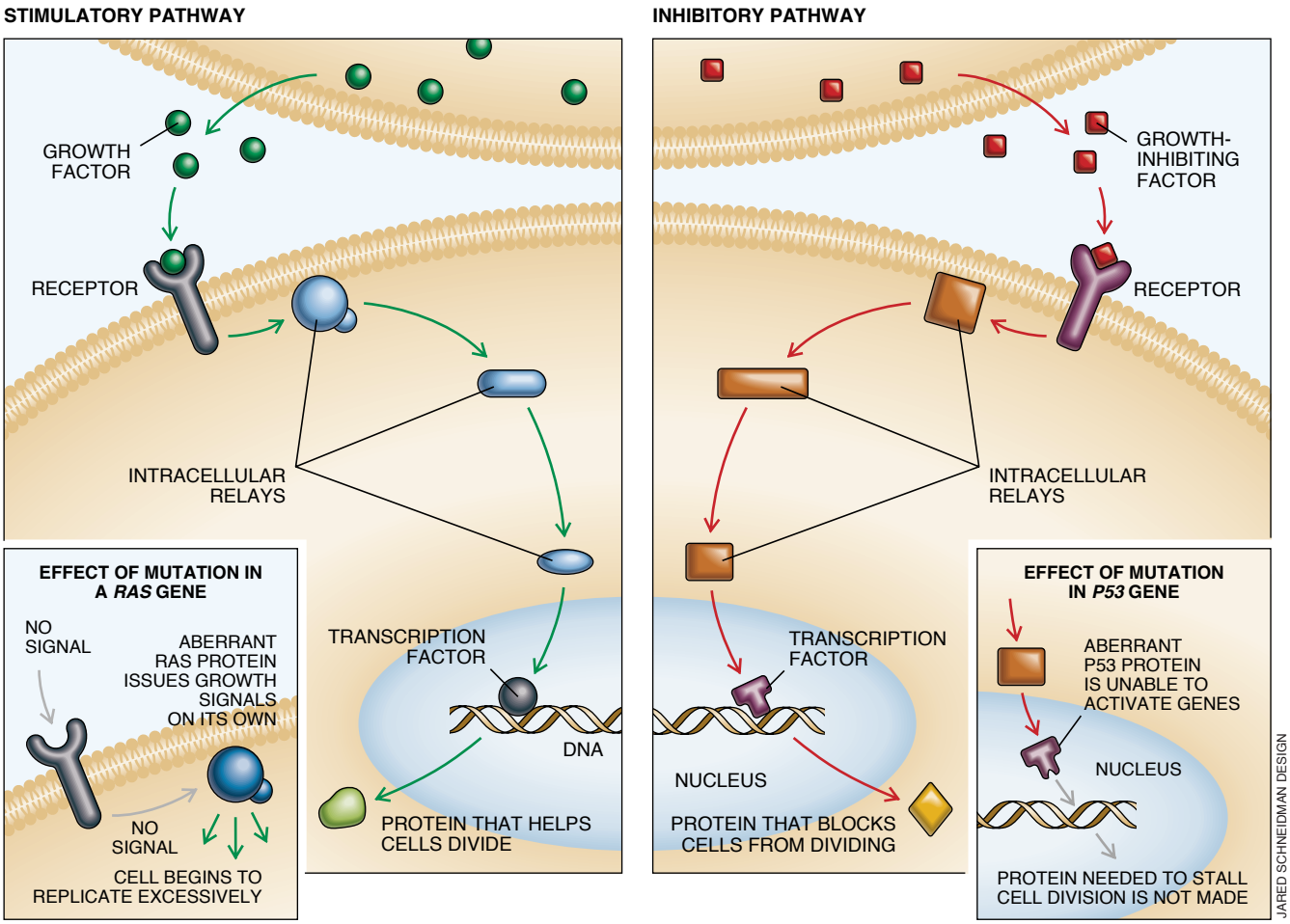
volved, they would accumulate in one cell and its direct descendants.

In this scheme, cancers are thought to arise and become more dangerous through a process known as clonal evolution. First, a single cell undergoes a genetic mutation that enables it to divide under conditions that cause normal cells to stop replicating. Because the inappropriately dividing cells copy their DNA and give identical sets to their offspring, the next generation of cells carries the same changes and shows the same inappropriate growth. Later, one of these cells or their descendants undergoes a mutation that further enhances its ability to escape normal regulation, perhaps allowing it to pass through surrounding tissue and enter the bloodstream. This mutation, too, is passed to daughter cells. Repetition of the process enables one cell to accumulate the mutations it needs to metastasize and colonize other organs.

If the theory were correct, it would mean the majority of cells in a tumor would carry the same defects. That being the case, therapy capable of counteracting one or more of those defects would be effective against all, or a great



TOMO NARASHIMA



JARED SCHNEIDMAN DESIGN

NORMAL CELL REPRODUCES ITSELF (*sequence at top*) in response to stimulation by external growth factors (*green*); it stops dividing in response to inhibitory factors (*red, far right*). For either reaction to occur, messages from the factors must be relayed deep into the target cell (*large panels*). Many cancer-causing genes are abnormal versions of ones that code for proteins in stimulatory pathways (*left panel*). The altered genes, called oncogenes, cause stimulatory proteins to be overproduced or overactive. In one example, mutation of a particular *ras* gene can lead to synthesis of a hyperactive ras protein (*inset at left*). Many other cancer-related genes code for proteins in inhibitory pathways (*right panel*) and are often called tumor suppressors. Damage to these genes can promote cancer if the defects prevent inhibitory proteins from being made or functioning properly—as often occurs when the *p53* gene is mutated (*inset at right*).

majority, of the cancer cells—a feature that is essential for eradicating any malignancy. For this reason and others, we set out to see if we could find evidence for the clonal evolution of tumors. One of us (White) focused primarily on colon cancer, and the other of us (Cavenee) on brain tumors. As part of this work, we had to identify many of the genes involved in these cancers.

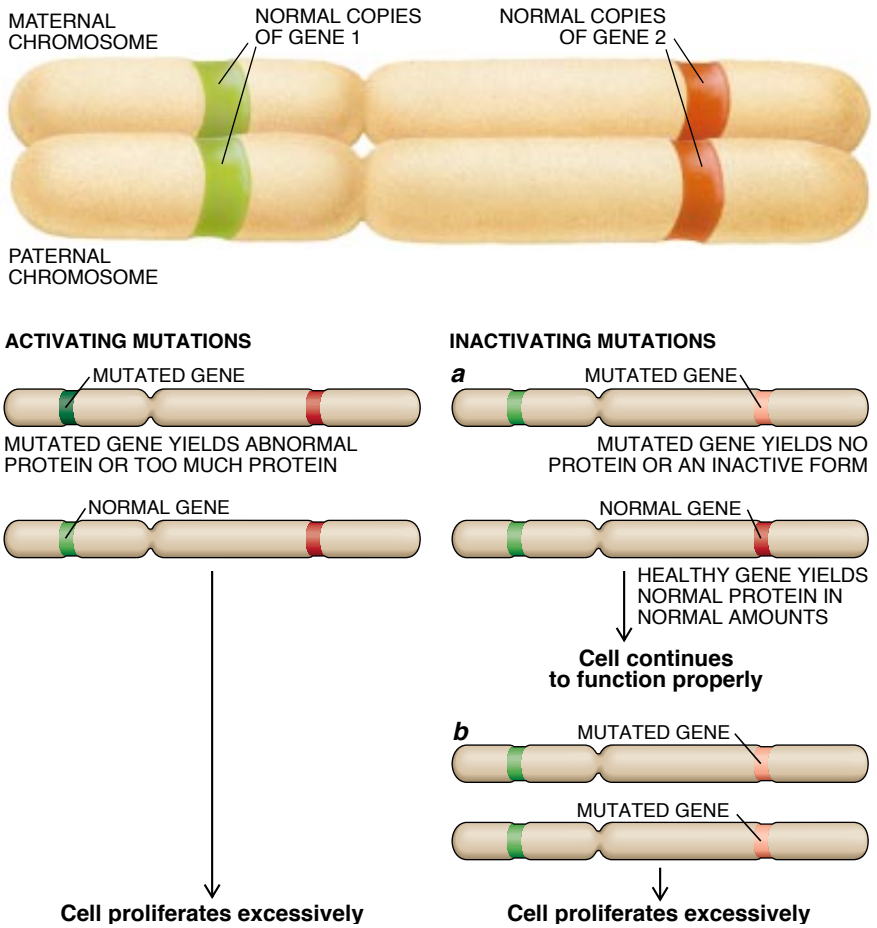
The Genetics of Colon Cancer

White turned to colon cancer in part because it usually emerges from a well-defined precursor—the colon polyp. If a cancer developed in a clonal fashion, mutations arising in an early stage of tumor development would be expected to be present in later stages, and each successive stage would be marked by additional mutations. To test this expectation experimentally, it is necessary to collect samples from the successive stages and compare their genes. In colon disease, samples are fairly easy to obtain. As a polyp, which is initially microscopic, becomes larger and more irregular, it becomes readily accessible to the gastroenterologist (who removes it for therapeutic purposes) and thus to the experimentalist.

Colon cancer also held appeal for our purpose because families that were genetically prone to a rare disease called familial adenomatous polyposis had been identified and were available for study. In affected individuals the colon becomes carpeted with hundreds or thousands of polyps, one or more of which is likely to become cancerous in midlife. Clearly, an inherited defect in some gene—called *APC* (for adenomatous polyposis coli)—was necessary for polyp formation and, in turn, for the development of colon cancer in such patients. It also seemed possible that appearance of a defect in the *APC* gene was one of the earliest steps, if not the first step, leading to many cases of sporadic colon cancer. If that gene could be isolated, these ideas could be tested, and investigators would have at least one of the genes needed for evaluating whether colon cancer developed in a clonal manner.

In 1987 Mark Leppert in White's laboratory at Utah and Walter F. Bodmer and his colleagues at the Imperial Cancer Research Fund in London separately demonstrated, through use of the marker technology described earlier, that the *APC* gene resided near the middle of the long arm of chromosome 5. Intensive work, often collaborative, by White's laboratory and those of two other investigators—Yusuke Nakamura of the Cancer Institute in Tokyo and Bert Vogelstein of Johns Hopkins University—eventually revealed the precise location of the gene. The research also identified several inherited *APC* mutations that appeared in sporadic as well as familial colon tumors. This work thus defined a first step in the evolution of colon cancer. It also provided additional confirmation of the speculation that the same genes are often mutated in both inherited and sporadic tumors.

The groups found, too, that all the cancer-related mutations in the *APC* gene led to production of an incomplete protein. Evidently, cells could operate relatively normally if they retained one normal *APC* allele and thus made some amount of the full APC protein. But if both alleles became damaged, a needed brake on replication disappeared. The precise function of the *APC* gene is unclear, but now that the gene is in hand, its normal responsibilities and its role in cancer should soon be defined.

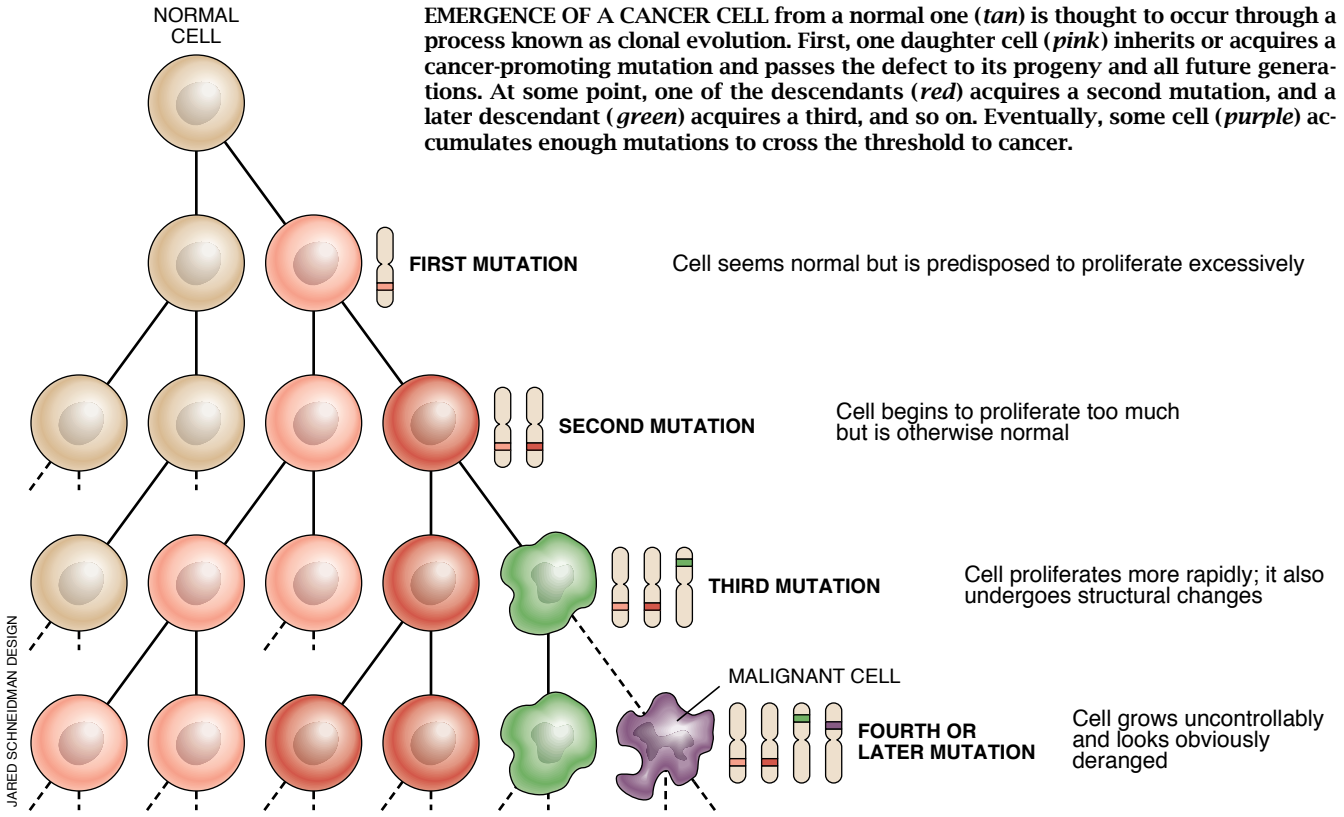


GENES ARE INHERITED IN MATCHING PAIRS—one from the mother and one from the father (*top*). Sometimes mutation of a single copy pushes a cell toward cancer (*left*)—such as when it leads to production of a protein that activates excessive cell division. (Oncogenic mutations fall into that category.) Other times both copies must be altered—such as when a gene coding for a protein that stalls cell division is inactivated (*right*). If only one copy of such a gene is affected (*a*), the other copy can still generate the needed protein. But if both copies are hobbled (*b*), an important brake on tumor development is lost.

Multiple Defects

The steps that follow immediately after the *APC* gene is inactivated are still obscure. In many cases, however, later mutation in a single allele of a particular proto-oncogene seems to push a polyp toward malignancy. This gene, as Manuel Perucho observed when he was at Cold Spring Harbor Laboratory, is one of several *ras* genes. The protein normally made under the direction of this gene sits under the cell membrane and relays stimulatory messages from growth factor receptors to other molecules in the cytoplasm. The mutant version does not wait for signals from the outside but issues its own autonomous growth signals.

Vogelstein and his group have shown that large polyps and colon cancers often carry only mutated copies of two additional tumor suppressor genes. One



EMERGENCE OF A CANCER CELL from a normal one (*tan*) is thought to occur through a process known as clonal evolution. First, one daughter cell (*pink*) inherits or acquires a cancer-promoting mutation and passes the defect to its progeny and all future generations. At some point, one of the descendants (*red*) acquires a second mutation, and a later descendant (*green*) acquires a third, and so on. Eventually, some cell (*purple*) accumulates enough mutations to cross the threshold to cancer.

is *p53,* which resides on chromosome 17 and is now known to be involved in many different cancers. The normal protein product of this gene functions in several biochemical pathways, including those enabling a cell to repair damage to DNA. The other is a gene—probably *DCC* (for deleted in colorectal cancer)—that resides on chromosome 18. *DCC* codes for a protein that appears on the cell surface and helps colon cells stick to one another.

The discovery that genetic changes in the *APC* gene occur early and persist, whereas other changes appear only in later stages, fits well with the theory of clonal evolution. But that conclusion was initially statistical and based on examining tissues removed from many different patients. That approach could not demonstrate conclusively that mutations appearing in one generation of cells are passed to later generations of those same cells. Another strategy, however, provided more convincing results.

Sometimes the polyp from which a cancer has emerged can be identified at the edge of a cancer. By comparing the DNA in a polyp with that in its adjacent cancer, Vogelstein showed that every mutational hit found in a polyp also appeared in the corresponding cancer, as would be expected if the tumor formed by clonal evolution. Further, the cancer invariably included mutations that were not found in the polyp, as would also be expected if the added mutations accounted for the increased aggressiveness of a cancer. For instance, some polyps carried a *ras* mutation without a *p53* defect, but the cancers growing from the polyps had both mutations. As yet, there is no strong evidence that mutation of *ras, p53* and *DCC* genes must happen in any particular order for a polyp to become cancerous, although the *ras* mutation seems to come first fairly often.

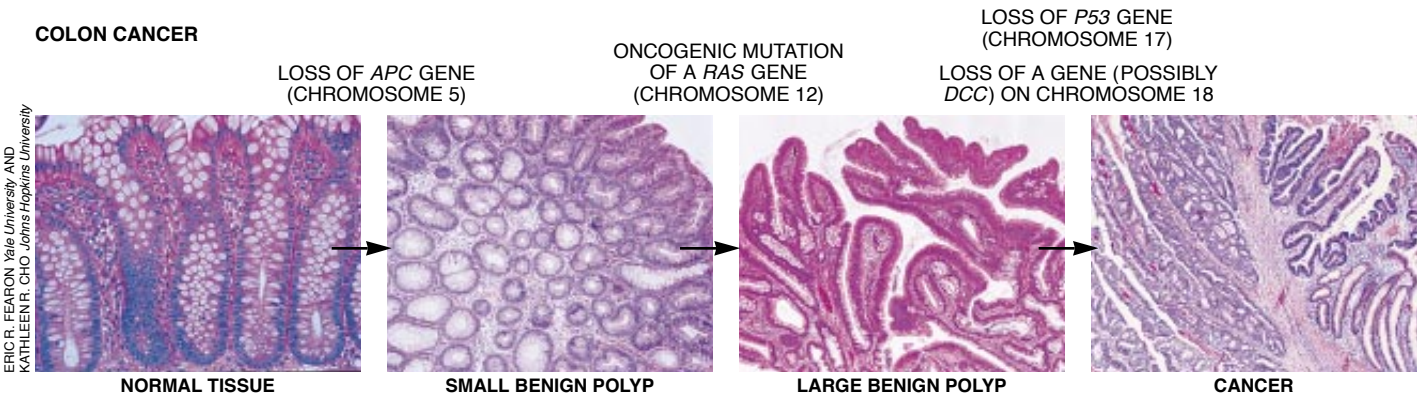
Brain Tumors Reveal Their Secrets

In spite of these encouraging findings, study of colon cancer has a major analytical limitation. To truly demonstrate that a given clone of cells is undergoing progressive changes in its genes, one needs to examine the same tumor over time. In the case of colon cancer, tumors are almost always removed at the earliest stage of detection. Such practice makes good clinical sense, but it prevents sequential observations. This consideration led Cavenee to seek out a disease in which removal of a tumor is sometimes followed by the reappearance of the tumor in a more aggressive form at the same site. In 1987, while he was at the Ludwig Institute for Cancer Research at McGill University, he and his co-workers settled on cancers known as astrocytomas—the most common tumors that originate in the brain.

Cancer of the brain is defined somewhat differently than it is in other tissues. In that organ, cells do not need to invade connective tissue or metastasize in order to be lethal; sadly, proliferation at a site critical to survival can sometimes be enough to kill a patient. Hence, most masses in the brain are called cancers. Cavenee's group examined progression of astrocytomas from their less malignant to more malignant stages, as determined by the size and shape of the tumors and by the structure of their constituent cells.

When the investigators began this work in 1987, they did not have the blueprint of genetic change that was emerging for colon cancer. They therefore began by laying the groundwork for future studies of individual patients. They obtained tumors from many different patients, grouped them according to stages, or grades, of advancing disease, and compared the genetic derangements found in each stage.

Over the next four years they made good headway. They learned, for instance, that tumors of every grade had inactivating alterations in chromosome 17, in a gene they had not yet identified. Moreover, the proportion of tumors displaying the mutation in the lowest stage was equal to that in all other stages; this pattern is a sign that the mutation came early and was retained. If a mutation generally occurred later in disease,

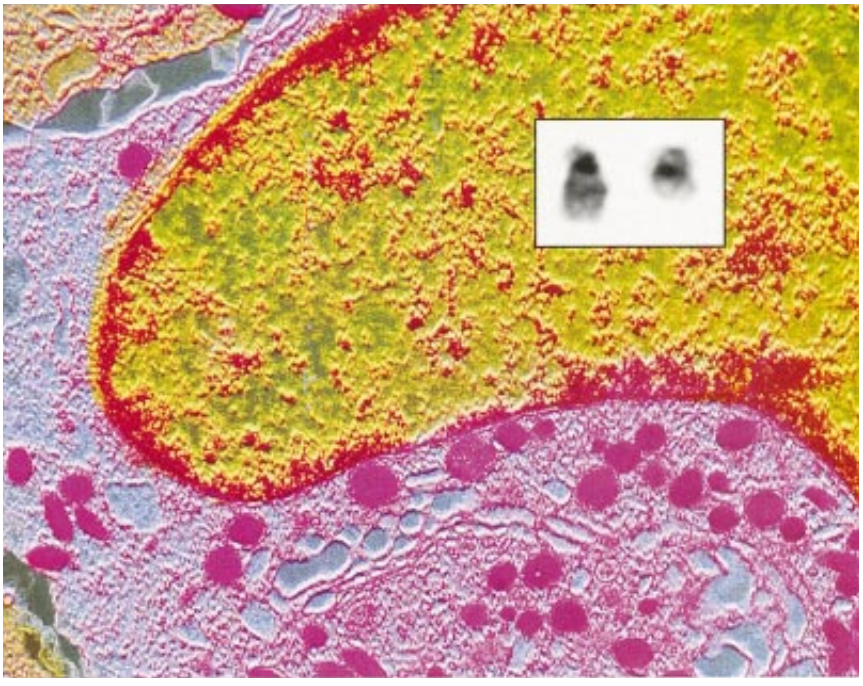


ERIC R. FEARON *Yale University* AND KATHLEEN R. CHO *Johns Hopkins University*

GENETIC CHANGES indicated at the top are among those thought to participate frequently in the development of colon cancer (*left*) or in the progression of a common brain cancer (astrocytoma) from its mildest to its most aggressive

the frequency would rise in the later stages. By the end of the 1980s Vogelstein's laboratory established that mutations in the *p53* gene, on chromosome 17, were among the most common alterations in human cancer. Subsequent analysis of Cavenee's tissue samples confirmed his growing suspicion that the chromosome 17 mutation was actually a defect in the *p53* gene.

Aware that a particular region of chromosome 9 was deleted in other kinds of brain tumors, C. David James on Cavenee's team, in conjunction with V. Peter Collins of the Ludwig Institute in Stockholm, examined this chromosome as well. Middle- and late-stage astrocytomas, but not early ones, often showed a loss in both copies of this chromosome. Thus, the deletion probably encouraged progression to middle-stage tumors from a lesser stage. The lost region contains a cluster of genes that code for proteins known as interferons. Such proteins can draw the attention of the immune system to diseased cells, and so elimination of their genes presumably helps cancer cells evade immune destruction. The missing region may additionally include two newly discovered genes, called *multiple tumor suppressors 1* and *2,* whose protein products are involved in regulating cell division. Disappearance of any of these genes could potentially contribute to a variety of cancers.



PETER C. NOWELL *University of Pennsylvania*

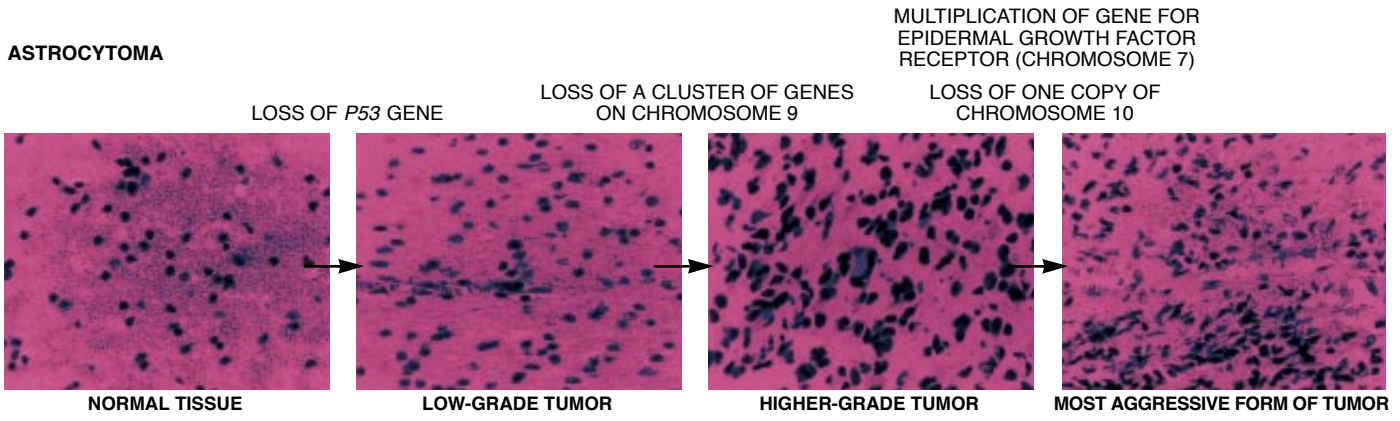
PHILADELPHIA CHROMOSOME (*at right in inset*) was the first chromosomal abnormality ever linked to a specific cancer. In the 1960s Peter C. Nowell of the University of Pennsylvania observed that the appearance of an unusually small chromosome in white blood cells was a hallmark of leukemia. It is now known that the aberrant structure forms when a normal version of chromosome 22 (*at left in inset*) swaps genetic material with another chromosome, in the process giving up more than it receives. Unfortunately, the DNA gained by chromosome 22 combines with a preexisting gene to form a hybrid oncogene.

The tissue studies also extended reports by Axel Ullrich of Genentech, Michael D. Waterfield of the Ludwig Institute in London and Joseph Schlessinger of the Weizmann Institute of Science in Israel that chromosomes in astrocytomas often carry more than one copy of the gene specifying the receptor for epidermal growth factor. Because each copy can be used to make the protein, cells will carry extra receptors on their surface. That abundance, in turn, can cause cells to overreact to the presence of the growth factor. This alteration seems to participate in bringing tumors from a middle to a late stage of disease.

Finally, Cavenee's group found that virtually all the end-stage tumors examined were missing one copy of chromosome 10 and that the loss was rare in earlier stages. This pattern says the loss is probably involved in advancement to the most virulent stage. Regrettably, though, we do not yet know which gene or genes on the lost chromosome are most important to the progression.

These results suggested by 1991 that formation of brain tumors involves, at a minimum, inactivation of the *p53* gene, loss of a gene on chromosome 9, oncogenic amplification of the gene for the epidermal growth factor receptor and, at a very late stage, loss of at least one copy of chromosome 10. But stronger proof that astrocytomas are caused by the accumulation of these, and possibly other, defects in cells required examining genetic changes in the cancer of single individuals over time.

At about that time Tom Mikkelsen joined Cavenee's laboratory and took on the challenge of comparing the genetic makeup of original astrocytomas with that of later recurrences arising at the same sites. This task was impossible earlier not only because the genes involved were not known but also be-



form (*right*). Other genes not listed here play roles as well. Unless otherwise indicated, the term "gene loss" indicates that both copies of a tumor suppressor gene have been damaged or deleted. The images show magnified slices of tissue.

cause matched pairs of tumors are hard to obtain. A patient seen initially at one institution may be cared for elsewhere when the cancer returns. Also, physicians do not remove tumors that reappear if it is thought that surgery is unlikely to extend survival. Luckily, however, two distinguished clinicians—Mark L. Rosenblum of the University of California at San Francisco and Karl Schwechheimer of Albert Ludwigs University in Freiberg, Germany—had come forward with collections of frozen tissue that included a few matched sets.

To Cavenee's satisfaction and delight, the genetic analysis of these tissues—done in collaboration with David Sidransky in Vogelstein's group—fulfilled the predictions of the theory of clonal evolution. The initial tumors possessed fewer mutations than did the recurrences. These alterations included one or more of the genetic hits (such as damage to chromosome 17) that had been identified in the low-grade tumors analyzed previously. And, most significant, the corresponding high-grade versions possessed each alteration found in the primary tumor as well as additional defects (of the kinds identified in the earlier studies). For reasons that are not obvious, progression of astrocytomas seems to follow a more defined sequence of genetic changes than is apparent in colon cancer.

Next on the Agenda

The collected results we have described offer strong support for the idea that cancer develops and becomes more dangerous primarily because cells in a single lineage accumulate defects in genes that normally regulate cell proliferation. Changes in other kinds of genes, many of which have not yet been identified, presumably facilitate the ability of tumors to grow, invade local tissue and establish distant metastases. Hormones and other factors in the environment around the genetically altered cells almost certainly enhance their genetically defined deregulation.

Questions remain. Why do cell types differ in the mix of mutations they require in order to become cancerous? And how is it possible for five or more mutations to accumulate in cells? After all, the probability is actually quite small that any given cell bearing a permanent mutation in a cancer-related gene will independently gain another mutation in such a gene.

Newly discovered genetic aberrations found in a second form of inherited colon tumors (hereditary nonpolyposis colon cancer) may offer a partial answer to the last question. The affected genes specify proteins responsible for identifying and repairing mistakes made when DNA in a replicating cell is copied. If these repair genes themselves are damaged, the number of mutations passed to daughter cells will go up dramatically. The daughter cells may then deliver DNA carrying still more mutations to their progeny. Defects in repair genes may thus play a role in making late-stage tumors highly aggressive. They may even account for the astonishingly fast rate at which some tumors arise and become killers.

Mutations in certain genes can also be especially devastating if the mutations have multiple effects. As a case in point, damage to the *p53* gene can apparently do more than release a brake on proliferation. Certain mutations seem to reduce the ability of cells to limit blood vessel formation. As extra vessels grow in a tumor, they help to nourish the mass and to serve as conduits through which malignant cells can spread to distant sites. In parallel, the abnormal proteins yielded by the altered gene may aid tumor cells in resisting the destructive effects of radiation.

As investigators gain clarity on the specific groups of genetic changes that lead to and exacerbate particular forms of cancer, their insights should point the way to practical benefits for patients. When the mutations follow in a fairly set sequence, their identification in a patient's tumor should be of value for clarifying the stage of disease and thus for tailoring therapy to the individual's needs. In addition, knowledge of the genes that are mutated in a primary tumor may make it possible to detect recurrences of some cancers earlier than is now possible—by spotting mutations that have occurred in tissues not yet displaying detectable masses.

Expanded understanding of the genetic bases of cancer can also be expected to lead to the introduction of drugs that will counteract the effects of selected mutations and thereby slow tumor development or halt it altogether. Some evidence suggests it may not be necessary to correct the effects of every mutation; doing so for one or two genes may well prove to be sufficient for taming renegade cells.

The process by which normal cells become cancerous and grow ever more dangerous is undoubtedly even more complicated than has been discovered so far. But continued investigation of the genetic changes underlying specific cancers seems a rational way to tease apart many of those complexities—and to gain new leads for treatment.

FURTHER READING

THE CLONAL EVOLUTION OF TUMOR CELL POPULATIONS. Peter C. Nowell in *Science,* Vol. 194, pages 23–28; October 1, 1976.

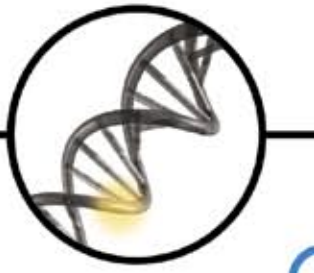
GENETIC AND EPIGENETIC LOSSES OF HETEROZYGOSITY IN CANCER PREDISPOSITION AND PROGRESSION. Heidi J. Scrable, Carmen Sapienza and Webster K. Cavenee in *Advances in Cancer Research,* Vol. 54, pages 25–62; 1990.

A GENETIC MODEL FOR COLORECTAL TUMORIGENESIS. Eric R. Fearon and Bert Vogelstein in *Cell,* Vol. 61, No. 5, pages 759–767; June 1, 1990.

TUMOR SUPPRESSOR GENES. Robert A. Weinberg in *Science,* Vol. 254, pages 1138–1146; November 22, 1991.

3

MAPPING THE CANCER GENOME



Pinpointing the genes involved in cancer will help chart a new course across the complex landscape of human malignancies

By Francis S. Collins and Anna D. Barker

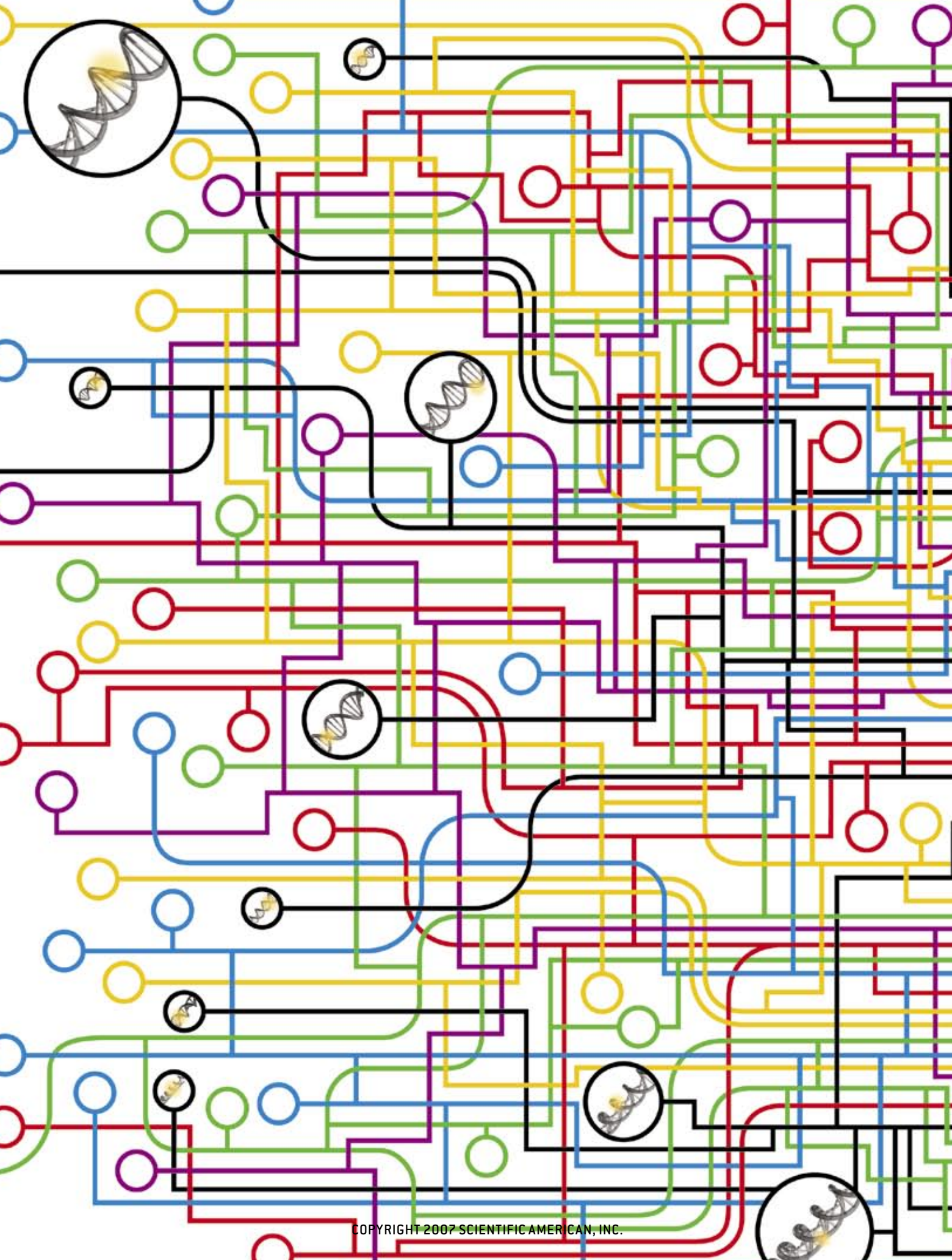
"If we wish to learn more about cancer, we must now concentrate on the cellular genome." Nobel laureate Renato Dulbecco penned those words more than 20 years ago in one of the earliest public calls for what would become the Human Genome Project. "We are at a turning point," Dulbecco, a pioneering cancer researcher, declared in 1986 in the journal *Science*. Discoveries in preceding years had made clear that much of the deranged behavior of cancer cells stemmed from damage to their genes and alterations in their functioning. "We have two options," he wrote. "Either try to discover the genes important in malignancy by a piecemeal approach, or … sequence the whole genome."

Dulbecco and others in the scientific community grasped that sequencing the human genome, though a monumental achievement itself, would mark just the first step of the quest to fully understand the biology of cancer. With the complete sequence of nucleotide bases in normal human DNA in hand, scientists would then need to classify the wide array of human genes according to their function—which in turn could reveal their roles in cancer. Over the span of two decades Dulbecco's vision has moved from pipe dream to reality. Less than three years after the Human Genome Project's completion, the National Institutes of Health has officially launched the pilot stage of an effort to create a comprehensive catalogue of the genomic changes involved in cancer: The Cancer Genome Atlas (TCGA).

The main reason to pursue this next ambitious venture in large-scale biology with great urgency is cancer's terrible toll on humankind. Every day more than 1,500 Americans die from cancer—about one person every minute. As the U.S. population ages, this rate is expected to rise significantly in the years ahead unless investigators find ways to accelerate the identification of new vulnerabilities within cancerous cells and develop novel strategies for attacking those targets.

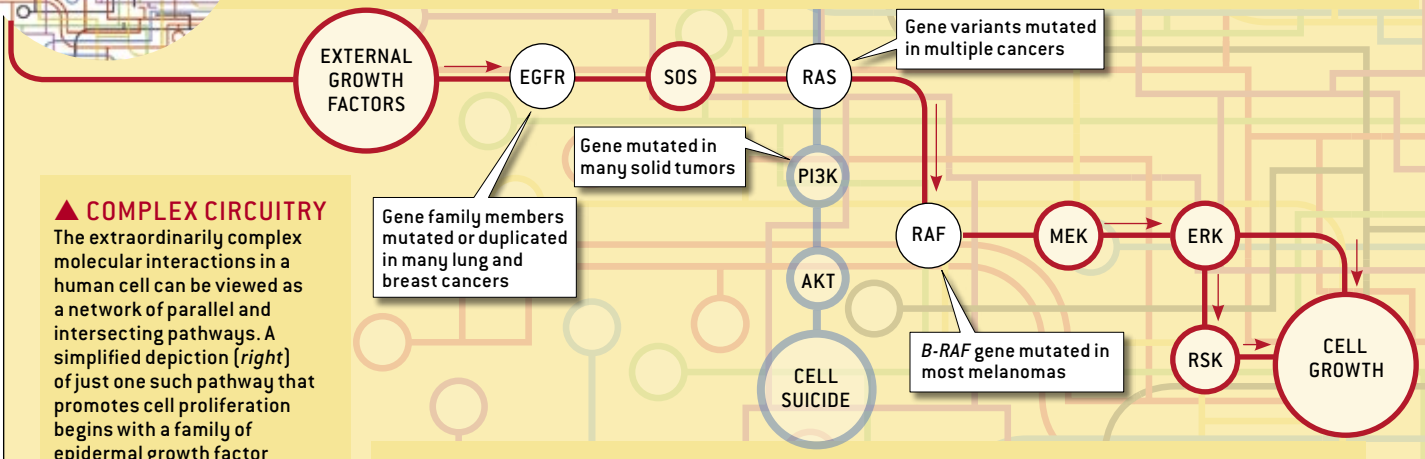
Still, however noble the intent, it takes more than a desire to ease human suffering to justify a research enterprise of this magnitude. When applied to the 50 most common types of cancer, this effort could ultimately prove to be the equivalent of more than 10,000 Human Genome Projects in terms of the sheer volume of DNA to be sequenced. The dream must therefore be matched with an ambitious but realistic assessment of the emerging scientific opportunities for waging a smarter war against cancer.

SLIM FILMS



MANY PATHWAYS TO MALIGNANCY

Gene malfunctions underlie the ability of cancer cells to escape normal constraints on a cell's behavior. Because genes give rise to proteins that serve as cellular building blocks, signals and regulators of other genes, a mutation that disables one gene, or causes it to be overactive, can have multiple deranging effects on the cell (*below*). Nevertheless, cells usually need to accrete several cancer-promoting, or oncogenic, mutations in separate genes to acquire the hallmark properties of malignancy (*box at right*). Identifying all the genes whose alteration can produce those traits should one day reveal which mutations are the true drivers of specific types of cancer—even of a specific patient's malignancy—and therefore the most effective ways to intervene in the disease.



▲ COMPLEX CIRCUITRY

The extraordinarily complex molecular interactions in a human cell can be viewed as a network of parallel and intersecting pathways. A simplified depiction (*right*) of just one such pathway that promotes cell proliferation begins with a family of epidermal growth factor receptors (EGFR) in the cell membrane. Their stimulation by growth factors outside the cell transmits signals to additional proteins and genes, ultimately prompting the cell to "grow" by dividing.

▲ ONCOGENIC MUTATIONS

In a significant portion of lung and breast tumors, members of the *EGFR* gene family are mutated or duplicated, which boosts the number or function of the receptors they encode, overstimulating this growth pathway. Damage to downstream genes can have similar results. Changes in the *B-RAF* gene, seen in some 70 percent of melanomas, also promote hyperactive cell proliferation. Versions of the *RAS* gene are mutated in many cancer types, which can affect cell growth as well as intersecting pathways—for example, interfering with a suicide program that normally destroys damaged cells.

A Disease of Genes

THE IDEA THAT ALTERATIONS to the cellular genome lie at the heart of all forms of cancer is not new. Since the first identification in 1981 of a cancer-promoting version of a human gene, known as an oncogene, scientists have increasingly come to understand that cancer is caused primarily by mutations in specific genes. The damage can be incurred through exposure to toxins or radiation, by faulty DNA repair processes or by errors that occur when DNA is copied prior to cell division. In relatively rare cases, a cancer-predisposing mutation is carried within a gene variant inherited from one's ancestors.

Whatever their origin, these mutations disrupt biological pathways in ways that result in the uncontrolled cell replication, or growth, that is characteristic of cancer as well as other hallmarks of malignancy, such as the ability to invade neighboring tissues and to spread to sites throughout the body. Some mutations may disable genes that normally protect against abnormal cell behavior, whereas others increase the activity of disruptive genes. Most cells must acquire at least several of these alterations before they become transformed into cancer cells—a process that can take years.

Over the past two decades many individual research groups have used groundbreaking molecular biology techniques to search for mutations in genes that are likely candidates for wreaking havoc on normal patterns of cell growth and behavior. This approach has identified about 350 cancer-related genes and yielded many significant insights into this diabolical disease. A database of these changes, called the catalogue of somatic mutations in cancer, or COSMIC, is maintained by Michael Stratton's group at the Wellcome Trust Sanger Institute in Cambridge, England. But no one imagines that it is the complete list.

So does it make sense to continue exploring the genomic basis of cancer at cottage-industry scale when we now possess the means to vastly increase the scope and speed of discovery? In recent years a number of ideas, tools and technologies have emerged and, more important, converged in a manner that

Overview/*Cancer Connections*

- Changes in the structure or activity of genes underlie the malignant behavior of cancer cells.
- Identification of genes involved in certain cancers is already advancing diagnosis and treatment.
- The Cancer Genome Atlas is a monumental initiative to eventually identify all the genetic alterations in different forms of cancer so that gene changes driving the disease can be targeted directly.

LUCY READING-IKKANDA; ACKNOWLEDGMENT: SPECIAL THANKS TO JEFFREY SETTLEMAN OF THE CENTER FOR CANCER RESEARCH AT MASSACHUSETTS GENERAL HOSPITAL AND DAPHNE W. BELL OF THE NHGRI CANCER GENETICS BRANCH FOR THEIR ADVICE ON THE PATHWAY ILLUSTRATION

Hallmarks of Cancer

The six abnormal capabilities listed below together give tumors their lethal power to overrun their native tissue and spread through the body.

Self-sufficiency in growth signaling
Cancer cells amplify external growth cues or generate their own.

Insensitivity to antigrowth signals
Cancer cells become deaf to quiescence cues from surrounding tissue.

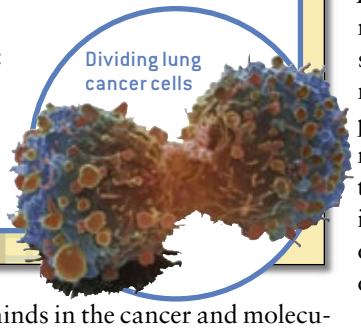
Evasion of cell suicide
Mechanisms that should trigger or carry out a self-destruct program in damaged cells are disabled or overridden.

Limitless replicative potential
Cancer cells evade intrinsic limits on the number of times a normal cell can divide.

Sustained blood vessel growth
Tumors emit signals promoting the development of new blood vessels to deliver oxygen and nutrients.

Invasiveness and motility
Cancer cells defy multiple signals and forces that hold a cell in place and prevent it from traveling to—and thriving in—other tissues.

Adapted from "The Hallmarks of Cancer," by Douglas Hanahan and Robert A. Weinberg, in Cell, *Vol. 100; January 7, 2000.*


Dividing lung cancer cells

has convinced many leading minds in the cancer and molecular biology communities that it is time for a systematic, collaborative and comprehensive exploration of the genomics of cancer.

The Human Genome Project laid a solid foundation for TCGA by creating a standardized reference sequence of the three billion DNA base pairs in the genome of normal human tissues. Now another initiative is needed to compare the DNA sequences and other physical characteristics of the genomes of normal cells with those of cancerous cells, to identify the major genetic changes that drive the hallmark features of cancer [*see box above*]. The importance of international partnerships in large-scale biology to pool resources and speed scientific discovery was also demonstrated by the Human Genome Project, and TCGA is exploring similar collaborations.

Finally, the Human Genome Project spurred significant advances in the technologies used to sequence and analyze genomes. At the start of that project in 1990, for example, the cost of DNA sequencing was more than $10 per "finished" nucleotide base. Today the cost is less than a penny per base and is expected to drop still further with the emergence of innovative sequencing methods [see "Genomes for All," by George M. Church; Scientific American, January 2006]. Because of these and other technological developments, the large-scale approach embodied in TCGA—unthinkable even a few years ago—has emerged as perhaps the most efficient and cost-effective way to identify the wide array of genomic factors involved in cancer.

Proofs of Concept

PILES OF DATA are, of course, not worth much without evidence that comprehensive knowledge of cancer's molecular origins can actually make a difference in the care of people. Several recent developments have provided proofs of concept that identifying specific genetic changes in cancer cells can indeed point to better ways to diagnose, treat and prevent the disease. They offer encouraging glimpses of what is to come and also demonstrate why the steps toward those rewards are complex, time-consuming and expensive.

In 2001, when the Wellcome Trust Sanger Institute began its own effort to use genomic technologies to explore cancer, the project's immediate goal was to optimize robotics and information management systems in test runs that involved sequencing 20 genes in 378 cancer samples. But the group hit pay dirt a year later when they found that a gene called *B-RAF* was mutated in about 70 percent of the malignant melanoma cases they examined. A variety of researchers swiftly set their sights on this potential new therapeutic target in the most deadly form of skin cancer. They tested multiple approaches—from classic chemical drugs to small interfering ribonucleic acids—in cell lines and in mice, to see if these interventions could block or reduce the activity of *B-RAF* or inhibit a protein called MEK that is overproduced as a result of *B-RAF* mutations. Just five years later the most promising of these therapies are being tested in clinical trials.

Other research groups have already zeroed in on genetic mutations linked to certain types of breast cancer, colon cancer, leukemia, lymphoma and additional cancers to develop molecular diagnostics, as well as prognostic tests that can point to an agent in the current arsenal of chemotherapies to which a particular patient is most likely to respond. Cancer genomics has also helped to directly shape the development and use of some of the newest treatments.

The drug Gleevec, for example, was designed to inhibit an enzyme produced by a mutant fused version of two genes, called *BCR-ABL*, that causes chronic myelogenous leukemia. Gleevec is proving dramatically effective against that disease and showing value in the treatment of more genetically complex malignancies, such as gastrointestinal stromal tumor and several other relatively rare cancers that involve similar

THE AUTHORS

FRANCIS S. COLLINS and *ANNA D. BARKER* are leaders of The Cancer Genome Atlas initiative in their positions as, respectively, director of the National Human Genome Research Institute and deputy director for Advanced Technologies and Strategic Partnerships of the National Cancer Institute. Collins led the Human Genome Project to its completion of the human DNA sequence, and Barker has headed drug development and biotechnology research efforts in the public and private sectors, with a particular focus on fighting cancer.

STEVE GSCHMEISSNER *Photo Researchers, Inc.*

Genes and Cancer

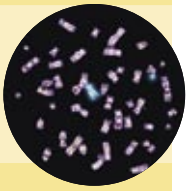
A connection between genetic abnormalities and the aberrant features of cancer cells was first suggested more than 100 years ago by German biologist Theodor Boveri and others. But over the past few decades evidence that gene alterations directly cause the deranged behavior of cancer cells began accumulating. Calls arose by 1986 to sequence the normal human genome to study malignant gene changes comprehensively. The Human Genome Project was completed in 2003. The Cancer Genome Atlas project will start cataloguing the gene mutations found in three types of human cancer this year.

1890–1914
Studies of abnormal chromosome distribution during cell division suggest a role in malignancy.

Theodor Boveri ▶

1950s–1960s
Multiple discoveries reveal that tumor viruses can cause cancer by injecting their genes into cells.

1960
First genetic defect associated with a specific cancer—an abnormality known as the Philadelphia chromosome—is discovered in chronic myelogenous leukemia (CML) cells.



1976
Scientists discover that *src,* a nonviral gene found in animal cells, can cause cancer.

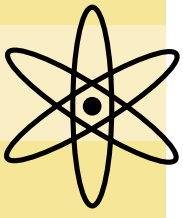
1979
P53, later found to be the most frequently mutated gene in human cancer, is discovered.

1981
H-RAS is the first human oncogene (a gene whose alteration is cancer-promoting) to be discovered.

1983
Altered methylation of DNA, suspected to affect gene activation, found in cancer cells.

1986
Renato Dulbecco, writing in *Science,* calls for sequencing the human genome to advance cancer research.

1986
U.S. Department of Energy considers sequencing the human genome to further study of radiation effects.



1986
First tumor suppressor gene, *RB1,* is identified.

1987
Fused gene *BCR-ABL* in the Philadelphia chromosome is found to cause CML.

1990
Model of multistep tumor genesis clarifies the role of accumulated gene changes in cellular transformation to malignancy.

1990
Human Genome Project begins.

enzymes. Herceptin, an agent that targets a cellular signal–receiving protein called *HER2,* is successful against breast cancers with an abnormal multiplication of the *HER2* gene that causes overproduction of the receptor protein.

Strategies for selecting treatments based on specific gene mutations in a patient's cancer are also being tested in studies of the drugs Iressa and Tarceva for lung cancer, as well as Avastin for lung, colon and other cancers. The performance of these new gene-based diagnostics, prognostics and therapeutics is certainly good news, although the list of such interventions remains far shorter than it would be if researchers in academia and the private sector had ready access to the entire atlas of genomic changes that occur in cancer.

A recent study led by investigators at Johns Hopkins University illustrates both the power of large-scale genomics applied to the discovery of cancer genes and the tremendous undertaking a comprehensive cancer genome atlas will be. The group sequenced about 13,000 genes in tumor tissues taken from 11 colorectal cancer patients and 11 breast cancer patients and reported finding potentially significant mutations in nearly 200 different genes. Interestingly, only about a dozen genes had previously been linked to these two types of cancer, and most scientists had generally expected to find just a few more.

Among the major challenges encountered by researchers sequencing cancer cell genomes is the difficulty of distinguishing meaningless mutations in the tumor samples from those that are cancer-related. Somewhat surprisingly, early sequencing studies have also found very little overlap among the genetic mutations present in different types of cancer and even substantial variation in the pattern of genetic mutations among tumor samples from patients with the same type of cancer. Such findings underscore the idea that many different possible combinations of mutations can transform a normal cell into a cancer cell. Therefore, even among patients with cancers of the same body organ or tissue, the genetic profile of each individual's tumor can differ greatly.

To grasp the full scope of what TCGA hopes to achieve, one must consider the complexities identified in such early efforts and imagine extending the work to more than 100 types of cancer. It is enough to give even veterans of the Human Genome Project and seasoned cancer biologists pause. Yet TCGA participants and other scientific pioneers from around the world are forging ahead, because we are convinced that amid the intricacies of the cancer genome may lie the greatest promise for saving the lives of patients.

Although researchers will probably take many years to complete a comprehensive catalogue of all the genomic mutations that cause normal cells to become malignant, findings with the potential to revolutionize cancer treatment are likely to appear well before this compendium is finished, as the proofs of concept have shown. As each new type of cancer is studied and added to TCGA, investigators will gain another rich new set of genomic targets and profiles that can be used to develop more tailored therapies.

PHOTO RESEARCHERS, INC. (*Boveri*); DEPARTMENT OF CLINICAL CYTOGENETICS, ADDENBROOKE'S HOSPITAL *Photo Researchers, Inc.* (*Philadelphia chromosome*); STEVE GSCHMEISSNER *Photo Researchers, Inc.* (*tumor cell*); MARK J. WINTER *Photo Researchers, Inc.* (*Gleevec molecule*); CECIL H. FOX *Photo Researchers, Inc.* (*Biospecimen Core Resource*); AFFYMETRIX (*Cancer Genome Characterization Centers*); NATIONAL HUMAN GENOME RESEARCH INSTITUTE (*Genome Sequencing Centers*); © CDC/PHIL *Corbis* (*Data Coordinating Center*)

Compiling a Colossal Atlas

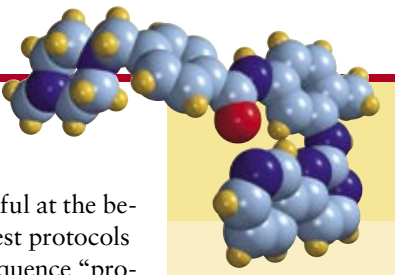
A PHASED-IN STRATEGY that proved successful at the beginning of the Human Genome Project was to test protocols and technology before scaling up to full DNA sequence "production." Similarly, TCGA is beginning with a pilot project to develop and test the scientific framework needed to ultimately map all the genomic abnormalities involved in cancer.

In 2006 the National Cancer Institute and National Human Genome Research Institute selected the scientific teams and facilities that will participate in this pilot project, along with the cancer types they will begin examining. Over the next three years these two institutes will devote $100 million to compiling an atlas of genomic changes in three tumor types: glioblastomas of the brain, lung cancer and ovarian cancer. These particular cancers were chosen for several reasons, including their value in gauging the feasibility of scaling up this project to a much larger number of cancer types. Indeed, only if this pilot phase achieves its goals will the NIH move forward with a full-fledged project to develop a complete cancer atlas.

The three malignancies that we selected for the pilot collectively account for more than 210,000 cancer cases in the U.S. every year and caused an estimated 191,000 deaths in this country in 2006 alone. Moreover, tumor specimen collections meeting the project's strict scientific, technical and ethical requirements exist for these cancer types. Last September our institutes announced the selection of three biorepositories to provide such specimens, along with new tumor samples as needed, and normal tissue from the same patients for comparison. Those facilities will deliver materials to a central Biospecimen Core Resource, one of four major structural components in TCGA's pilot project.

Cancer Genome Characterization Centers, Genome Sequencing Centers and a Data Coordinating Center constitute the project's other three main elements [*see illustration at right*], and all these groups will collaborate and exchange data openly. Specifically, the seven Cancer Genome Characterization Centers will use a variety of technologies to examine the activity levels of genes within tumor samples and to uncover and catalogue so-called large-scale genomic changes that contribute to the development and progression of cancer. Such alterations include chromosome rearrangements, changes in gene copy numbers and epigenetic changes, which are chemical modifications of the DNA strand that can turn gene activity on or off without actually altering the DNA sequence.

Genes and other chromosomal areas of interest identified by the Cancer Genome Characterization Centers will become targets for sequencing by the three Genome Sequencing Centers. In addition, families of genes suspected to be important in cancer, such as those encoding enzymes involved in cell-cycle control known as tyrosine kinases and phosphatases, will be sequenced to identify genetic mutations or other small-scale changes in their DNA code. At present, we estimate that some 2,000 genes—in each of perhaps 1,500 tumor samples—will be sequenced during this pilot project. The exact numbers will, of course, depend on the samples obtained and what is discovered



◀ Gleevec model

1993
Preclinical testing starts on drug that would become Gleevec, the first therapy developed to target a known gene-based cause of a cancer.

1999
Gene-activity profiles are first shown to distinguish between cancer types and to predict chemotherapy response.

2001
Gleevec earns FDA approval.

2002
Wellcome Trust Sanger Institute tumor genome survey discovers a mutation in *B-RAF* gene common to 70 percent of melanomas.

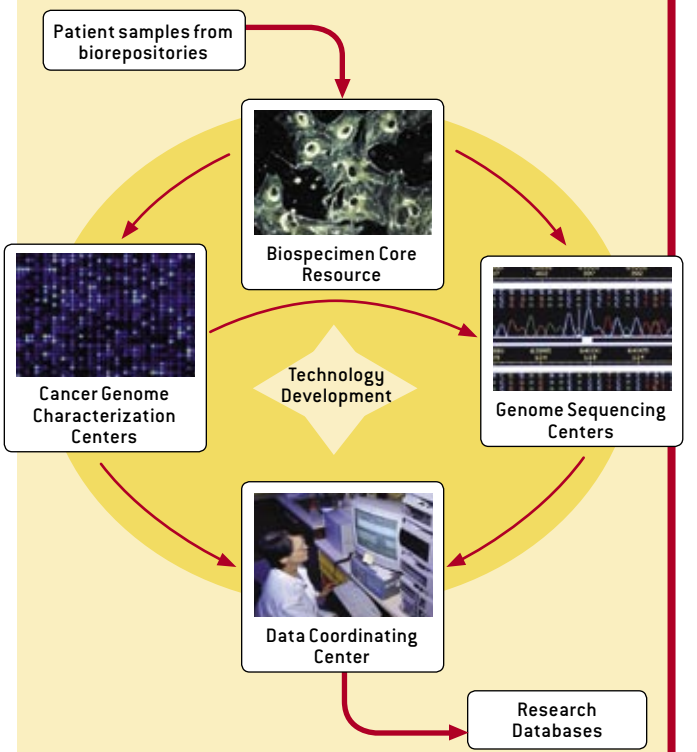
2003
Human Genome Project is completed.

2005
The Cancer Genome Atlas (TCGA) pilot project is announced by the National Institutes of Health.

2006
TCGA names pilot project participants and three cancer types for sequencing and genetic analysis.

2007–2010
TCGA will collect and analyze tumor samples obtained from designated biorepository institutions treating patients with cancer. The project's four primary components—a Biospecimen Core Resource, seven Cancer Genome Characterization Centers, three Genome Sequencing Centers and a Data Coordinating Center—will cooperate to test methods and technologies and to generate and manage data that will be made available to the wider research community.

How Will It Work?



about them by the Cancer Genome Characterization Centers.

Both the sequencing and genome characterization groups, many of which were participants in the Human Genome Project, can expect to encounter a far greater level of complexity than that in the DNA of normal cells. Once cells become cancerous, they are prone to an even greater rate of mutation as their self-control and repair mechanisms fail. The genomic makeup of individual cells can therefore vary dramatically within a single tumor, and the integrated teams will need to develop robust methods for efficiently distinguishing the "signal" of a potentially biologically significant mutation from the "noise" of the high background rate of mutations seen in many tumors. Furthermore, tumors almost always harbor some nonmalignant cells, which can dilute the sample. If the tumor DNA to be sequenced is too heterogeneous, some important mutations may be missed.

Following the lead of the Human Genome Project and other recent medical genomics efforts, all these data will be made swiftly and freely available to the worldwide research community. To further enhance its usefulness to both basic and clinical researchers and, ultimately, health care professionals, TCGA will link its sequence data and genome analyses with

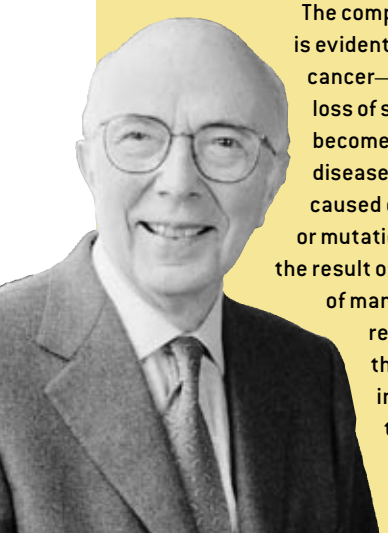
From Genome to Cancer—Why the Time Is Right

By Renato Dulbecco

When in 1986 I suggested a new project directed at identifying all human genes, one of my overriding goals was to find those genes involved in cancer development—a feat I hoped would lead to new tools for cancer research and, ultimately, to new therapies. That original human genome project has now been carried out and has demonstrated its usefulness for the discovery of genes involved in many diseases, including cancer. Moreover, the genome sequencing effort has been extended to other organisms—from bacteria to chimpanzees—and is showing the unity of life by revealing how many genes distant species share in common.

In the course of this work, new technologies have also provided a much more detailed understanding of the complicated processes by which genes give rise to a variety of functional molecules. An important outcome of this research is the realization that genes do not act alone but are participants in extensive networks of activity within cells. Any change in the functioning of one gene can therefore be accompanied by changes in the workings of multiple genes and proteins involved in the cells' self-maintenance.

Cancer results from the stepwise loss of cellular self-control.



The complexity of this system in normal cells is evident in what we already know about cancer—that it results from the stepwise loss of such cellular self-control, which becomes more and more complete as the disease progresses. That progression is caused only in part by physical alterations, or mutations, in specific genes; mostly it is the result of consequent changes in the activity of many other genes involved in cell regulation. Single genes may therefore be responsible in the initiation of cancer and so potential therapeutic targets. To reach the more advanced stages of these cancers (such as the acute phase of myeloid leukemia or the metastatic phase of other cancers), however, the participation of many other genes is required. Most of them are still unknown.

An exception is the recently observed phenomenon of oncogene addiction in certain tumor cells: despite the presence of numerous mutations to the cellular genome, turning off the activity of one so-called oncogene causes the cells to commit suicide via a mechanism known as apoptosis. But how generally this phenomenon occurs is also unknown. To approach these questions, it will be necessary to have a complete catalogue of the structural and functional alterations of genes and other cellular components that cause the loss of regulation in cancer cells. This process, in turn, will require a complete determination of their connections into networks by computational means—a task for the future.

On the way to this goal, however, many other unanswered questions can be explored by the research community. A possible role for stem cells in cancer, for example, is supported by similarities in the behavior of stem cells and cancer cells: both have an unlimited ability to divide; both are very sensitive to the cellular environment, or niche, in which they grow; and many of the genes known to be active in stem cells are also activated in cancer cells.

The advent of genomics has provided welcome insight into the mechanisms by which normal cells become cancerous, but our picture is still incomplete. The time has come to obtain a truly comprehensive catalogue of the genes involved in cancer, bringing to bear all the power of the new tools of genomics and molecular biology to the problem. The Cancer Genome Atlas project aims to do just that.

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SALK INSTITUTE FOR BIOLOGICAL STUDIES

information about observable characteristics of the original tumors and the clinical outcomes of the sample donors. Developing the bioinformatic tools to gather, integrate and analyze those massive amounts of data, while safeguarding the confidentiality of patient information, is therefore another hurdle that must be cleared to turn our vision into reality.

Uncharted Territory

THE ROAD AHEAD is fraught with scientific, technological and policy challenges—some of which are known and others as yet unknown. Among the uncertainties to be resolved: Will new sequencing technologies deliver on their early promise in time to make this effort economically feasible? How quickly can we improve and expand our toolbox for systematically detecting epigenetic changes and other large-scale genomic alterations involved in cancer, especially those associated with metastasis? How can we harness the power of computational biology to create data portals that prove useful to basic biologists, clinical researchers and, eventually, health care professionals on the front lines? How can we balance intellectual-property rights in a way that promotes both basic research and the development of therapies? When will Congress finally pass genetic nondiscrimination legislation so that knowledge gained through TCGA will have the maximum positive influence on Americans' health? The list goes on.

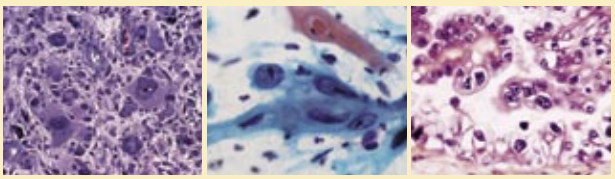
To avoid raising false expectations, we also must be clear about the questions this project will not attempt to answer. Although it will serve as a resource for a broad range of biological exploration, TCGA is only a foundation for the future of cancer research and certainly not the entire house. And we face the sobering issue of time—something that is in short supply for many cancer patients and their families. As we survey the considerable empty spaces that exist in our current map of genomic knowledge about cancer, the prospect of filling those gaps is both exhilarating and daunting. Scientists and the public need to know up front that this unprecedented foray into molecular cartography is going to take years of hard work and creative problem solving by thousands of researchers from many different disciplines.

Where all this work will lead can only be dimly glimpsed today. In this sense, our position is similar to that of the early 19th-century explorers Meriwether Lewis and William Clark. As they ventured up the Missouri River into the largely uncharted Northwest Territory in 1804, their orders from President Thomas Jefferson were to "take observations of latitude and longitude at all remarkable points.... Your observations are to be taken with great pains and accuracy; to be entered distinctly and intelligibly for others, as well as yourself."

Although Lewis and Clark did not find the much-longed-for water route across the continent, their detailed maps proved valuable to their fledgling nation in myriad ways that Jefferson could never have imagined. For the sake of all those whose lives have and will be touched by cancer, we can only hope our 21st-century expedition into cancer biology exceeds even Renato Dulbecco's grandest dreams. SA

Targeting Gene Changes in Cancer

TCGA pilot project teams will examine the DNA of some 1,500 tumor samples from patients with cancers of the lung, ovaries or brain (glioblastoma), looking for genetic changes. Approximately 2,000 suspect genes in each sample will be sequenced to identify specific mutations. The list of target genes will be tailored to each cancer type and largely determined by what the Cancer Genome Characterization Centers find in the samples, although candidates will also be drawn from categories of genes already associated with cancer.



From left to right: Glioblastoma, lung cancer, ovarian cancer

GENE CATEGORIES	EXAMPLES
Genes identified by TCGA Cancer Genome Characterization Centers as having aberrant structure or activity in a significant number of tumor samples	In some brain tumor cell lines, a gene encoding the intracellular protein NF-KAPPA B is much more active than in normal brain tissue
Well-known oncogenes (genes whose overactivity or alteration is cancer-promoting)	• Growth factor receptor genes: *HER2* (breast and lung cancers), *EGFR* (lung and colon cancers) • Signaling protein genes: *BCR-ABL* (chronic myelogenous leukemia), *RAS* (many cancers), *B-RAF* (skin cancers) • Regulators of cell death: *BCL-3* (lymphoma)
Well-known tumor suppressors (genes that protect cells from malignant transformation, unless disabled by mutation)	• Controllers of cell division: *RB1* (retinoblastoma) • DNA repairers: *HNPCC* (colon cancer, endometrial cancer) • Promoters of programmed cell suicide: *P53* (lung, colon, breast and brain tumors)
Genes related to known oncogenes and tumor suppressor genes by similarity or pathway membership	The oncogenes *HER2* and *EGFR* are part of the epidermal growth factor receptor signaling pathway, which contains at least half a dozen other genes suspected of playing key roles in cancer development and progression

MORE TO EXPLORE

The New Era in Cancer Research. Harold Varmus in *Science,* Vol. 312, pages 1162–1165; May 26, 2006.

The Consensus Coding Sequences of Human Breast and Colorectal Cancers. Tobias Sjöblom et al. in *Science,* Vol. 314, pages 268–274; October 13, 2006. (Published online September 7, 2006.)

The Cancer Genome Atlas: **http://cancergenome.nih.gov**

CNRI *Photo Researchers, Inc.* (*glioblastoma* and *ovarian cancer*); JONATHAN ASHTON *Photo Researchers, Inc.* (*lung cancer*)