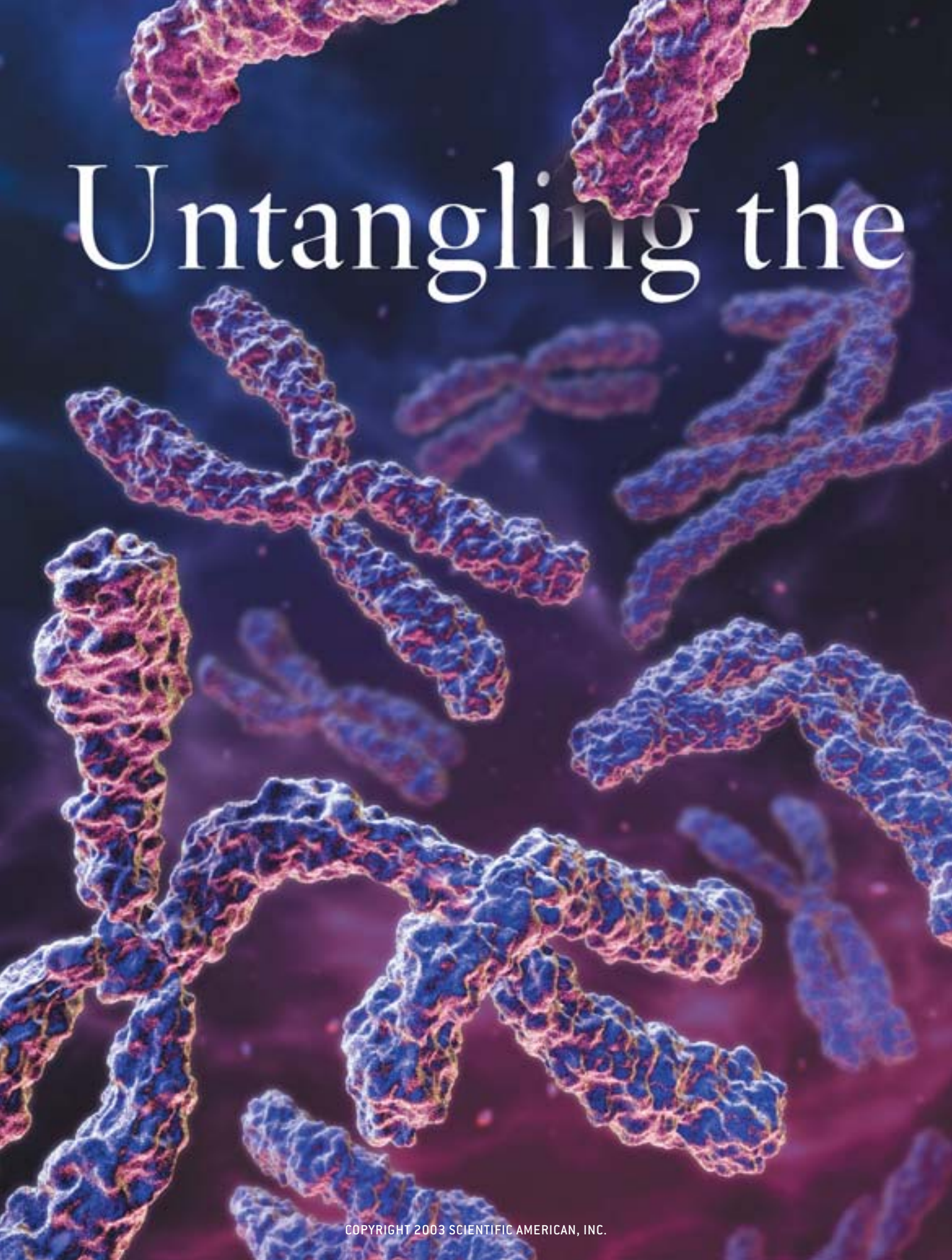
Untangling the



Roots of Cancer

RECENT EVIDENCE CHALLENGES LONG-HELD THEORIES OF HOW CELLS TURN MALIGNANT—AND SUGGESTS NEW WAYS TO STOP TUMORS BEFORE THEY SPREAD

By W. Wayt Gibbs

What causes cancer?

Tobacco smoke, most people would say. Probably too much alcohol, sunshine or grilled meat; infection with cervical papillomaviruses; asbestos. All have strong links to cancer, certainly. But they cannot be root causes. Much of the population is exposed to these carcinogens, yet only a tiny minority suffers dangerous tumors as a consequence.

A cause, by definition, leads invariably to its effect. The immediate cause of cancer must be some combination of insults and accidents that induces normal cells in a healthy human body to turn malignant, growing like weeds and sprouting in unnatural places.

At this level, the cause of cancer is not entirely a mystery. In fact, a decade ago many geneticists were confident that science was homing in on a final answer: cancer is the result of cumulative mutations that alter specific locations in a cell's DNA and thus change the particular proteins encoded by cancer-related genes at those spots. The mutations affect two kinds of cancer genes. The first are called tumor suppressors. They normally restrain cells' ability to divide, and mutations permanently disable the genes. The second variety, known as oncogenes, stimulate growth—in other words, cell division. Mutations lock oncogenes into an active state. Some researchers still take it as axiomatic that such growth-promoting changes to a small number of cancer genes are the initial event and root cause of every human cancer.

Others, however, including a few very prominent oncologists, are increasingly challenging that theory. No one questions that cancer is ultimately a disease of the DNA. But as biologists trace tumors to their roots, they have discovered many other abnormalities at work inside the nuclei of cells that, though not yet cancerous, are headed that way. Whole chromosomes, each containing 1,000 or more genes, are often lost or duplicated in their entirety. Pieces of chromosomes are frequently scrambled, truncated or fused together. Chemical additions to the DNA, or to the histone proteins around which it coils, somehow silence important genes, but in a reversible process quite different from mutation.

The accumulating evidence has spawned at least three hypotheses that compete with the standard dogma to explain what changes come first and which aberrations matter most in the decade-long transformation of a cell and its descendants from well-behaved tissue to invasive tumor. The challengers dispute the dominant view of the disease as the product of a defined genetic state. They argue that it is more useful to think of cancer as the consequence of a chaotic process, a combination of Murphy's Law and Darwin's Law: anything that can go wrong will, and in a competitive environment, the best adapted survive and prosper.

Despite that shared underlying principle, the new theories make different predictions about what kind of treatments will work best.

JEFF JOHNSON *Hybrid Medical Animation*

CAREFULLY CHOREOGRAPHED dance of chromosomes occurs during cell division. Missteps that mangle chromosomes or that send the wrong number to each daughter cell may be critical events early in the development of cancer, according to new theories.

Some suggest that many cancers could be prevented altogether by better screening, changes in diet, and new drugs—or even by old drugs, such as aspirin. Other theories cast doubt on that hope.

Marks of Malignancy

A WORKABLE THEORY of cancer has to explain both why it is predominantly a disease of old age and why we do not all die from it. A 70-year-old is roughly 100 times as likely to be diagnosed with a malignancy as a 19-year-old is. Yet most people make it to old age without getting cancer.

Biologists estimate that more than 10 million billion cells must cooperate to keep a human being healthy over the course of an 80-year life span. If any one of those myriad cells could give rise to a tumor, why is it that fewer than half the population will ever contract a cancer serious enough to catch a doctor's attention?

One explanation is that a cell must acquire several extraordinary skills to be malignant. "Five or six different regulatory systems must be perturbed in order for a normal cell to grow as a cancer," asserts Robert A. Weinberg of the Whitehead Institute at the Massachusetts Institute of Technology. In a review paper last November, he and William C. Hahn of the Dana-Farber Cancer Institute in Boston argued that all life-threatening cancers manifest at least six special abilities. (Although Weinberg is one of the founding proponents of the standard paradigm, even those who challenge that theory tend to agree with this view.)

For example, cancer cells continue dividing in situations in which normal cells would quietly wait for a special chemical signal—say, from an injured neighbor. Somehow they counterfeit these pro-growth messages. Conversely, tumor cells must ignore "stop dividing" commands that are sent out by the adjacent tissues they squeeze and by their own internal aging mechanisms.

All cancerous cells have serious problems of some sort with their DNA, and as they double again and again, many cells in the resulting colony end up far from the blood vessels that supply oxygen and nutrients. Such stresses trigger autodestruct mechanisms in healthy cells. Tumor cells find some way to avoid this kind of suicide. Then they have to persuade nearby blood vessels to build the infrastructure they need to thrive.

A fifth superpower that almost all cancers acquire is immortality. A culture of normal human cells stops dividing after 50 to 70 generations. That is more than enough doublings to sustain a person through even a century of healthy life. But the great majority of cells in tumors quickly die of their genetic defects, so those that survive must reproduce indefinitely if the tumor is to grow. The survivors do so in part by manipulating their telomeres, gene-free complexes of DNA and protein that protect the ends of each chromosome.

Tumors that develop these five faculties are trouble, but they are probably not deadly. It is the sixth property, the ability to invade nearby tissue and then metastasize to distant parts of the body, that gives cancer its lethal character. Local invasions can usually be removed surgically. But nine of every 10 deaths from the disease are the result of metastases.

Only an elite few cells in a tumor seem to acquire this ability to detach from the initial mass, float through the circulation and start a new colony in a different organ from the one that gave birth to them. Unfortunately, by the time they are discovered, many cancers have already metastasized—including, in the U.S., 72 percent of lung cancers, 57 percent of colorectal, and 34 percent of breast. By then the prognosis is frequently grim.

> **"If you look at most solid tumors in adults, it looks like someone SET OFF A BOMB in the nucleus."**
>
> *—William C. Hahn, Dana-Farber Cancer Institute*

Overview/*How Cancer Arises*

- Cancer is a genetic disease. Alterations to the DNA inside cells can endow cells with morbid "superpowers," such as the ability to grow anywhere and to continue dividing indefinitely.
- Most cancer researchers have long focused on mutations to a relatively small set of cancer-related genes as the decisive events in the transformation of healthy cells to malignant tumors.
- Recently, however, other theories have emerged to challenge this view. One hypothesizes that a breakdown in DNA duplication or repair leads to many thousands of random mutations in cells. Another suggests that damage to a few "master" genes mangles the chromosomes, which then become dangerous. A third challenger proposes that abnormal numbers of chromosomes in a cell may be the first milestone on the road to cancer.

The Order of Disorder

DOCTORS COULD CATCH incipient tumors sooner if scientists could trace the steps that cells take down the road to cancer after the initial assault to their DNA by a carcinogen or some random biochemical mishap. Researchers broadly agree on the traits of the diseased cells that emerge from the journey. It is the propelling force and the order of each milestone that are under active debate.

The dominant paradigm for 25 years has been that tumors grow in spurts of mutation and expansion. Genetic dam-

SIX DIABOLICAL SUPERPOWERS OF CANCER

1. GROWTH EVEN IN THE ABSENCE OF NORMAL "GO" SIGNALS

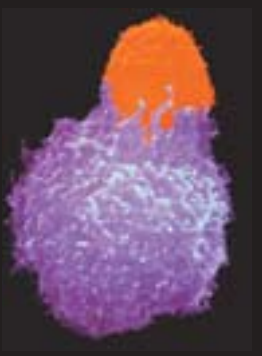
Most normal cells wait for an external message before dividing. Cancer cells (*image*) often counterfeit their own pro-growth messages.

2. GROWTH DESPITE "STOP" COMMANDS ISSUED BY NEIGHBORING CELLS

As the tumor (*yellow*) expands, it squeezes adjacent tissue, which sends out chemical messages that would normally bring cell division to a halt. Malignant cells ignore the commands.

3. EVASION OF BUILT-IN AUTODESTRUCT MECHANISMS

In healthy cells, genetic damage above a critical level usually activates a suicide program. Cancerous cells (*magenta*) bypass this mechanism, although agents of the immune system (*orange*) can sometimes successfully order the cancer cells to self-destruct.

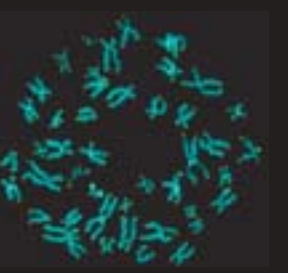


4. ABILITY TO STIMULATE BLOOD VESSEL CONSTRUCTION

Tumors need oxygen and nutrients to survive. They obtain them by co-opting nearby blood vessels to form new branches (*brown streaks*) that run throughout the growing mass.

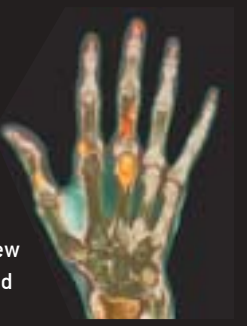
5. EFFECTIVE IMMORTALITY

Healthy cells can divide no more than 70 times. Malignant cells need more than that to make tumors. So they work around systems—such as the telomeres (*yellow*) at the end of chromosomes (*blue*)—that enforce the reproductive limit.



6. POWER TO INVADE OTHER TISSUES AND SPREAD TO OTHER ORGANS

Cancers usually become life-threatening only after they somehow disable the cellular circuitry that confines them to a specific part of the particular organ in which they arose. New growths (*orange* and *yellow*) appear and eventually interfere with vital systems.



Clockwise from top right: CHRIS JONES *Corbis;* PETER LANSDORP *University of British Columbia;* SCIENCE PHOTO LIBRARY; FRANK LYNCH *QualTek Molecular Laboratories;* ANDREJS LIEPINS/SPL; CNRI/SPL; SPL

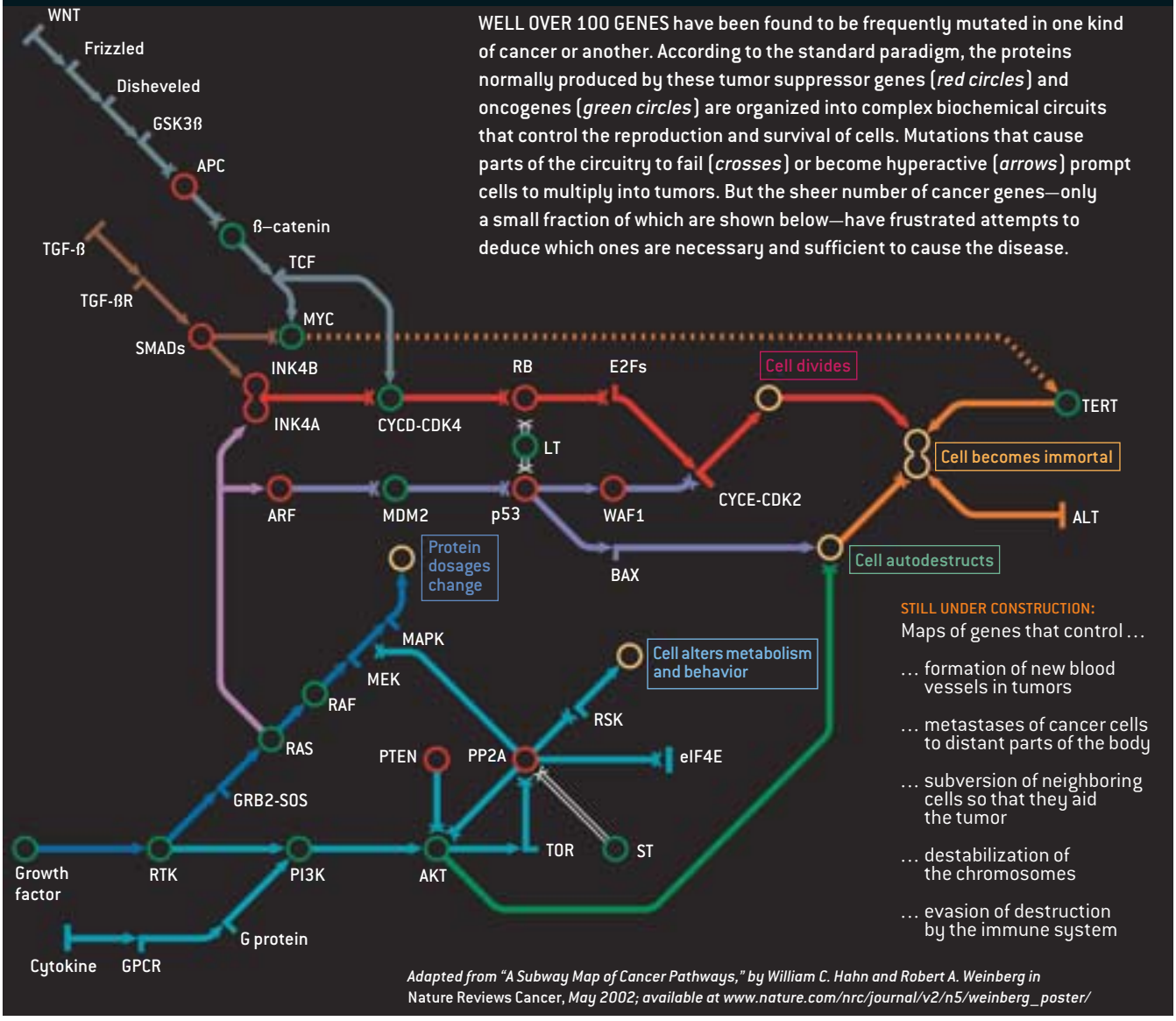
age to a cell deletes or disrupts a tumor suppressor gene—*RB*, *p53* and *APC* are among the best known—thereby suppressing proteins that normally ensure the integrity of the genome and the process of cell division. Alternatively, a mutation may increase the activity of an oncogene—such as *BRAF*, *c-fos* or *c-erbb3*—whose proteins then stimulate the cell to reproduce.

Changes to cancer genes endow the cell with one or more superpowers, allowing it to outbreed its neighbors. The cell passes abnormalities in its DNA sequence on to its descendants, which become a kind of clone army that grows to the limits of its capacity. Eventually another random mutation to a cancer gene knocks down another obstacle, initiating another burst of growth.

Cells normally have two copies of every chromosome—one from the mother, the other from the father—and thus two copies, or alleles, of every gene. (In males, the single X and Y chromosomes are notable exceptions.) A mutation to just one allele is enough to activate an oncogene permanently. But it takes two hits to knock out both alleles of a tumor suppressor gene. Four to 10 mutations in the right genes can transform any cell. Or so the theory goes.

The mutant-gene paradigm gained almost universal acceptance because it explained very well what scientists saw in their experiments on genetically engineered mice and human cell cultures. But new technologies now allow researchers to study the genomes of cancerous and

MALIGNANT MUTATIONS: A PARTIAL MAP



Adapted from "A Subway Map of Cancer Pathways," by William C. Hahn and Robert A. Weinberg in Nature Reviews Cancer, *May 2002; available at www.nature.com/nrc/journal/v2/n5/weinberg_poster/*

precancerous cells taken directly from people. Many recent observations seem to contradict the idea that mutations to a few specific genes lie at the root of all cancers.

Unexplained Phenomena

IN APRIL, FOR EXAMPLE, Muhammad Al-Hajj of the University of Michigan at Ann Arbor and his colleagues reported that they had identified distinguishing marks for a rare subset of cells within human breast cancers that can form new tumors. As few as 100 cells of this type quickly spawned disease when injected into mice lacking an immune system. Tens of thousands of other cells, harvested from the same nine breast malignancies but lacking the telltale marks, failed to do so. "This is the first tumor-initiating cell anyone has isolated for solid tumors," says John E. Dick, a biologist at the University of Toronto who has identified similar cells for leukemia.

The tantalizing implication, Dick says, is that just a small fraction of the cells in a tumor are responsible for its growth and metastasis—and so for the illness and death of the patient. If that is shown to be true for humans as well as mice, it could pose a problem for the mutant-gene theory of cancer. If mutations, which are copied from a cell to its progeny, give tumor cells their powers, then shouldn't all clones in the army be equally powerful?

In fact, most tumors are not masses of identical clones. On the contrary, closer examination has revealed amazing genetic diversity among their cells, some of which are so different from normal human cells (and from one another) that they might fairly be called new species.

A few cancer-related genes, such as *p53*, do seem to be mutated in the majority of tumors. But many other cancer genes are changed in only a small fraction of cancer types, a minority of patients, or a sprinkling of cells within a tumor. David Sidransky of the Johns Hopkins University School of Medicine and his coworkers tested DNA from 476 tumors of various kinds. They reported in April that

the oncogene *BRAF* was altered in two thirds of papillary thyroid cancers. But *BRAF* was not mutated in any of several other kinds of thyroid cancers.

Moreover, some of the most commonly altered cancer genes have oddly inconsistent effects. Bert E. Vogelstein's group at Johns Hopkins found that the much studied oncogenes *c-fos* and *c-erbb3* are curiously less active in tumors than they are in nearby normal tissues. The tumor suppressor gene *RB* was recently shown to be hyperactive—not disabled—in some colon cancers, and, perversely, it appears to protect those tumors from their autodestruct mechanisms.

The "two hit" hypothesis—that both alleles of a tumor suppressor gene must be deactivated—has also been upended by the discovery of a phenomenon called haploinsufficiency. In some cancers, it turns out, tumor suppressors are not mutated at all. Their output is simply reduced, and that seems to be enough to push cells toward malignancy. This effect has now been seen for more than a dozen tumor suppressor genes, and investigators expect to find many more like them. Searching for the mere presence or absence of a gene's protein is too simplistic. Dosage matters.

Beyond Mutation

RESEARCHERS ARE NOW looking more closely at other phenomena, besides errors in a gene's DNA sequence, that can dramatically alter the dosage of a protein in a cell. Candidates include the loss or gain of a chromosome (or part of one) containing the gene; changes in the concentration of other proteins that regulate how the gene is transcribed from DNA to RNA and translated into a protein; even so-called epigenetic phenomena that alter gene activity by reversible means. All these changes are nearly ubiquitous in established cancers.

"If you look at most solid tumors in adults, it looks like someone set off a bomb in the nucleus," Hahn says. "In most cells, there are big pieces of chromosomes hooked together and duplications or losses of whole chromosomes."

Scientists have yet to settle on a term for the suite of chromosomal aberrations seen in cancer. The word "aneuploidy" once referred specifically to an abnormal number of chromosomes. But more recently, it has been used in a broader sense that also encompasses chromosomes with truncations, extensions or swapped segments. That more inclusive definition serves our purposes here.

Almost a century ago German biologist Theodor Boveri noticed the strange imbalance in cancer cells between the numbers of maternal versus paternal chromosomes. He even suggested that aneuploid cells might cause the disease. But scientists could find no recurrent pattern to the chromosomal chaos—indeed, the genome of a typical cancer cell is not merely aneuploid but is unstable as well, changing every few generations. So Boveri's idea was dropped as the search for oncogenes started to bear fruit. The aneuploidy and massive genomic instability inside tumor cells were dismissed as side effects of cancer, not prerequisites.

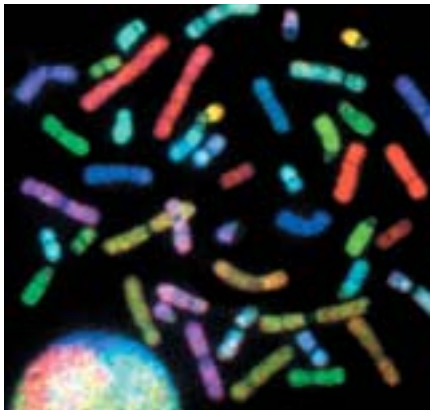
But the oncogene/tumor suppressor gene hypothesis has also failed, despite two decades of effort, to identify a particular set of gene mutations that occurs in every instance of any of the most common and deadly kinds of human cancer. The list of cancer-related mutations has grown to more than 100 oncogenes and 15 tumor suppressor genes. "The rate at which these molecular markers are being identified continues to increase rapidly," Weinberg and Hahn lamented in their November review. "As a consequence," they added, "it remains possible that each tumor is unique" in the pattern of its genetic disarray.

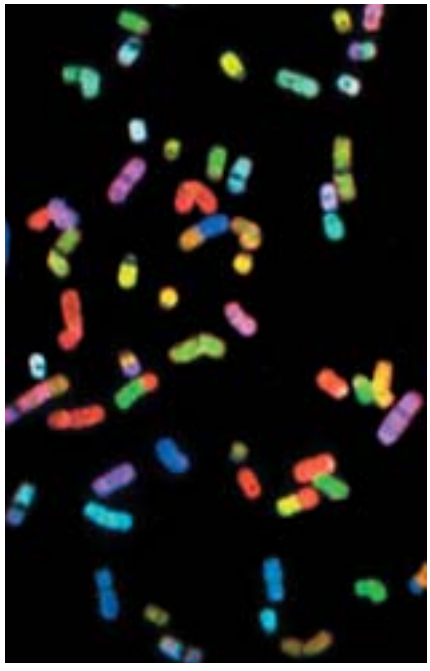
Hahn reflected on this possibility in his Boston office in January. Along with Weinberg, he has pioneered the construction of artificial tumors using mutant cancer genes. But he acknowledged that they cannot be the whole story. "The question is which comes first," he said. "Mutations or aneuploidy?"

There are at least three competing answers. Let us call them the modified dogma, the early instability theory and the all-aneuploidy theory. Encouragingly, the theories seem to be converging as they bend to accommodate new experimental results.

The modified form of the standard dogma revives an idea proposed in 1974 by Lawrence A. Loeb, now at the University of Washington. He and other geneticists have estimated that, on average, random mutation will affect just one gene in any given cell over the course of a lifetime. Something—a carcinogen, reactive oxidants, or perhaps a malfunction in the DNA duplication and repair machinery of the cell—must dramatically accelerate

ABERRANT CHROMOSOMES IN A CANCER CELL can alter the dosage of thousands of genes at once. A healthy cell (*below*) contains one pair of each of the 22 kinds of chromosomes (*distinct colors*), plus two sex chromosomes. In a malignant cell (*right*), some chromosomes contain arms of different types (*multicolored, at left edge*). Others are missing limbs (*royal blue*) or are present in the wrong number (*lime green*).

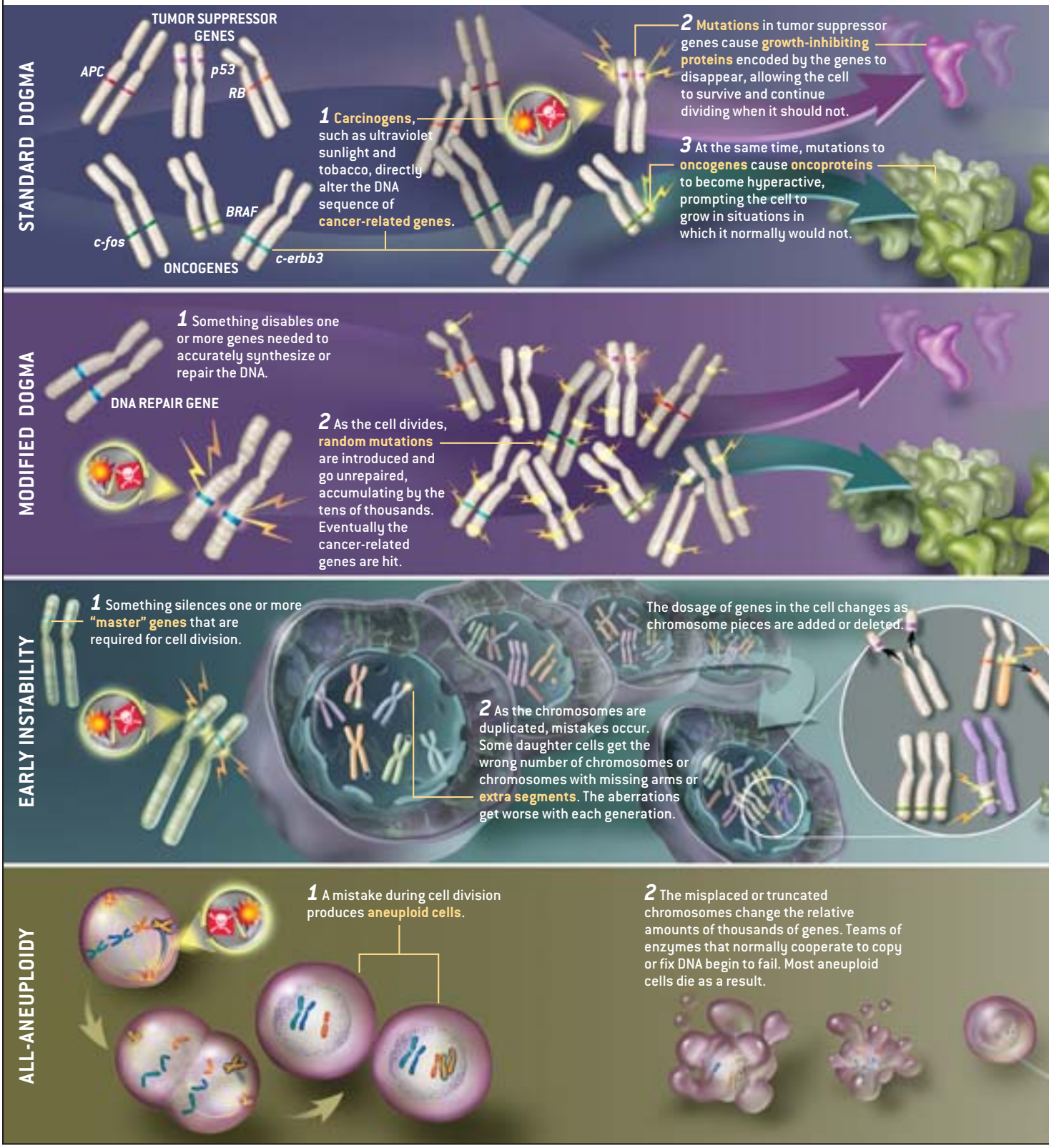




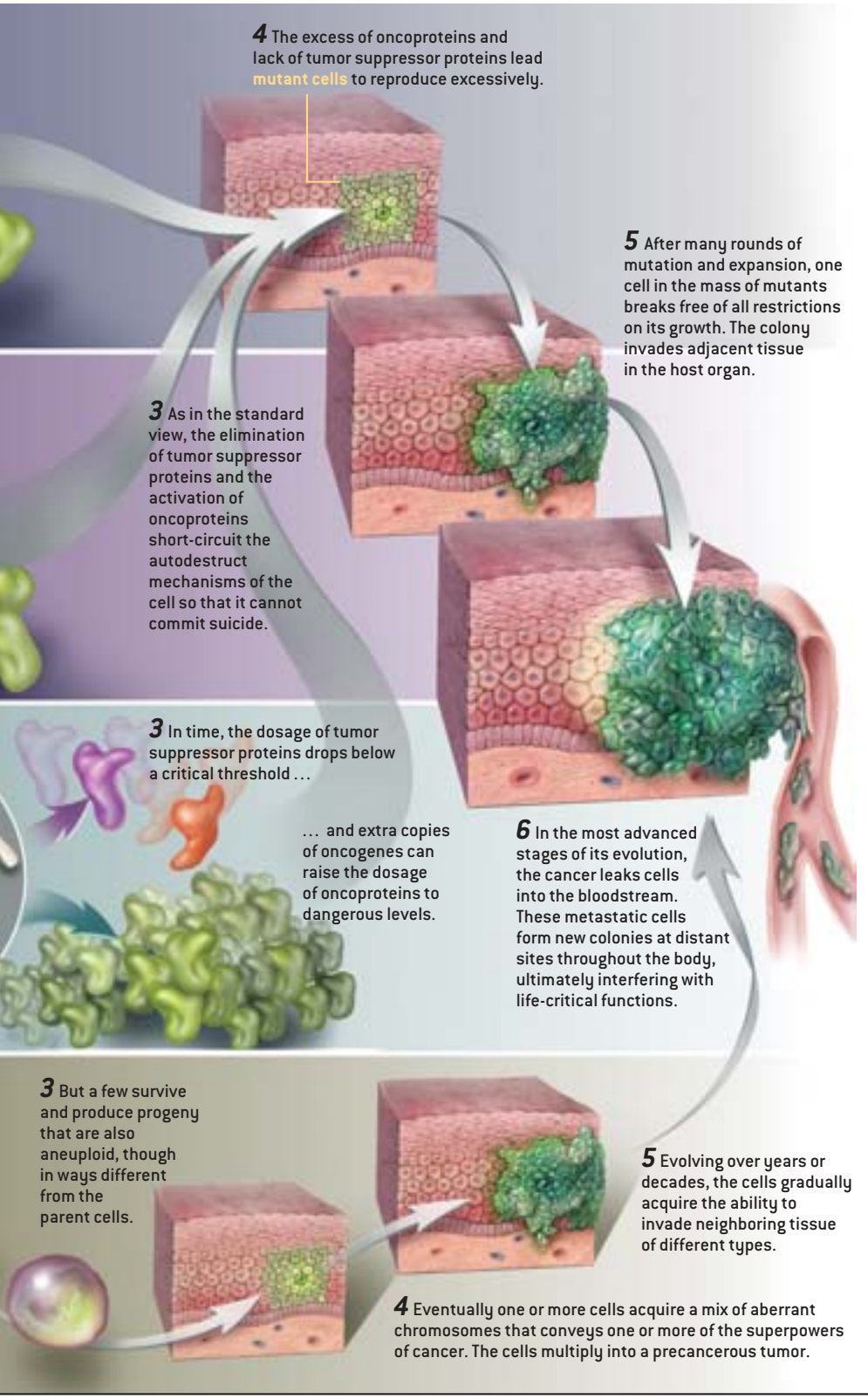
HESED M. PADILLA-NASH AND THOMAS REID *National Cancer Institute*

THE GENESIS OF CANCER: FOUR THEORIES

FOR DECADES, the most widely accepted view of how cancer begins has been that mutations to a handful of special genes eliminate tumor suppressor proteins and activate oncoproteins. More recently, three alternative theories have gained currency. One modifies the standard paradigm by postulating a dramatic increase in the accumulation of random mutations throughout the genomes of precancerous cells. Two other theories focus on the role of aneuploidy:



large-scale aberrations in the chromosomes. Aneuploidy could lead to genomic instability early on and later mutate known cancer genes. Or it may form tumors through an almost infinite variety of genetic changes.



the mutation rate, Loeb argues. "I think that is probably right," Hahn concurs. Otherwise, he says, "cells wouldn't accumulate a sufficient number of mutations to form a tumor."

Loeb believes that "early during the genesis of cancer there are enormous numbers of random mutations—10,000 to 100,000 per cell." Evidence for the theory is still slim, he acknowledges. Counting random mutations is hard; scientists must compare the genomes of individual cells letter by letter. Advances in biotechnology have only recently made that feasible.

The modified dogma would thus add a prologue to the long-accepted life history of cancer. But the most important plot points in that story are still mutations to genes that serve to increase the reproductive success of cells. Mangled and ever changing chromosomes are but fortuitous by-products.

Unstable from the Outset

CRISTOPH LENGAUER and Vogelstein of Johns Hopkins, both well-known colon cancer specialists, have proposed an alternative theory in which chromosomal instability can occur early on. The genetic flux then combines forces with natural selection to produce a benign growth that may later be converted to an invasive malignancy and life-threatening metastases.

In their hypothesis, there are several "master" genes whose function is critical for a cell to reproduce correctly. If as few as one of these genes is disabled, either by mutation or epigenetically, the cell stumbles each time it attempts the carefully choreographed dance of cell division, muddling some of the chromosomes into an aneuploid state. One result is to increase 100,000-fold the rate at which cells randomly lose one of the two alleles of their genes. For a tumor suppressor gene, a lost allele may effectively put the gene out of commission, either because the remaining copy is already mutated or because of the haploinsufficiency effect. Lengauer and Vogelstein still assume that some cancer genes must be altered before a malignancy can erupt.

In December 2002, together with Martin A. Nowak and Natalia L. Komarova

CHRISTY KRAMES

of the Institute for Advanced Study in Princeton, N.J., Lengauer and Vogelstein published a mathematical analysis that applied this theory to nonhereditary colon cancer. Even if there are as few as half a dozen master genes in the human genome, they calculated, it is very likely that a master gene will be disabled before a particular cancer gene is hit.

Calculations are fine, but only empirical evidence is persuasive. Some recent studies do support the early instability theory. In 2000 Lengauer's laboratory examined colon adenomas—benign polyps that occasionally turn malignant—and observed that more than 90 percent had extra or missing pieces of at least one chromosome. More than half had lost the long arm of chromosome 5, home to the *APC* tumor suppressor gene, long implicated in the formation of colon cancer. Other researchers have discovered similarly aberrant chromosomes in precancerous growths taken from the stomach, esophagus and breast.

The early instability theory still has some loose ends, however. How can cells with shifty chromosomes outcompete their stable counterparts? Under normal conditions, they probably do not, suggests immunologist Jarle Breivik of the University of Oslo. But in a "war zone," where a carcinogen or other stressor is continually inflicting damage to cells, normal cells stop dividing until they have completed repairs to their DNA. Genetically unstable cells get that way because their DNA repair systems are already broken. So they simply ignore the damage, keep on proliferating, and thus pull ahead, Breivik hypothesizes.

He cites an experiment in which Lengauer and his colleagues exposed human cell lines to toxic levels of a carcinogen in broiled meat. Only a few cells developed resistance and survived. All were genetically unstable before exposure to the toxin.

But what jumbles the chromosomes in the first place? No genes have yet been conclusively identified as master genes, although several strong suspects have surfaced. German A. Pihan of the University of Massachusetts Medical School and his co-workers may have uncovered a clue in their study, published in March, of 116 premalignant tumors caught before they had invaded neighboring tissues of the cervix, prostate and breast. Thirty to 72 percent of the growths contained defective centrosomes, structures that appear during cell division to help separate the newly duplicated chromosomes from the originals. Unsurprisingly, most of those cells were aneuploid. Scientists are still working out all the genes that control centrosome formation and function; any of them might be a master gene.

Aneuploidy All the Way Down

ON THE OTHER HAND, maybe cells can become malignant even before any master genes, oncogenes or tumor suppressor genes are mutated. Peter H. Duesberg and Ruhong Li of the University of California at Berkeley have put forth a third theory: nearly all cancer cells are aneuploid (leukemia being one exception) because they start that way. Lots of things can interfere with a dividing cell so that one of its daughter cells is cheated of its normal complement of 46 chromosomes and the other daughter is endowed with a bonus. Asbestos fibers, Duesberg notes, can physically disrupt the process.

Most aneuploid cells are stillborn or growth-retarded. But in the rare survivor, he suggests, the dosage of thousands of genes is altered. That corrupts teams of enzymes that synthesize and maintain DNA. Breaks appear in the double helix, destabilizing the genome further. "The more aneuploid the cell is, the more unstable it is, and the more likely it will produce new combinations of chromosomes that will allow it to grow anywhere," Duesberg explains.

Unlike the three other theories, the all-aneuploidy hypothesis predicts that the emergence and progress of a tumor are more closely connected to the assortment of chromosomes in its cells than to the mutations in the genes on those chromosomes. Some observations do seem to corroborate the idea.

In May, for instance, Duesberg, working with scientists at the University of Heidelberg, reported on experiments with normal and aneuploid hamster embryos. The more the cells deviated from the correct number of chromosomes, the faster aberrations accumulated in their chromosomes. Genomic instability rose exponentially with the degree of aneuploidy.

Thomas Reid, chief of cancer genomics at the National Cancer Institute, has obtained supporting evidence in humans from his investigation of aneuploidy in cervical and colorectal cancers. "Unequivocally, there are recurrent patterns of genomic imbalances," Reid avers. "Every single case of [nonhereditary] colorectal cancer, for example, has gains of chromosomes 7, 8, 13 or 20 or a loss of 18. In cervical cancer, aneuploidy of chromosome 3 happens very early, and those cells seem to have a selective advantage." Reid finds the average number of abnormal chromosomes increasing gradually from 0.2 in a normal cell to 12 in the cells of metastatic colon tumors.

"So I actually think Duesberg is right that aneuploidy can be the first genetic aberration in cancer cells," Reid says. "But he also argues that no gene mutations are required. This is simply not true."

Stopping Cancer at Its Roots

NEITHER THE STANDARD dogma nor any of the new theories that challenge it can fully untangle the knotted roots of

BRANCHING POINTS IN THE

1914 Boveri suggests that aberrant chromosomes may cause cancer

1927 Hermann J. Muller observes that radiation mutates cells

1951 Muller proposes theory that multiple mutations turn a cell malignant

1915 1920 1925 1930 1935

EVOLUTION OF CANCER THEORY


Muller


Vogelstein


Duesberg

1960 Discovery that an exchange of DNA between chromosomes 9 and 22 leads to chronic myelogenous leukemia

1971 Alfred G. Knudson explains different rates of inherited and spontaneous retinal cancer with the hypothesis that two "hits," or damaging mutations, are needed to disable both alleles of the *RB* gene and that one mutation can be inherited

1974 Loeb argues that random mutations must accumulate much faster than is normal inside cells that become malignant

1986 Weinberg and colleagues isolate *RB*, the first tumor suppressor gene

1990 Vogelstein and Eric R. Fearon publish a model of sequential gene mutations that lead to colon cancer

1997 Lengauer, Vogelstein and co-workers demonstrate dramatic increase in gain and loss of chromosomes in colon tumor cells and propose that chromosomal instability is a critical early event that leads to the mutation of oncogenes and tumor suppressor genes

1999 Duesberg and collaborators publish detailed theory of how aneuploidy may be sufficient to cause cancer itself, even without mutations to any particular set of genes

2002 Reid identifies recurrent patterns of aneuploidy in human cervical and colon cancers

2003 The number of identified cancer genes, now well over 100, continues to grow rapidly

1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000

From left to right: SPL (*Boveri*); HULTON-DEUTSCH COLLECTION/CORBIS (*Muller*); ALEX WONG Getty Images (*Vogelstein*); MARC GELLER (*Duesberg*)

the 100-odd diseases we call cancer and explain them as variations of a single principle. And all the theories will need to be expanded to incorporate the role of epigenetic phenomena, which may be pivotal but is still rather mysterious.

It is important to determine which of the ideas is more right than the others, because they each make different predictions about the kinds of therapy that will succeed best against the most common and lethal cancers. In the standard view, tumors are in effect addicted to the proteins produced by oncogenes and are poisoned by tumor suppressor proteins. Medicines should therefore be designed to break the addiction or supply the poison. Indeed, this strategy is exploited by some newer drugs, such as Gleevec (for rare forms of leukemia and stomach cancer) and Herceptin (for one variety of advanced breast cancer).

But all existing therapies, including Gleevec and Herceptin, fail in some patients because their tumors evolve into a resistant strain. Loeb fears that there may be no easy way around that problem. "If I am right, then within any given tumor, which contains roughly 100 million cells, there will be cells with random mutations that protect them from any treatment you can conceive," Loeb says. "So the best you can hope for is to delay the tumor's growth. You are not going to cure it."

For the elderly—who, after all, are the main victims of cancer—a sufficient delay may be as good as a cure. And even better than slowing the growth of a tumor would be to delay its formation in the first place. If Lengauer and other adherents of the early instability theory succeed in identifying master genes, then it should also be possible to make drugs that protect or restore their function. Lengauer says his group has already licensed cell lines to the pharmaceutical industry to use in drug screening.

Screening of a different kind may be the best approach if the all-aneuploidy theory is correct. There are no known means of selectively killing cells with abnormal chromosomes. But a biopsy that turns up a surfeit of aneuploid cells might warrant careful monitoring or even preventive surgery in certain cases. And Duesberg suggests that foods, drugs and chemicals should be tested to identify compounds that cause aneuploidy.

One day science will produce a definitive answer to the question of what causes cancer. It will probably be a very complicated answer, and it may force us to shift our hope from drugs that cure the disease to medicines that prevent it. Even without a clear understanding of why, doctors have discovered that a daily baby aspirin seems to prevent colon adenomas in some adults. The effect is small. But it is a step from chemotherapy toward a better alternative: chemoprevention. SA

W. Wayt Gibbs is senior writer.

MORE TO EXPLORE

Aneuploidy Precedes and Segregates with Chemical Carcinogenesis. Peter Duesberg, Ruhong Li, David Rasnick, Charlotte Rausch, Andreas Willer, Alwin Kraemer, George Yerganian and Ruediger Hehlmann in *Cancer Genetics and Cytogenetics,* Vol. 119, No. 2, pages 83–93; June 2000.

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