How Cancer Arises

An explosion of research is uncovering the long-hidden molecular underpinnings of cancer—and suggesting new therapies

by Robert A. Weinberg

How cancer develops is no longer a mystery. During the past two decades, investigators have made astonishing progress in identifying the deepest bases of the process—those at the molecular level. These discoveries are robust: they will survive the scrutiny of future generations of researchers, and they will form the foundation for revolutionary approaches to treatment. No one can predict exactly when therapies targeted to the molecular alterations in cancer cells will find wide use, given that the translation of new understanding into clinical practice is complicated, slow and expensive. But the effort is now under way.

In truth, the term "cancer" refers to more than 100 forms of the disease. Almost every tissue in the body can spawn malignancies; some even yield several types. What is more, each cancer has unique features. Still, the basic processes that produce these diverse tumors appear to be quite similar. For that reason, I will refer in this article to "cancer" in generic terms, drawing on one or another type to illustrate the rules that seem to apply universally.

The 30 trillion cells of the normal, healthy body live in a complex, interdependent condominium, regulating one another's proliferation. Indeed, normal cells reproduce only when instructed to do so by other cells in their vicinity. Such unceasing collaboration ensures that each tissue maintains a size and architecture appropriate to the body's needs.

Cancer cells, in stark contrast, violate this scheme; they become deaf to the usual controls on proliferation and follow their own internal agenda for reproduction. They also possess an even more insidious property—the ability to migrate from the site where they began, invading nearby tissues and forming masses at distant sites in the body. Tumors composed of such malignant cells become more and more aggressive over time, and they become lethal when they disrupt the tissues and organs needed for the survival of the organism as a whole.

This much is not new. But over the past 20 years, scientists have uncovered a set of basic principles that govern the development of cancer. We now know that the cells in a tumor descend from a common ancestral cell that at one point—usually decades before a tumor becomes palpable—initiated a program of inappropriate reproduction. Further, the malignant transformation of a cell comes about through the accumulation of mutations in specific classes of the genes within it. These genes provide the key to understanding the processes at the root of human cancer.

Genes are carried in the DNA molecules of the chromosomes in the cell nucleus. A gene specifies a sequence of amino acids that must be linked together to make a particular protein; the protein then carries out the work of the gene. When a gene is switched on, the cell responds by synthesizing the encoded protein. Mutations in a gene can perturb a cell by changing the amounts or the activities of the protein product.

Two gene classes, which together constitute only a small proportion of the full genetic set, play major roles in triggering cancer. In their normal configuration, they choreograph the life cycle of the cell—the intricate sequence of events by which a cell enlarges and divides. Proto-oncogenes encourage such growth, whereas tumor suppressor genes inhibit it. Collectively these two gene classes ac-

Tumor Development Occurs in Stages

The creation of a malignant tumor in epithelial tissue is depicted schematically below. Epithelial cancers are the most common malignancies and are called carcinomas. The mass seen here emerges as a result of mutations in four genes, but the number of genes involved in real tumors can vary.

GENETICALLY ALTERED CELL

HYPERPLASIA

DYSPLASIA

1 Tumor development begins when some cell (*orange*) within a normal population (*beige*) sustains a genetic mutation that increases its propensity to proliferate when it would normally rest.

2 The altered cell and its descendants continue to look normal, but they reproduce too much—a condition termed hyperplasia. After years, one in a million of these cells (*pink*) suffers another mutation that further loosens controls on cell growth.

3 In addition to proliferating excessively, the offspring of this cell appear abnormal in shape and in orientation; the tissue is now said to exhibit dysplasia. Once again, after a time, a rare mutation that alters cell behavior occurs (*purple*).

DANA BURNS-PIZER

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count for much of the uncontrolled cell proliferation seen in human cancers.

When mutated, proto-oncogenes can become carcinogenic oncogenes that drive excessive multiplication. The mutations may cause the proto-oncogene to yield too much of its encoded growth-stimulatory protein or an overly active form of it. Tumor suppressor genes, in contrast, contribute to cancer when they are inactivated by mutations. The resulting loss of functional suppressor proteins deprives the cell of crucial brakes that prevent inappropriate growth.

For a cancerous tumor to develop, mutations must occur in half a dozen or more of the founding cell's growth-controlling genes. Altered forms of yet other classes of genes may also participate in the creation of a malignancy, by specifically enabling a proliferating cell to become invasive or capable of spreading (metastasizing) throughout the body.

Signaling Systems Go Awry

Vital clues to how mutated proto-oncogenes and tumor suppressor genes contribute to cancer came from studying the roles played within the cell by the normal counterparts of these genes. After almost two decades of research, we now view the normal genetic functions with unprecedented clarity and detail.

Many proto-oncogenes code for proteins in molecular "bucket brigades" that relay growth-stimulating signals from outside the cell deep into its interior. The growth of a cell becomes deregulated when a mutation in one of its proto-oncogenes energizes a critical growth-stimulatory pathway, keeping it continuously active when it should be silent.

These pathways within a cell receive and process growth-stimulatory signals transmitted by other cells in a tissue. Such cell-to-cell signaling usually begins when one cell secretes growth factors. After release, these proteins move through the spaces between cells and bind to specific receptors—antennalike molecules—on the surface of other cells nearby. Receptors span the outer membrane of the target cells, so that one end protrudes into the extracellular space, and the other end projects into the cell's interior, its cytoplasm. When a growth-stimulatory factor attaches to a receptor, the receptor conveys a proliferative signal to proteins in the cytoplasm. These downstream proteins then emit stimulatory signals to a succession of other proteins, in a chain that ends in the heart of the cell, its nucleus. Within the nucleus, proteins known as transcription factors respond by activating a cohort of genes that help to usher the cell through its growth cycle.

Some oncogenes force cells to overproduce growth factors. Sarcomas and gliomas (cancers, respectively, of connective tissues and nonneuronal brain cells) release excessive amounts of platelet-derived growth factor. A number of other cancer types secrete too much transforming growth factor alpha. These factors act, as usual, on nearby cells, but, more important, they may also turn back and drive proliferation of the same cells that just produced them.
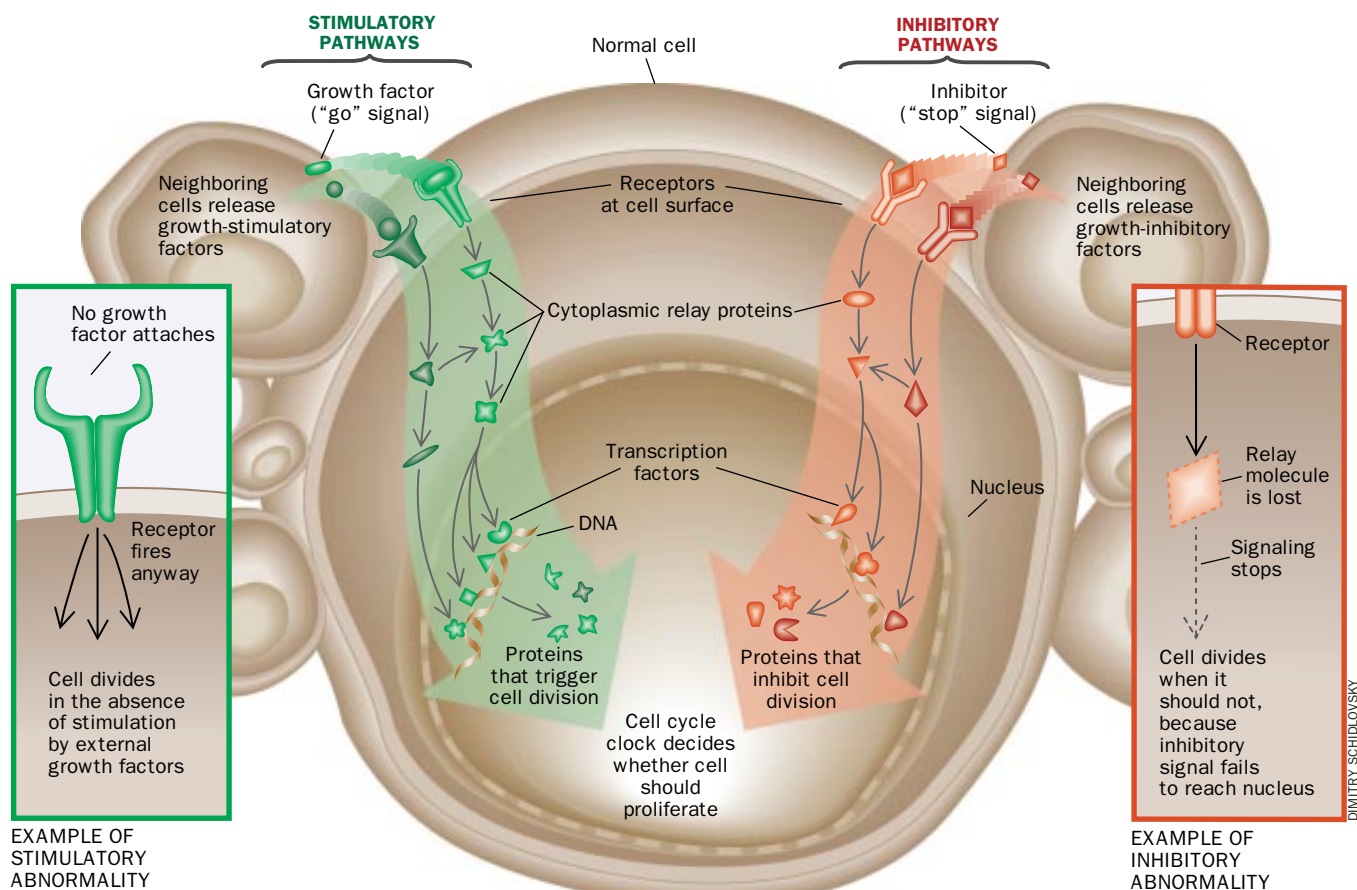
Researchers have also identified oncogenic versions of receptor genes. The aberrant receptors specified by these oncogenes release a flood of proliferative signals into the cell cytoplasm even when no growth factors are present to urge the cell to replicate. For instance, breast cancer cells often display Erb-B2 receptor molecules that behave in this way.

Still other oncogenes in human tumors perturb parts of the signal cascade found in the cytoplasm. The best understood example comes from the *ras* family of oncogenes. The proteins encoded by normal *ras* genes transmit stimulatory signals from growth factor receptors to other proteins farther down the line. The proteins encoded by mutant *ras* genes, however, fire continuously, even when growth factor receptors are not prompting them. Hyperactive Ras proteins are found in about a quarter of all human tumors, including carcinomas of the colon, pancreas and lung. (Carcinomas are by far the most common forms of cancer; they originate in epithelial cells, which line the body cavities

INVASIVE CANCER

IN SITU CANCER

BLOOD VESSEL
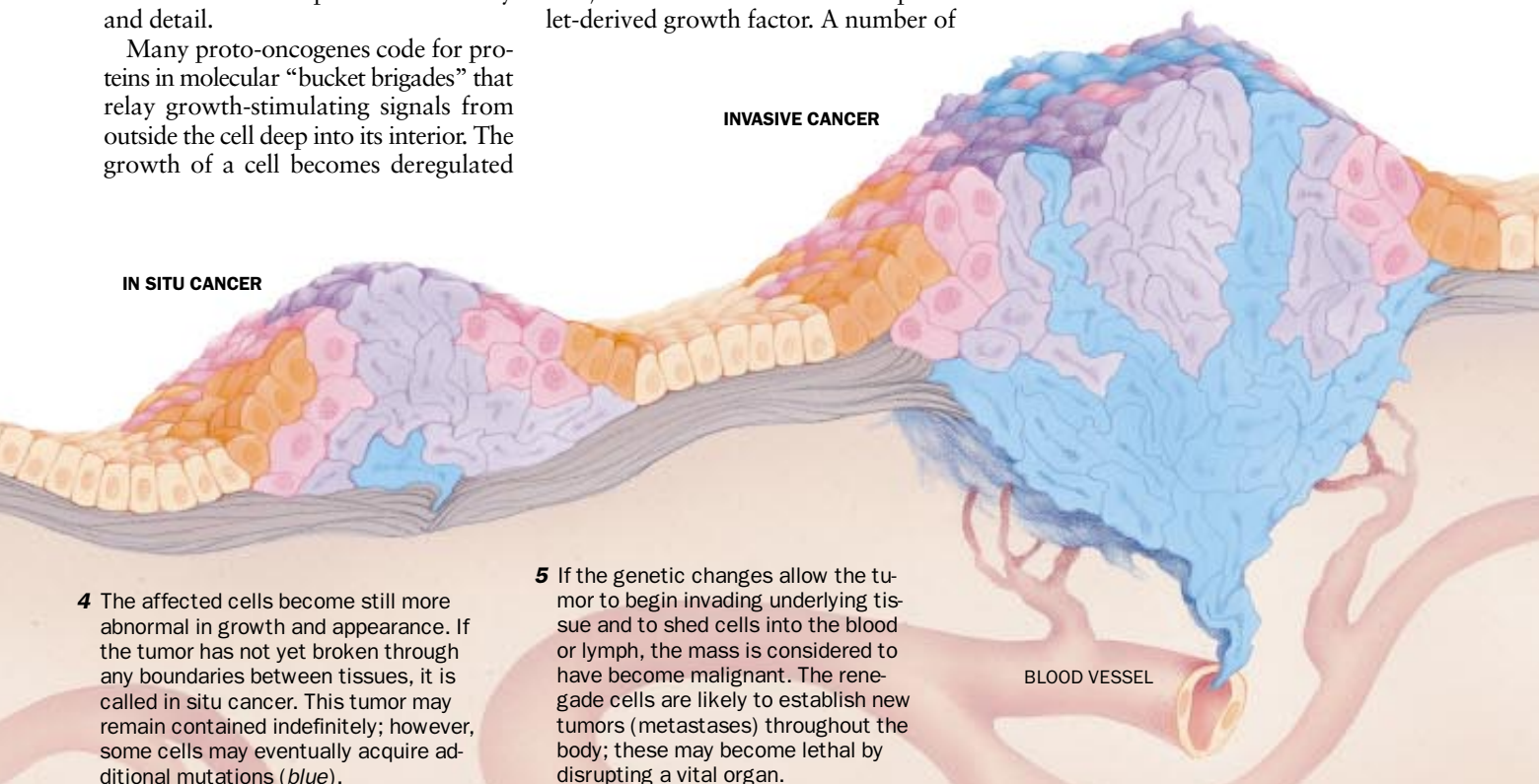
4 The affected cells become still more abnormal in growth and appearance. If the tumor has not yet broken through any boundaries between tissues, it is called in situ cancer. This tumor may remain contained indefinitely; however, some cells may eventually acquire additional mutations (*blue*).

5 If the genetic changes allow the tumor to begin invading underlying tissue and to shed cells into the blood or lymph, the mass is considered to have become malignant. The renegade cells are likely to establish new tumors (metastases) throughout the body; these may become lethal by disrupting a vital organ.

STIMULATORY PATHWAYS

Growth factor ("go" signal)

Normal cell

INHIBITORY PATHWAYS

Inhibitor ("stop" signal)

Neighboring cells release growth-stimulatory factors

Receptors at cell surface

Neighboring cells release growth-inhibitory factors

Cytoplasmic relay proteins

No growth factor attaches

Receptor

Transcription factors

Nucleus

Relay molecule is lost

Receptor fires anyway

DNA

Signaling stops

Cell divides in the absence of stimulation by external growth factors

Proteins that trigger cell division

Proteins that inhibit cell division

Cell divides when it should not, because inhibitory signal fails to reach nucleus

Cell cycle clock decides whether cell should proliferate

EXAMPLE OF STIMULATORY ABNORMALITY

EXAMPLE OF INHIBITORY ABNORMALITY

DIMITRY SCHIDLOVSKY

SIGNALING PATHWAYS in normal cells convey growth-controlling messages from the outer surface deep into the nucleus. There a molecular apparatus known as the cell cycle clock collects the messages and decides whether the cell should divide. Cancer cells often proliferate excessively because genetic mutations cause stimulatory pathways (*green*) to issue too many "go" signals or because inhibitory pathways (*red*) can no longer convey "stop" signals. A stimulatory pathway will become hyperactive if a mutation causes any component, such as a growth factor receptor (*box at left*), to issue stimulatory messages autonomously, without waiting for commands from upstream. Conversely, inhibitory pathways will shut down when some constituent, such as a cytoplasmic relay (*box at right*), is eliminated and thus breaks the signaling chain.

and form the outer layer of the skin.)

Yet other oncogenes, such as those in the *myc* family, alter the activity of transcription factors in the nucleus. Cells normally manufacture Myc transcription factors only after they have been stimulated by growth factors impinging on the cell surface. Once made, Myc proteins activate genes that force cell growth forward. But in many types of cancer, especially malignancies of the blood-forming tissues, Myc levels are kept constantly high even in the absence of growth factors.

Discovery of trunk lines that carry proliferative messages from the cell surface to its nucleus has been more than intellectually satisfying. Because these pathways energize the multiplication of malignant cells, they constitute attractive targets for scientists intent on developing new types of anticancer thera-

peutics. In an exciting turn of events, as many as half a dozen pharmaceutical companies are working on drugs designed to shut down aberrantly firing growth factor receptors. At least three other companies are attempting to develop compounds that block the synthesis of aberrant Ras proteins. Both groups of agents halt excessive signaling in cultured cancer cells, but their utility in blocking the growth of tumors in animals and humans remains to be demonstrated.

Tumor Suppressors Stop Working

To become malignant, cells must do more than overstimulate their growth-promoting machinery. They must also devise ways to evade or ignore braking signals issued by their normal neighbors in the tissue. Inhibitory messages received by a normal cell flow

to the nucleus much as stimulatory signals do—via molecular bucket brigades. In cancer cells, these inhibitory brigades may be disrupted, thereby enabling the cell to ignore normally potent inhibitory signals at the surface. Critical components of these brigades, which are specified by tumor suppressor genes, are absent or inactive in many types of cancer cells.

A secreted substance called transforming growth factor beta (TGF-ß) can stop the growth of various kinds of normal cells. Some colon cancer cells become oblivious to TGF-ß by inactivating a gene that encodes a surface receptor for this substance. Some pancreatic cancers inactivate the *DPC4* gene, whose protein product may operate downstream of the growth factor receptor. And a variety of cancers discard the *p15* gene, which codes for a protein that, in re-

sponse to signals from TGF-ß, normally shuts down the machinery that guides the cell through its growth cycle.

Tumor suppressor proteins can also restrain cell proliferation in other ways. Some, for example, block the flow of signals through growth-stimulatory circuits. One such suppressor is the product of the *NF-1* gene. This cytoplasmic molecule ambushes the Ras protein before it can emit its growth-promoting directives. Cells lacking *NF-1*, then, are missing an important counterbalance to Ras and to unchecked proliferation.

Various studies have shown that the introduction of a tumor suppressor gene into cancer cells that lack it can restore a degree of normalcy to the cells. This response suggests a tantalizing way of combating cancer—by providing cancer cells with intact versions of tumor suppressor genes they lost during tumor development. Although the concept is attractive, this strategy is held back by the technical difficulties still encumbering gene therapy for many diseases. Current procedures fail to deliver genes to a large proportion of the cells in a tumor. Until this logistical obstacle is surmounted, the use of gene therapy to cure cancer will remain a highly appealing but unfulfilled idea.

The Clock Is Struck

Over the past five years, impressive evidence has uncovered the destination of stimulatory and inhibitory pathways in the cell. They converge on a molecular apparatus in the cell nucleus that is often referred to as the cell cycle clock. The clock is the executive decision maker of the cell, and it apparently runs amok in virtually all types of human cancer. In the normal cell, the clock integrates the mixture of growth-regulating signals received by the cell and decides whether the cell should pass through its life cycle. If the answer is positive, the clock leads the process.

The cell cycle is composed of four stages. In the G_1 (gap 1) phase, the cell increases in size and prepares to copy its DNA. This copying occurs in the next stage, termed S (for synthesis), and enables the cell to duplicate precisely its complement of chromosomes. After the chromosomes are replicated, a second gap period, termed G_2, follows during which the cell prepares itself for M (mitosis)—the time when the enlarged par-

Some Genes Involved in Human Cancers

Genes known as proto-oncogenes code for proteins that stimulate cell division; mutated forms, called oncogenes, can cause the stimulatory proteins to be overactive, with the result that cells proliferate excessively. Tumor suppressor genes code for proteins that inhibit cell division. Mutations can cause the proteins to be inactivated and may thus deprive cells of needed restraints on proliferation. Investigators are still trying to decipher the specific functions of many tumor suppressor genes.

ONCOGENES

Genes for growth factors or their receptors

PDGF	Codes for platelet-derived growth factor. Involved in glioma (a brain cancer)
erb-B	Codes for the receptor for epidermal growth factor. Involved in glioblastoma (a brain cancer) and breast cancer
erb-B2	Also called *HER-2* or *neu*. Codes for a growth factor receptor. Involved in breast, salivary gland and ovarian cancers
RET	Codes for a growth factor receptor. Involved in thyroid cancer

Genes for cytoplasmic relays in stimulatory signaling pathways

Ki-ras	Involved in lung, ovarian, colon and pancreatic cancers
N-ras	Involved in leukemias

Genes for transcription factors that activate growth-promoting genes

c-myc	Involved in leukemias and breast, stomach and lung cancers
N-myc	Involved in neuroblastoma (a nerve cell cancer) and glioblastoma
L-myc	Involved in lung cancer

Genes for other kinds of molecules

Bcl-2	Codes for a protein that normally blocks cell suicide. Involved in follicular *B* cell lymphoma
Bcl-1	Also called *PRAD1.* Codes for cyclin D1, a stimulatory component of the cell cycle clock. Involved in breast, head and neck cancers
MDM2	Codes for an antagonist of the p53 tumor suppressor protein. Involved in sarcomas (connective tissue cancers) and other cancers

TUMOR SUPPRESSOR GENES

Genes for proteins in the cytoplasm

APC	Involved in colon and stomach cancers
DPC4	Codes for a relay molecule in a signaling pathway that inhibits cell division. Involved in pancreatic cancer
NF-1	Codes for a protein that inhibits a stimulatory (Ras) protein. Involved in neurofibroma and pheochromocytoma (cancers of the peripheral nervous system) and myeloid leukemia
NF-2	Involved in meningioma and ependymoma (brain cancers) and schwannoma (affecting the wrapping around peripheral nerves)

Genes for proteins in the nucleus

MTS1	Codes for the p16 protein, a braking component of the cell cycle clock. Involved in a wide range of cancers
RB	Codes for the pRB protein, a master brake of the cell cycle. Involved in retinoblastoma and bone, bladder, small cell lung and breast cancer
p53	Codes for the p53 protein, which can halt cell division and induce abnormal cells to kill themselves. Involved in a wide range of cancers
WT1	Involved in Wilms' tumor of the kidney

Genes for proteins whose cellular location is not yet clear

BRCA1	Involved in breast and ovarian cancers
BRCA2	Involved in breast cancer
VHL	Involved in renal cell cancer

ent cell finally divides in half to produce its two daughters, each of which is endowed with a complete set of chromosomes. The new daughter cells immediately enter G_1 and may go through the full cycle again. Alternatively, they may stop cycling temporarily or permanently.

The cell cycle clock programs this elaborate succession of events by means of a variety of molecules. Its two essential components, cyclins and cyclin-dependent kinases (CDKs), associate with one another and initiate entrance into the various stages of the cell cycle. In G_1, for instance, D-type cyclins bind to CDKs 4 or 6, and the resulting complexes act on a powerful growth-inhibitory molecule—the protein known as pRB.

This action releases the braking effect of pRB and enables the cell to progress into late G_1 and thence into S (DNA synthesis) phase [see b in box below].
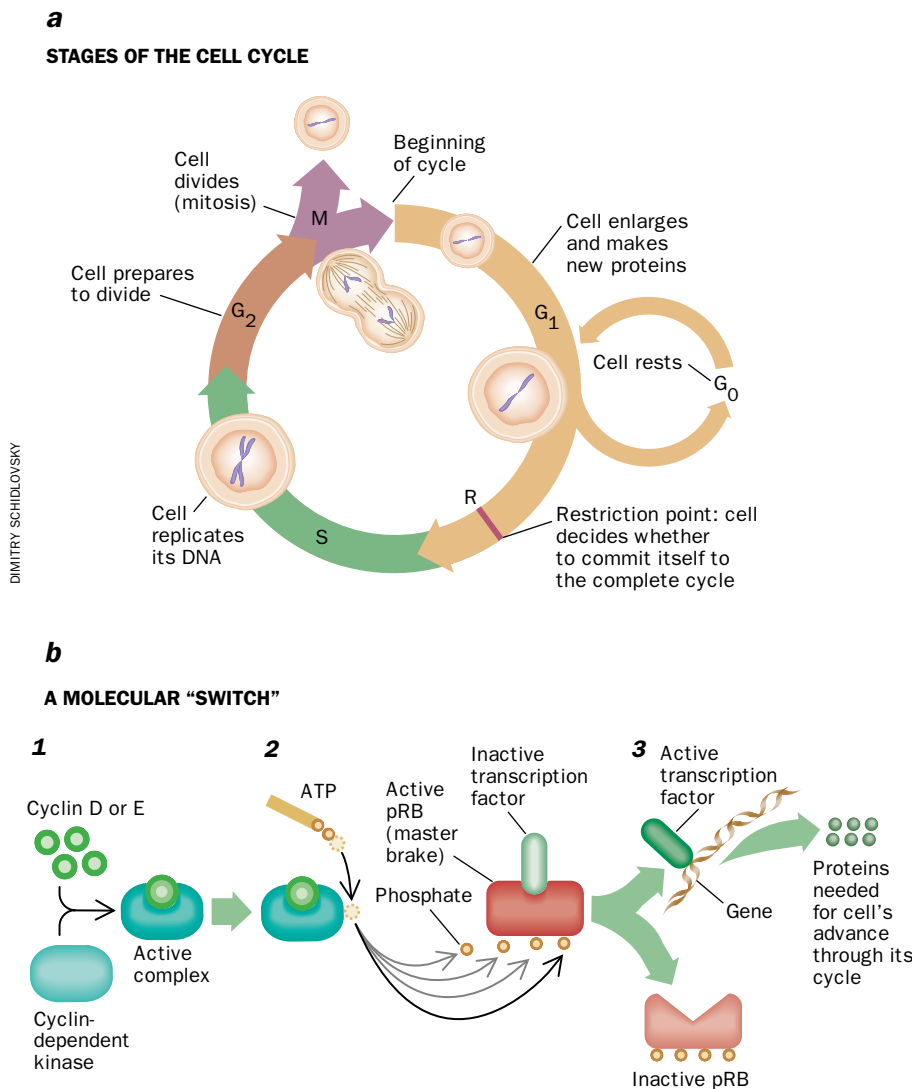
Various inhibitory proteins can restrain forward movement through the cycle. Among them are p15 (mentioned earlier) and p16, both of which block the activity of the CDK partners of cy-

The Cell Cycle Clock and Cancer

Most, perhaps all, human cancers grow inappropriately not only because signaling pathways in cells are perturbed but also because the so-called cell cycle clock becomes deranged. The clock—composed of an assembly of interacting proteins in the nucleus—normally integrates messages from the stimulatory and inhibitory pathways and, if the stimulatory messages win out, programs a cell's advance through its cycle of growth and division. Progression through the four stages of the cell cycle (a) is driven to a large extent by rising levels of proteins called cyclins: first the D type, followed by E, A and then B.

A crucial step in the cycle occurs late in G_1 at the restriction point (R), when the cell decides whether to commit itself to completing the cycle. For the cell to pass through R and enter S, a molecular "switch" must be flipped from "off" to "on." The switch works as follows (b): As levels of cyclin D and, later, cyclin E rise, these proteins combine with and activate enzymes called cyclin-dependent kinases (1). The kinases (acting as part of cyclin-kinase complexes) grab phosphate groups (2) from molecules of

a

STAGES OF THE CELL CYCLE

Cell divides (mitosis)

Beginning of cycle

M

Cell enlarges and makes new proteins

Cell prepares to divide

G_2

G_1

Cell rests — G_0

Cell replicates its DNA

S

R

Restriction point: cell decides whether to commit itself to the complete cycle

DIMITRY SCHIDLOVSKY

b

A MOLECULAR "SWITCH"

1

Cyclin D or E

Active complex

Cyclin-dependent kinase

2

ATP

Active pRB (master brake)

Phosphate

Inactive transcription factor

3

Active transcription factor

Gene

Proteins needed for cell's advance through its cycle

Inactive pRB

c

THE CELL CYCLE CLOCK IN ACTION

Growth-promoting signals issued by neighboring cells

Growth-inhibitory signals issued by neighboring cells

p27

Inactive pRB protein

Cyclin D*

Cyclin D–CDK4/6 complex

Cyclin-dependent kinase 4* or 6 (CDK4/6)

p15*

Transforming growth factor beta (an inhibitor)

Early G_1

PHASES OF CELL CYCLE

     How Cancer Arises

clin D, thus preventing the advance of the cell from G_1 into S. Another inhibitor of CDKs, termed p21, can act throughout the cell cycle. P21 is under control of a tumor suppressor protein, p53, that monitors the health of the cell, the integrity of its chromosomal DNA and the successful completion of the different steps in the cycle.

Breast cancer cells often produce excesses of cyclin D and cyclin E. In many cases of melanoma, skin cells have lost the gene encoding the braking protein p16. Half of all types of human tumors lack a functional p53 protein. And in cervical cancers triggered by infection of cells with a human papillomavirus, both the pRB and p53 proteins are fre-

quently disabled, eliminating two of the clock's most vital restraints. The end result in all these cases is that the clock begins to spin out of control, ignoring any external warnings to stop. If investigators can devise ways to impose clamps on the cyclins and CDKs active in the cell cycle, they may be able to halt cancer cells in their tracks.

ATP (adenosine triphosphate) and transfer them to a protein called pRB, the master brake of the cell cycle clock. When pRB lacks phosphates, it actively blocks cycling (and keeps the switch in the "off" position) by sequestering other proteins termed transcription factors. But after the cyclin-kinase complexes add enough phosphates to pRB, the brake stops working (3; bottom);

it releases the factors, freeing them to act on genes (3; top). The liberated factors then spur production of various proteins required for continued progression through the cell cycle.

In figure c below, the switch is placed in the larger context of the many molecular interactions that regulate the cell cycle. Flipping of the switch to "on" can be seen above the R point. Overactivity of the stimulatory proteins cyclin D, cyclin E and CDK4 have been implicated in certain human cancers. Inactivation of various inhibitory proteins has also been documented. The affected proteins include p53 (lost or ineffective in more than half of all tumor types), pRB, p16 and p15. The net effect of any of these changes is deregulation of the clock and, in turn, excessive proliferation of the cell.   —R.A.W.
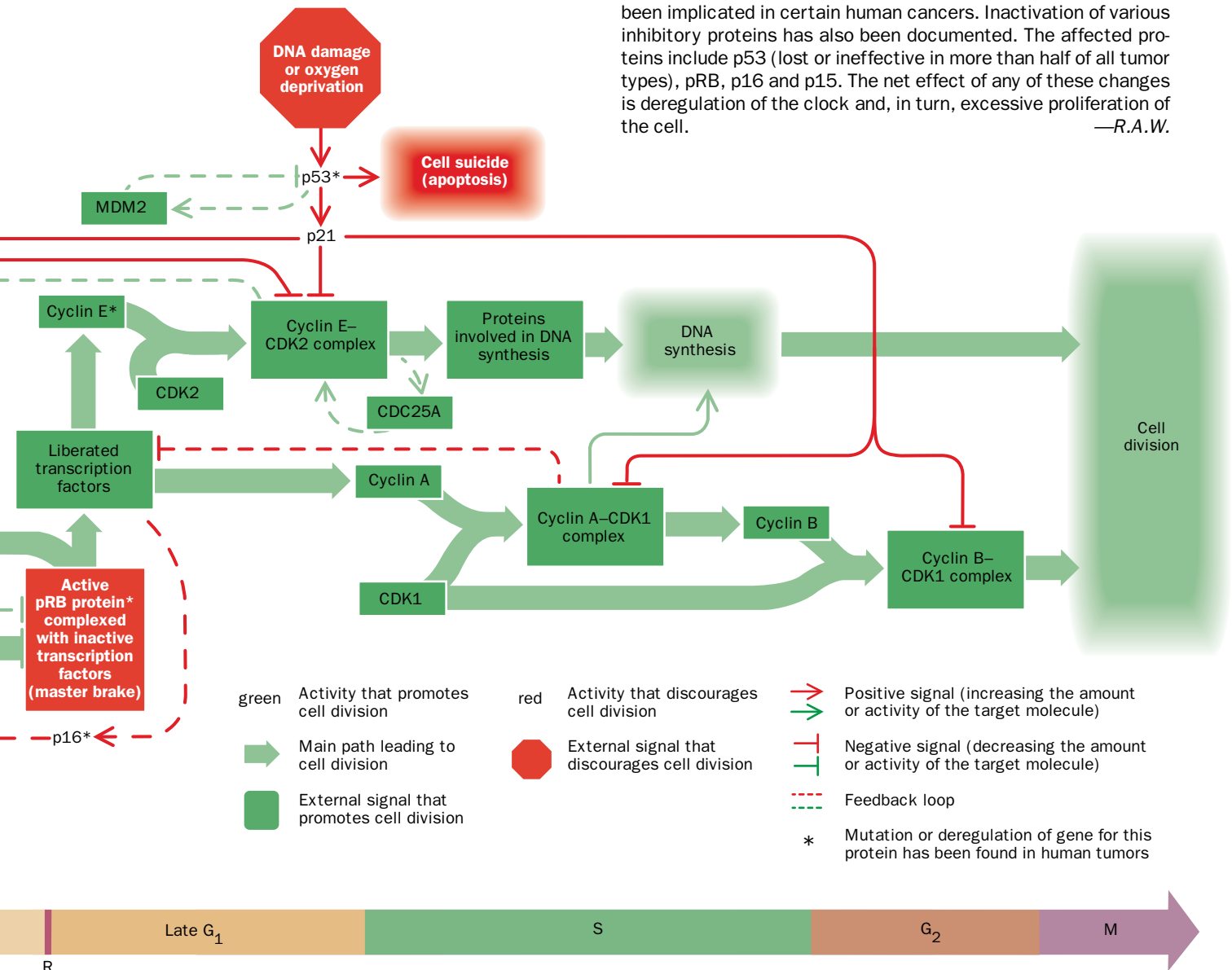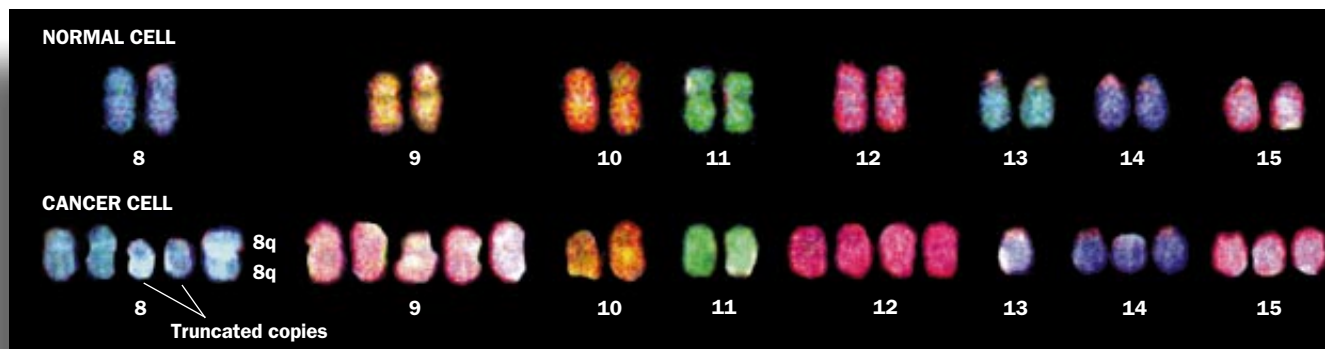
I have so far discussed two ways that our tissues normally hold down cell proliferation and avoid cancer. They prevent excess multiplication by depriving a cell of growth-stimulatory factors or, conversely, by showering it with antiproliferative factors. Still, as we have seen, cells on their way to becoming cancerous often circumvent these controls: they stimulate themselves and turn a deaf ear

whole: the potential dangers posed to the organism by carcinogenic mutations are far greater than the small price paid in the loss of a single cell. The tumors that emerge in our tissues, then, would seem to arise from the rare, genetically disturbed cell that somehow succeeds in evading the apoptotic program hardwired into its control circuitry.

Developing cancer cells devise several

evade apoptosis will be far less responsive to treatment. By the same token, it suggests that therapies able to restore a cell's capacity for suicide could combat cancer by improving the effectiveness of existing radiation and chemotherapeutic treatment strategies.

A second defense against runaway proliferation, quite distinct from the apoptotic program, is built into our cells

NORMAL CELL

8   9   10   11   12   13   14   15

CANCER CELL

8q
8q

8   9   10   11   12   13   14   15

Truncated copies

HUMAN CHROMOSOMES from a normal dividing cell (*top*) occur as identical pairs; those numbered 8 to 18 are shown. Chromosomes from a cervical cancer cell, in contrast, display many abnormalities (*bottom*). Chromosome 8, for instance, exhibits three disturbances: gain of copy number; deletion of genetic material from individual copies; and breakage followed by joining of segments that do not belong together (*far right in 8*). Copy loss, as in chromosome 13, is also common. These various changes can favor tumor progression if they activate an oncogene, increase the copies of an oncogene or eliminate a tumor suppressor gene. The images were generated by spectral karyotyping, a new method for analyzing chromosomes.

to inhibitory signals. Prepared for such eventualities, the human body equips cells with certain backup systems that guard against runaway division. But additional mutations in the cell's genetic repertoire can overcome even these defenses and contribute to cancer.

Fail-Safe Systems Fail

One such backup system, present in each human cell, provokes the cell to commit suicide (undergo "apoptosis") if some of its essential components are damaged or if its control systems are deregulated. For example, injury to chromosomal DNA can trigger apoptosis. Further, recent work from a number of laboratories indicates that creation of an oncogene or the disabling of a tumor suppressor gene within a cell can also induce this response. Destruction of a damaged cell is bad for the cell itself but makes sense for the body as a

means of evading apoptosis. The p53 protein, among its many functions, helps to trigger cell suicide; its inactivation by many tumor cells reduces the likelihood that genetically troubled cells will be eliminated. Cancer cells may also make excessive amounts of the protein Bcl-2, which wards off apoptosis efficiently.

Recently scientists have realized that this ability to escape apoptosis may endanger patients not only by contributing to the expansion of a tumor but also by making the resulting tumors resistant to therapy. For years, it was assumed that radiation therapy and many chemotherapeutic drugs killed malignant cells directly, by wreaking widespread havoc in their DNA. We now know that the treatments often harm DNA to a relatively minor extent. Nevertheless, the affected cells perceive that the inflicted damage cannot be repaired easily, and they actively kill themselves. This discovery implies that cancer cells able to

as well. This mechanism counts and limits the total number of times cells can reproduce themselves.

Cells Become Immortal

Much of what is known about this safeguard has been learned from studies of cells cultured in a petri dish. When cells are taken from a mouse or human embryo and grown in culture, the population doubles every day or so. But after a predictable number of doublings—50 to 60 in human cells—growth stops, at which point the cells are said to be senescent. That, at least, is what happens when cells have intact *RB* and *p53* genes. Cells that sustain inactivating mutations in either of these genes continue to divide after their normal counterparts enter senescence. Eventually, though, the survivors reach a second stage, termed crisis, in which they die in large numbers. An occasional cell in this dying population, however, will escape crisis and become immortal: it and its descendants will multiply indefinitely.

These events imply the existence of a mechanism that counts the number of doublings through which a cell population has passed. During the past several years, scientists have discovered the molecular device that does this counting. DNA segments at the ends of chromo-

somes, known as telomeres, tally the number of replicative generations through which cell populations pass and, at appropriate times, initiate senescence and crisis. In so doing, they circumscribe the ability of cell populations to expand indefinitely [see "Telomeres, Telomerase and Cancer," by Carol W. Greider and Elizabeth H. Blackburn; SCIENTIFIC AMERICAN, February].
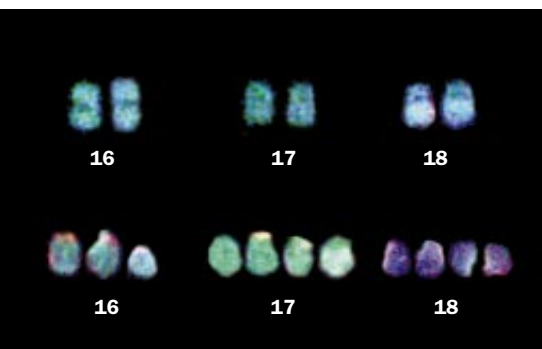
Like the plastic tips on shoelaces, the telomere caps protect chromosomal ends from damage. In most human cells, telomeres shorten a bit every time chromosomes are replicated during the S phase of the cell cycle. Once the telomeres shrink below some threshold length, they sound an alarm that instructs cells to enter senescence. If cells bypass senescence, further shrinkage of the telomere will eventually trigger crisis: extreme shortening of the telomeres will cause the chromosomes in a cell to fuse with one another or to break apart, creating genetic chaos that is fatal to the cell.

If the telomere-based counting system operated properly in cancerous cells, their excessive proliferation would be aborted long before tumors became very large. Dangerous expansion would be stemmed by the senescence program or, if the cell evaded that blockade, by disruption of the chromosomal array at crisis. But this last defense is breached during the development of most cancer cells, overcome by activation of a gene that codes for the enzyme telomerase.

This enzyme, virtually absent from most healthy cell types but present in almost all tumor cells, systematically replaces telomeric segments that are usually trimmed away during each cell cycle. In so doing, it maintains the integrity of the telomeres and thereby enables

cells to replicate endlessly. The resulting cell immortality can be troublesome in a couple of ways. Obviously, it allows tumors to grow large. It also gives precancerous or already cancerous cells time to accumulate additional mutations that will increase their ability to replicate, invade and ultimately metastasize.

From the point of view of a cancer cell, production of a single enzyme is a clever way to topple the mortality barrier. Yet dependence on one enzyme may represent an Achilles' heel as well. If telomerase could be blocked in cancer cells, their telomeres would once again shrink whenever they divided, pushing these cells into crisis and death. For that reason, a number of pharmaceutical firms are attempting to develop drugs that target telomerase.

Why Some Cancers Appear Early

It normally takes decades for an incipient tumor to collect all the mutations required for its malignant growth. In some individuals, however, the time for tumor development is clearly compressed; they contract certain types of cancer decades before the typical age of onset of these cancers. How can tumor formation be accelerated?

In many cases, this early onset is explained by the inheritance from one or the other parent of a mutant cancer-causing gene. As a fertilized egg begins to divide and replicate, the set of genes provided by the sperm and egg is copied and distributed to all the body's cells. Now a typically rare event—a mutation in a critical growth-controlling gene—becomes ubiquitous, because the mutation is implanted in all the body's cells, not merely in some randomly stricken cell. In other words, the process of tumor formation leapfrogs over one of its early, slowly occurring steps, accelerating the process as a whole. As a consequence, tumor development, which usually requires three or four decades to reach completion, may culminate in one or two. Because such mutant genes can pass from generation to generation, many members of a family may be at risk for the early development of cancer.

An inherited form of colon cancer provides a dramatic example. Most cases of colon cancer occur sporadically, the results of random genetic events occurring during a person's lifetime. In certain families, however, many individuals are af-

flicted with early-onset colonic tumors, preordained by an inherited gene. In the sporadic cases, a rare mutation silences a tumor suppressor gene called *APC* in an intestinal epithelial cell. The resulting proliferation of the mutant cell yields a benign polyp that may eventually progress to a malignant carcinoma. But defective forms of *APC* may pass from parents to children in certain families. Members of these families develop hundreds, even thousands of colonic polyps during the first decades of life, some of which are likely to become transformed into carcinomas.

The list of familial cancer syndromes that are now traceable directly to inheritance of mutant tumor suppressor genes is growing. For instance, inherited defective versions of the gene for *pRB* often lead to development of an eye cancer—retinoblastoma—in children; later in life the mutations account for a greatly increased risk of osteosarcomas (bone cancers). Mutant inherited versions of the *p53* tumor suppressor gene yield tumors at multiple sites, a condition known as the Li-Fraumeni syndrome (named in part for Frederick Li, co-author of "What Causes Cancer?", page 80). And the recently isolated *BRCA1* and *BRCA2* genes seem to account for the bulk of familial breast cancers, encompassing as many as 20 percent of all premenopausal breast cancers in this country and a substantial proportion of familial ovarian cancers as well.

Early onset of tumors is sometimes explained by inheritance of mutations in another class of genes as well. As I implied earlier, most people avoid cancer until late in life or indefinitely because they enter the world with pristine genes. During the course of a lifetime, however, our genes are attacked by carcinogens imported into our bodies from the environment and also by chemicals produced in our own cells. And genetic errors may be introduced when the enzymes that replicate DNA during cell cycling make copying mistakes. For the most part, such errors are rapidly corrected by a repair system that operates in every cell. Should the repair system slip up and fail to erase an error, the damage will become a permanent mutation in one of the cell's genes and in that same gene in all descendant cells.

The system's high repair efficiency is one reason many decades can pass before all the mutations needed for a ma-

lignancy to develop will, by chance, come together within a single cell. Certain inherited defects, though, can accelerate tumor development through a particularly insidious means: they impair the operation of proteins that repair damaged DNA. As a result, mutations that would normally accumulate slowly will appear with alarming frequency throughout the DNA of cells. Among the affected genes are inevitably those controlling cell proliferation.

Such is the case in another inherited colon cancer, hereditary nonpolyposis colon cancer. Afflicted individuals make defective versions of a protein responsible for repairing the copying mistakes made by the DNA replication apparatus. Because of this impairment, colonic cells cannot fix DNA damage efficiently; they therefore collect mutations rapidly, accelerating cancer development by two decades or more. People affected by another familial cancer syndrome, xeroderma pigmentosum, have inherited a defective copy of a gene that directs the repair of DNA damaged by ultraviolet rays. These patients are prone to several types of sunlight-induced skin cancer.

Similarly, cells of people born with a defective *ATM* gene have difficulty recognizing the presence of certain lesions in the DNA and mobilizing the appropriate repair response. These people are susceptible to neurological degeneration, blood vessel malformation and a variety of tumors. Some researchers have proposed that as many as 10 percent of inherited breast cancers may arise in patients with a defective copy of this gene.

Over the next decade, the list of cancer susceptibility genes will grow dramatically, one of the fruits of the Human Genome Project (which seeks to identify every gene in the human cell). Together with the increasingly powerful tools of DNA analysis, knowledge of these genes will enable us to predict which members of cancer-prone families are at high risk and which have, through good fortune, inherited intact copies of these genes.

Beyond Proliferation

Although we have learned an enormous amount about the genetic basis of runaway cell proliferation, we still know rather little about the mutant genes that contribute to later stages of tumor development, specifically those that allow tumor cells to attract blood vessels for nourishment, to invade nearby tissues and to metastasize. But research in these areas is moving rapidly. (Judah Folkman describes the ingenuity of tumor cells in generating their own blood supply in "Fighting Cancer by Attacking Its Blood Supply," on page 150. Erkki Ruoslahti takes up metastasis in "How Cancer Spreads" on page 72.)

We are within striking distance of writing the detailed life histories of many human tumors from start to life-threatening finish. These biographies will be written in the language of genes and molecules. Within a decade, we will know with extraordinary precision the succession of events that constitute the complex evolution of normal cells into highly malignant, invasive derivatives.

By then, we may come to understand why certain localized masses never progress beyond their benign, noninvasive form to confront us with aggressive malignancy. Such benign growths can be found in almost every organ of the body. Perhaps we will also discern why certain mutant genes contribute to the formation of some types of cancer but not others. For example, mutant versions of the *RB* tumor suppressor gene appear often in retinoblastoma, bladder carcinoma and small cell lung carcinoma but are seen only occasionally in breast and colon carcinomas. Very likely, many of the solutions to these mysteries will flow from research in developmental biology (embryology). After all, the genes that govern embryonic development are, much later, the sources of our malignancies.

By any measure, the amount of information gathered over the past two decades about the origins of cancer is without parallel in the history of biomedical research. Some of this knowledge has already been put to good use, to build molecular tools for detecting and determining the aggressiveness of certain types of cancer, as David Sidransky discusses in "Advances in Cancer Detection," on page 104. Still, despite so much insight into cause, new curative therapies have so far remained elusive. One reason is that tumor cells differ only minimally from healthy ones; a minute fraction of the tens of thousands of genes in a cell suffers damage during malignant transformation. Thus, normal friend and malignant foe are woven of very similar cloth, and any fire directed against the enemy may do as much damage to normal tissue as to the intended target.

Yet the course of the battle is changing. The differences between normal and cancer cells may be subtle, but they are real. And the unique characteristics of tumors provide excellent targets for intervention by newly developed drugs [see the section "Therapies of the Future," beginning on page 135]. The development of targeted anticancer therapeutics is still in its infancy. This enterprise will soon move from hit-or-miss, serendipitous discovery to rational design and accurate targeting. I suspect that the first decade of the new century will reward us with cancer therapies that earlier generations could not have dreamed possible. Then this nation's long investment in basic cancer research will begin to pay off handsomely. **SA**

The Author

ROBERT A. WEINBERG is Member of the Whitehead Institute for Biomedical Research and a professor of biology at the Massachusetts Institute of Technology, where he earned his doctoral degree in biology in 1969. His laboratory was instrumental in isolating the first human oncogene and the first human tumor suppressor gene. Weinberg, a member of the National Academy of Sciences, has won many awards for his contributions to the understanding of cancer genetics, most recently the G.H.A. Clowes Memorial Award of the American Association for Cancer Research. This is his fourth article for *Scientific American*.

Further Reading

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How Cancer Arises