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

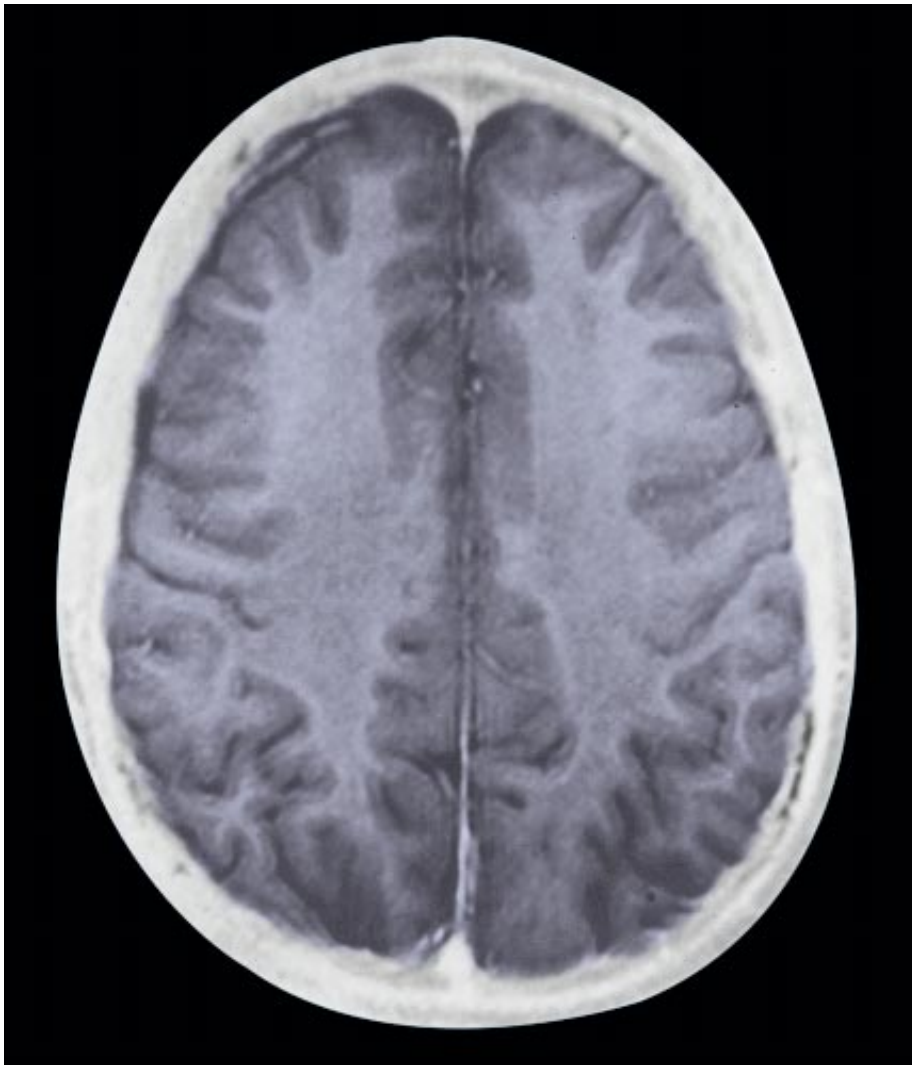
Patients stricken with cancer feel as if they have been invaded by an alien force. Yet malignancies arise from our own tissue. In fact, the weight of evidence today indicates that cancers generally derive from a single cell that is changed dramatically by a series of genetic alterations.

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.*

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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

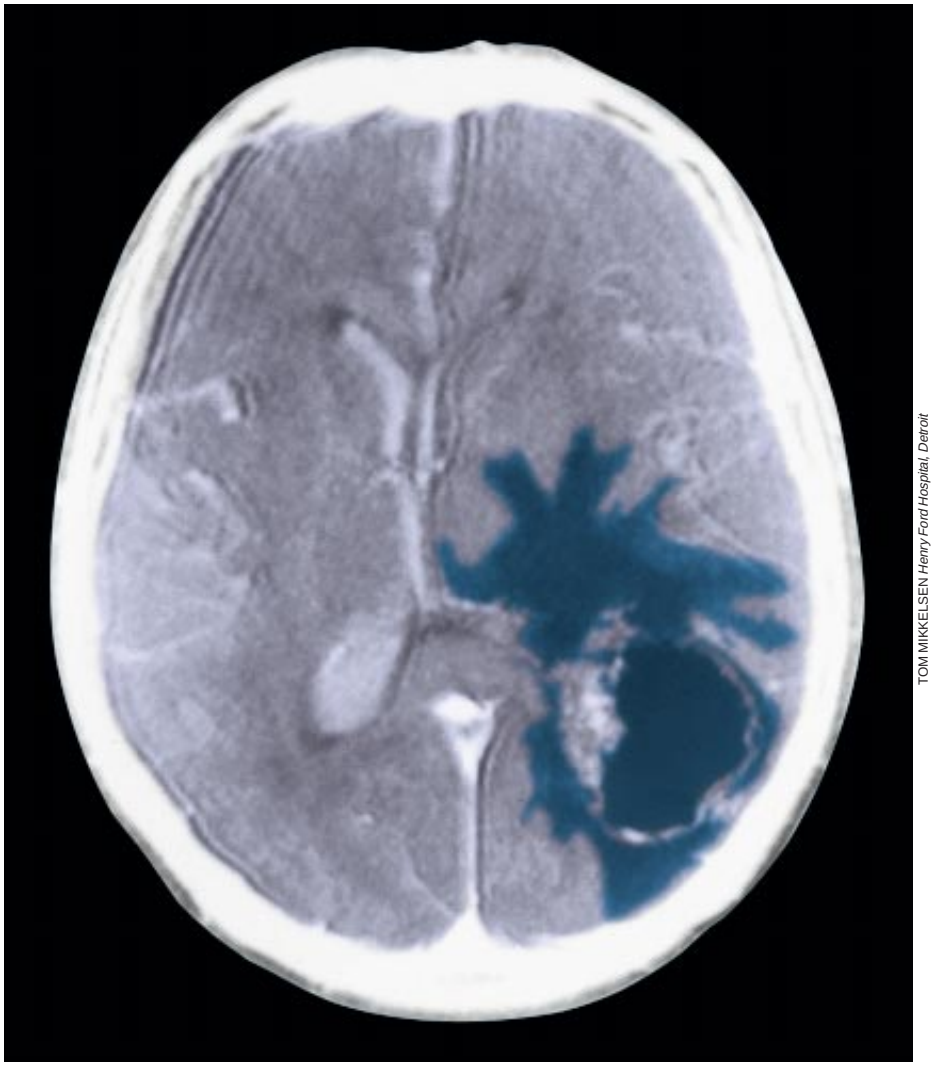
Quite different evidence that genes had a role to play came from observations that some extended families suffered an unusually high incidence of certain cancers. When particular diseases "run" in families in predictable patterns, an inherited defect is usually at fault.

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.

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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-

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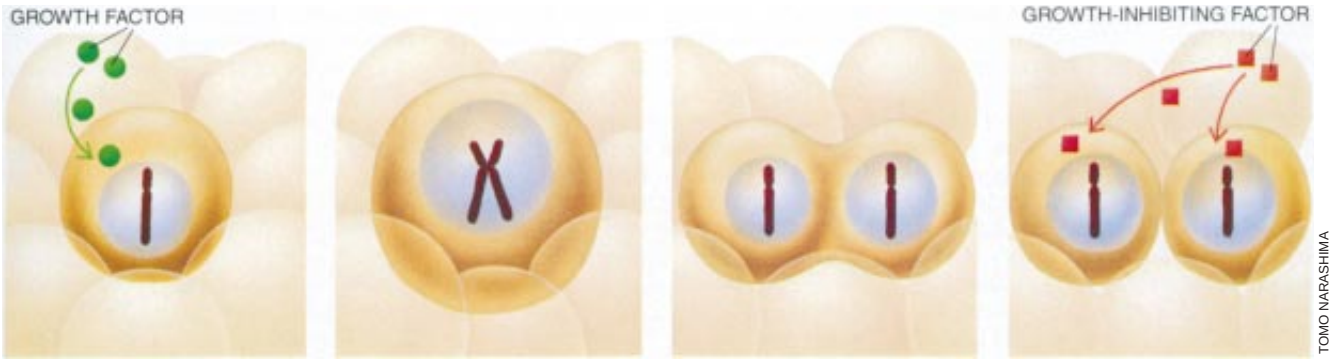
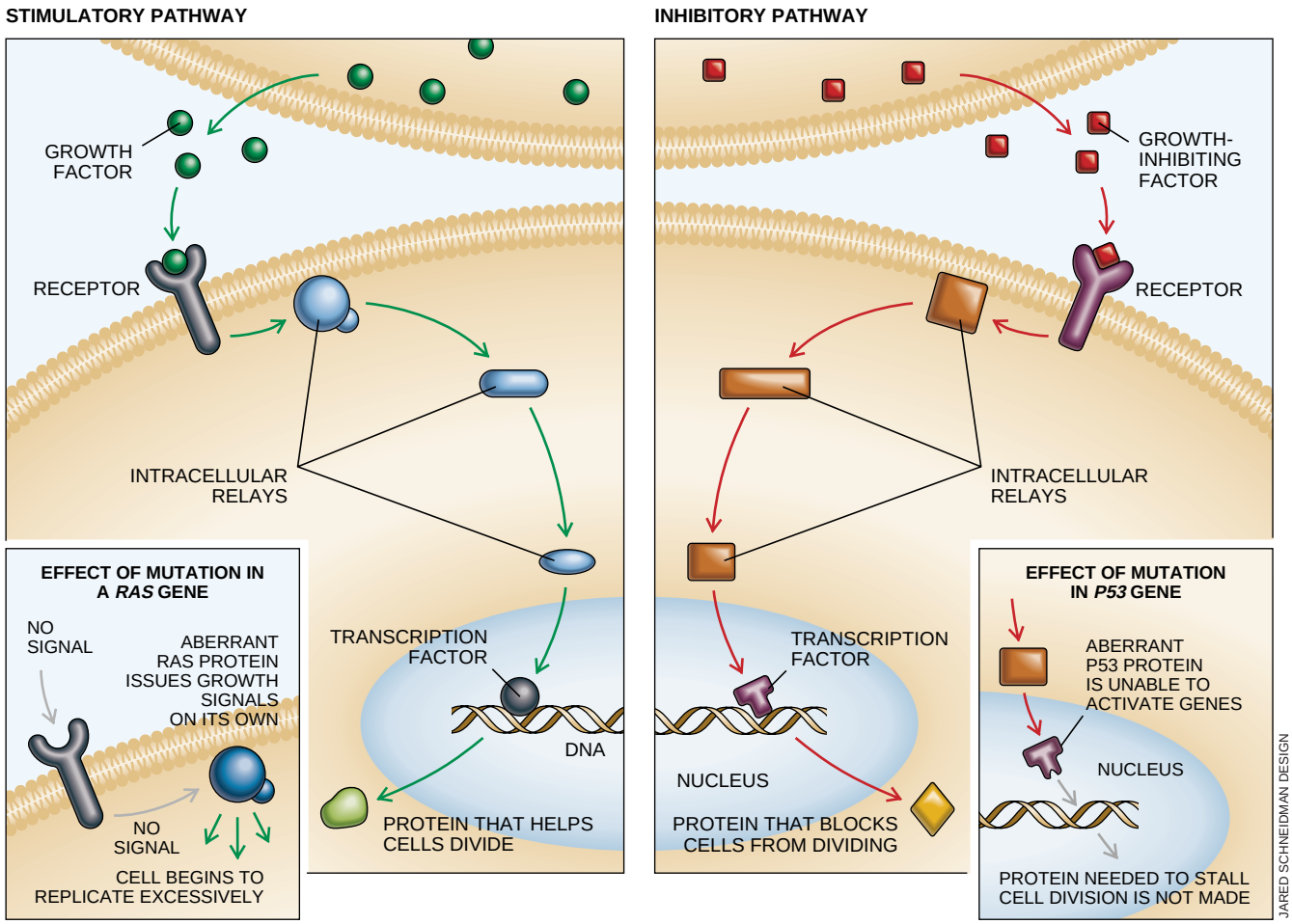
volved, they would accumulate in one cell and its direct descendants.

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*).

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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.

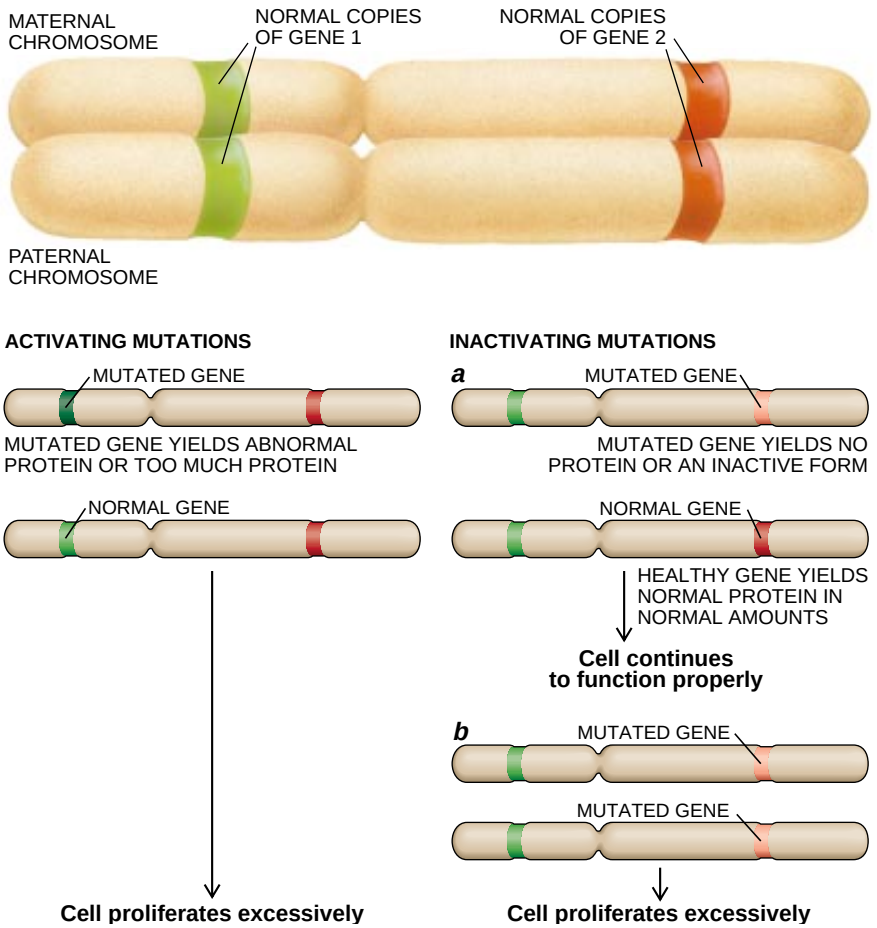
The Genetics of Colon Cancer

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

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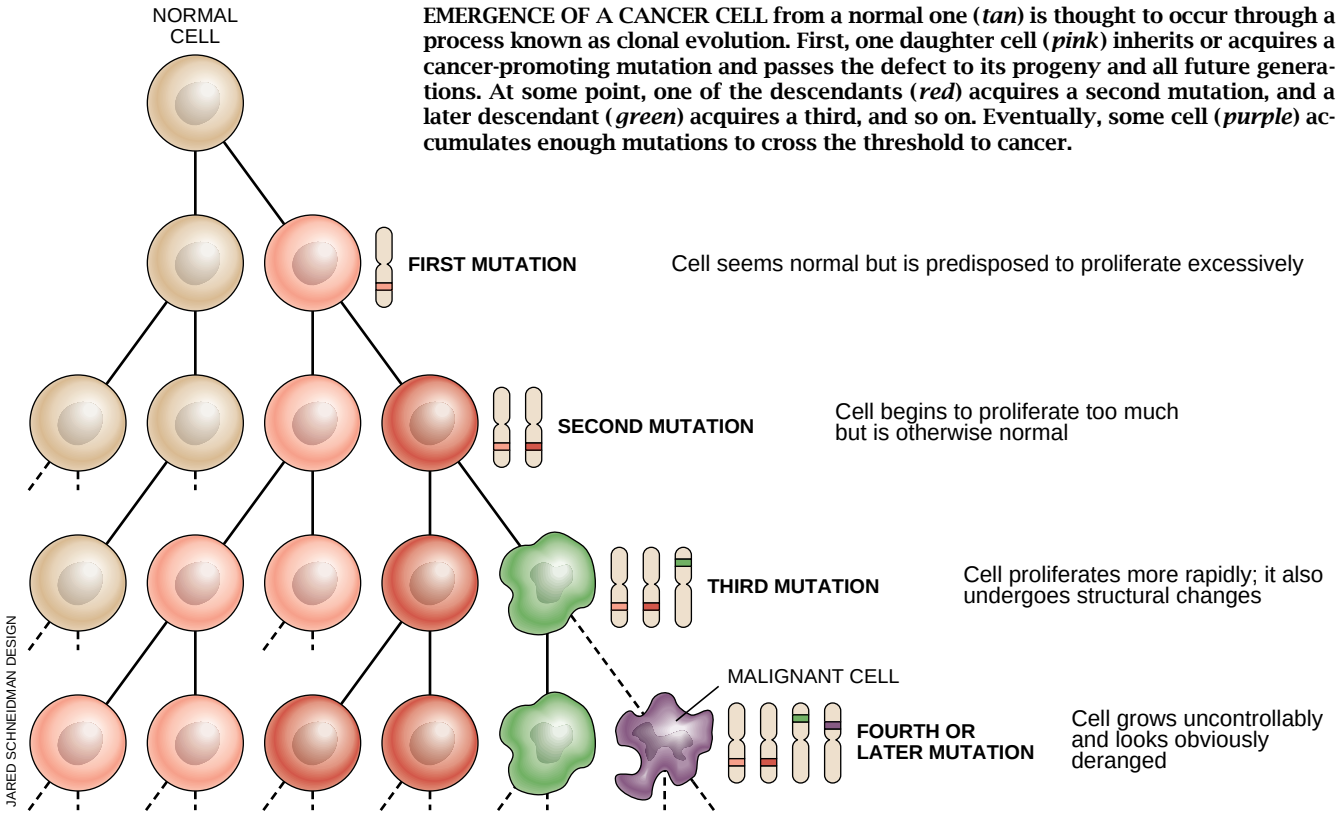

EMERGENCE OF A CANCER CELL from a normal one (*tan*) is thought to occur through a process known as clonal evolution. First, one daughter cell (*pink*) inherits or acquires a cancer-promoting mutation and passes the defect to its progeny and all future generations. At some point, one of the descendants (*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,

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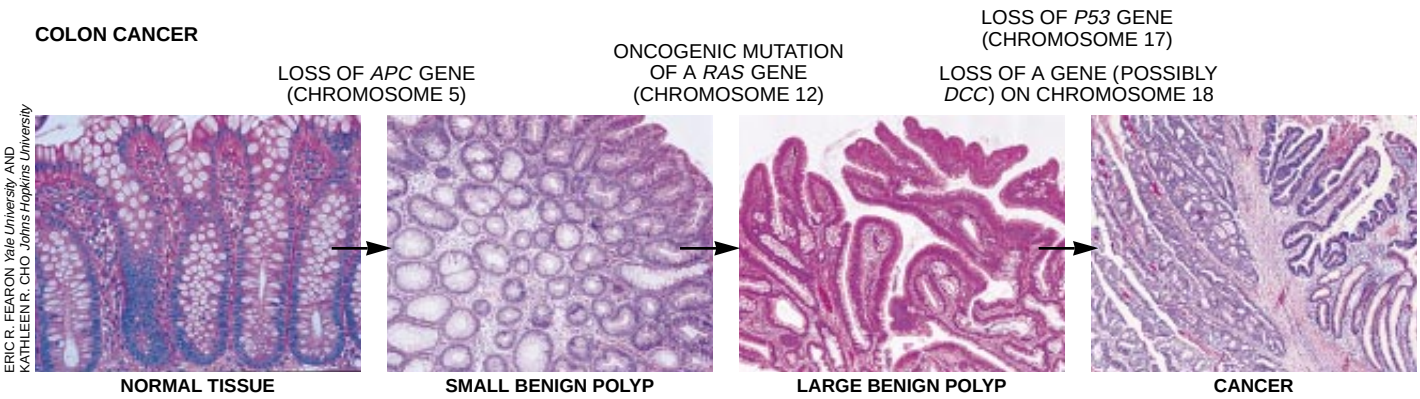
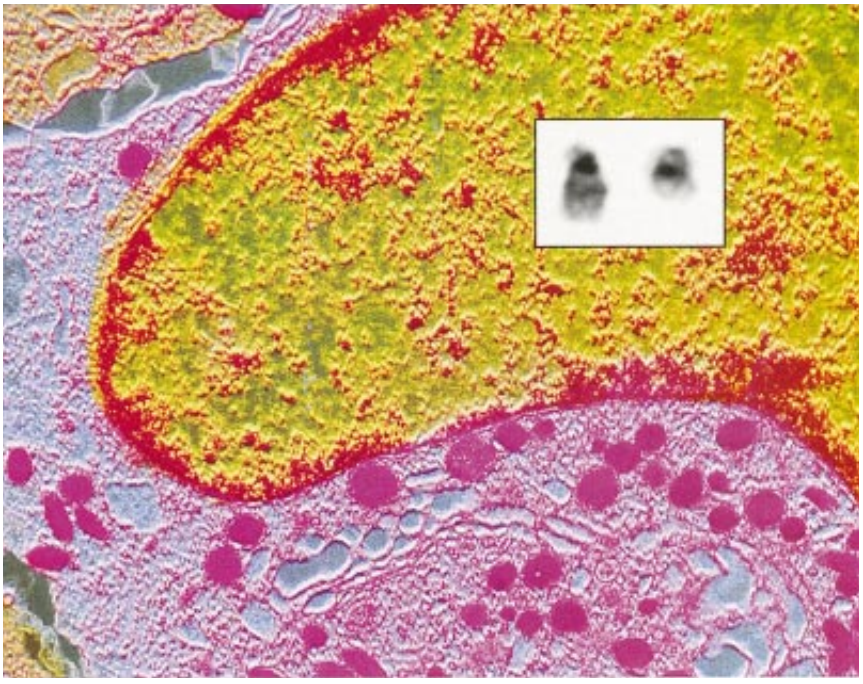


ERIC R. FEARON *Yale University* AND KATHLEEN R. CHO *Johns Hopkins University*

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-

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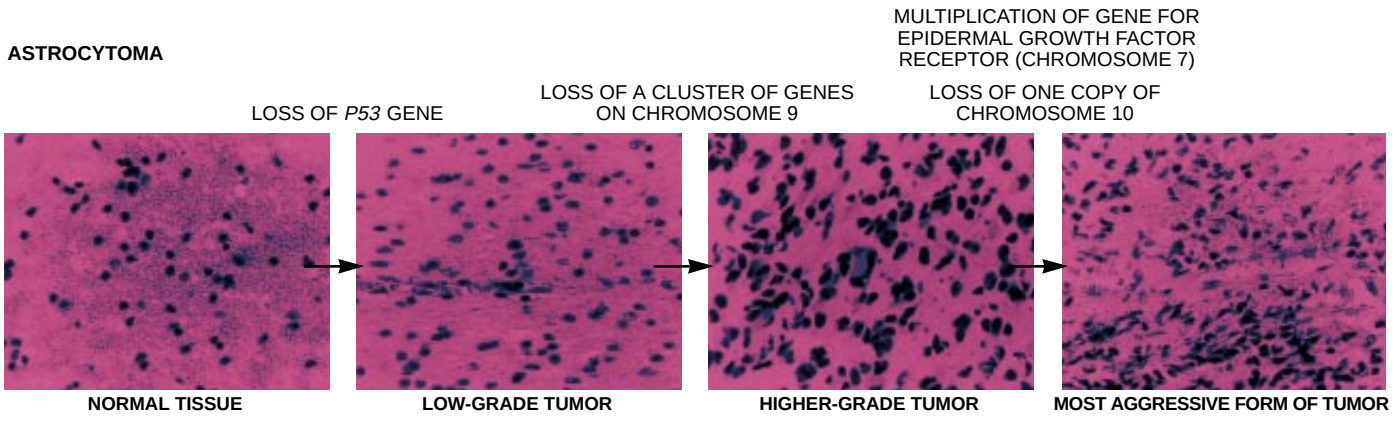

form (*right*). Other genes not listed here play roles as well. Unless otherwise indicated, the term "gene loss" indicates that both copies of a tumor suppressor gene have been damaged or deleted. The images show magnified slices of tissue.

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

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