Horizons Of Cancer Research

PROGRESS AND PROSPECTS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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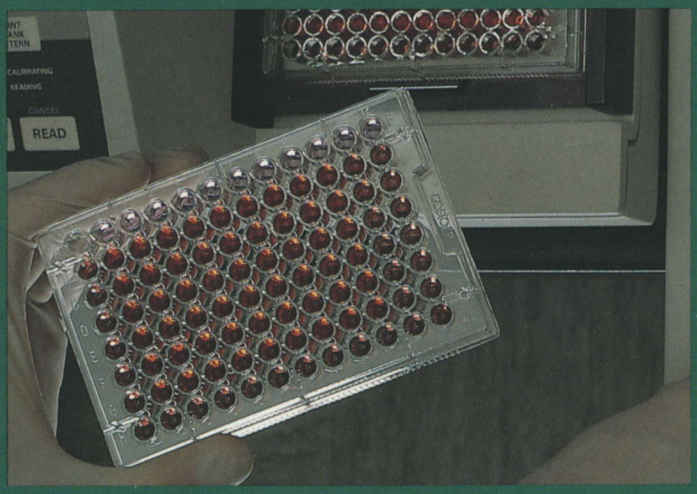
BASIC RESEARCH



"You can't go to a cancer research meeting these days without finding many people in a state of great exhilaration," says Dr. Janet Rowley, an expert on cancer genetics at the University of Chicago's Beverley E. Duchossis Cancer Research Center.

The fervor stems from a number of rapid-fire discoveries in the past ten years that pinpoint flaws at specific chromosomal sites as the cause of many cancers. These genes seem to govern cell growth and foster cancer development when they are switched "on" or "off" at the wrong times.

Scientists have suspected for decades that the root of a cancer cell's wayward behavior lies in the genetic machinery of the cell.

"In the past few years, five different cancer research areas — viruses, oncogenes, growth factors, growth regulation, and chemical carcinogenesis — have all come together," says Dr. George Vande Woude, of the NCI-Frederick Cancer Research Facility in Frederick, Maryland. "Their common language is the genes that are the molecular basis of cancer."

Tracing Cancer To Flawed And Wayward Genes

By Margie Patlak

Cancer patients deal not only with the medical realities of a diagnosis of cancer, but with gnawing questions like, "Why did it happen to me?" and, "Where did it come from?" With time, they may worry about whether other family members are at risk. Young people with cancer wonder if they will ever be able to have children, and whether their children might inherit a risk of cancer. Some of the remarkable scientific advances of the last seventeen years in basic cancer research begin to answer some of these questions. Thanks to advances in molecular biology, scientists are pinpointing the kinds of changes that signal the development of many forms of cancer.

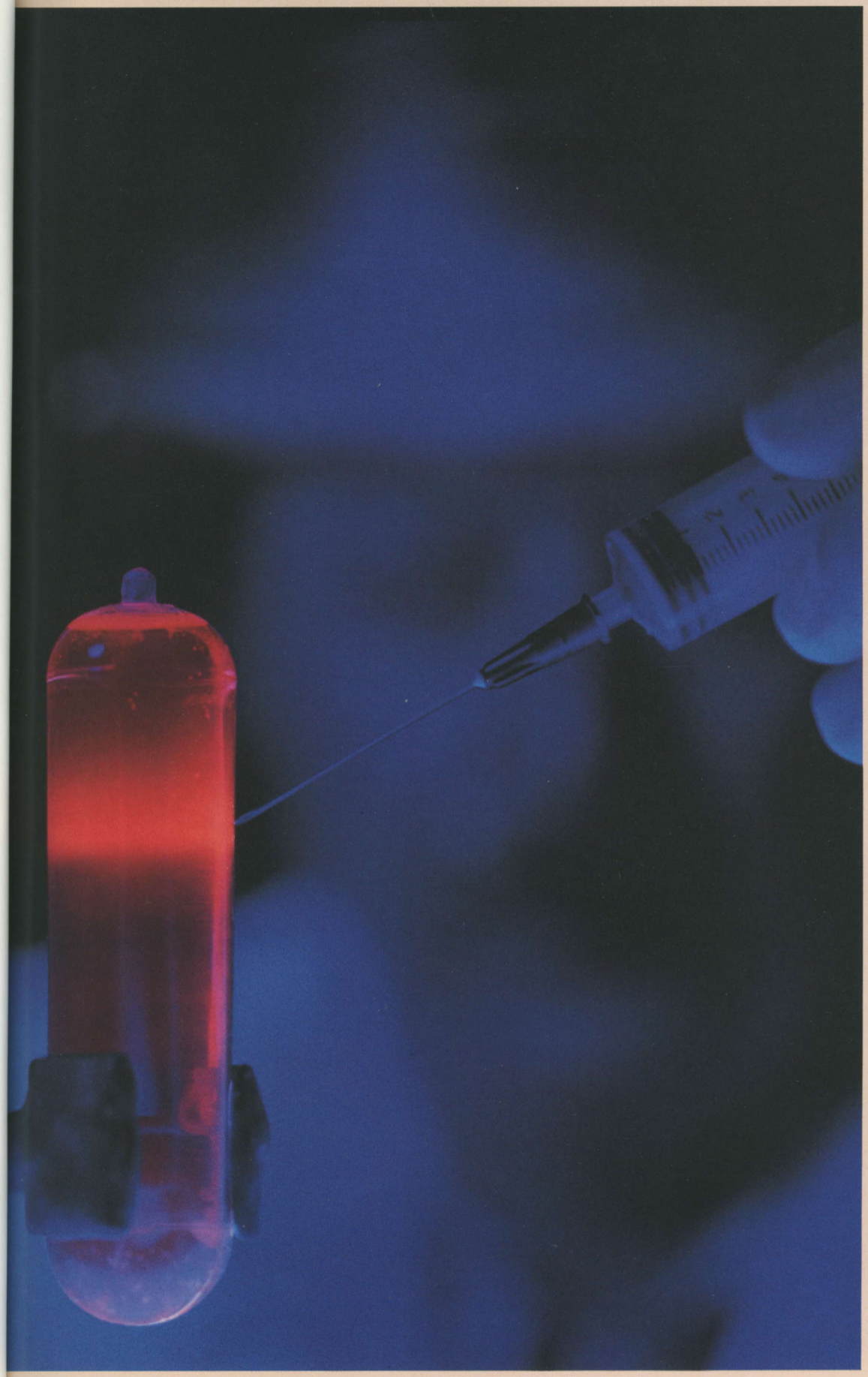
"It's a very exciting time," says Dr. Alfred G. Knudson, an expert in cancer genetics at the Fox Chase Cancer Center in Philadelphia. "The genes that seem to cause cancer are being cloned at a number of centers, and soon we'll understand how they work."

When a cell divides, it carefully copies its genes and distributes the copies to offspring cells. Although errors in copying occur only rarely, about once in every million cell divisions, they can have profound effects.

If the mistake occurs in the cells that form body tissues or organs, medical problems, including cancer, can result. If it occurs in developing sperm and egg cells, the error may be passed on to the patient's children.

For years, scientists have observed that some families have more cancer than others. Even in noninherited cancers, they have seen a variety of genetic changes in the cancer cells.

About 50 of the more than 120 different types of cancer occasionally have shown some



DNA, which is visible in the test tube, carries instructions that determine how each molecule in a living organism will function. Using a array of techniques to penetrate DNA's secrets, scientists are exploring fundamental life processes as well as diseases such as cancer.

type of familial clustering. However, "cancer families" in which many members develop one or more types of cancer, are uncommon.

Most cancers occur randomly in the human population, presumably due to genetic changes caused by environmental exposures. Scientists now believe that genetic changes, inherited or acquired, are the basis of cancer.

One of the first cancers recognized as hereditary was familial retinoblastoma, a rare eye cancer that develops in children and often affects both eyes. As many as 40 percent of retinoblastomas are considered hereditary, meaning that the cancer risk can be passed on to the patient's children. Yet, only about 5 percent of the cases in the United States each year occur in children with a known family history of the disease.

Most retinoblastomas are not inherited. They occur randomly in the population and commonly affect only one eye. Overall, about 5 of every 100,000 children develop retinoblastoma between birth and age seven.

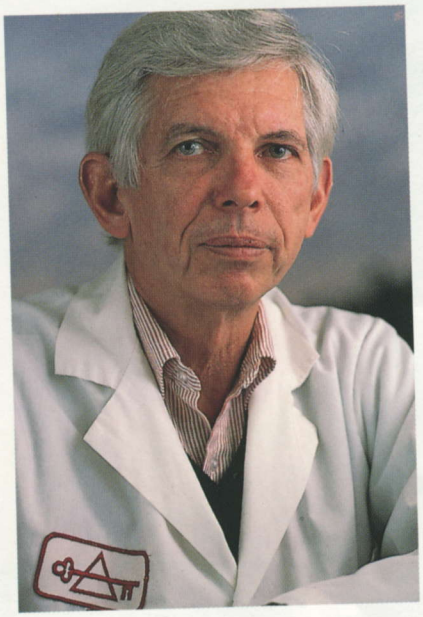
More than fifteen years ago, Knudson noticed that children under age one who developed retinoblastoma frequently suffered from the more aggressive disease, with cancers in both eyes.

Knudson was impressed that a child from a family with retinoblastoma, with a 50 percent chance of inheriting the disease, could have the cancer in one eye, both, or neither. "This implied to me that having a familial predisposition wasn't enough to get the cancer—something else had to happen to spur cancer development," Knudson says.

"We have two copies of every gene in most of our cells. The simplest explanation for retinoblastoma would involve knocking out both copies of the gene," Knudson explains.

In the 1950s and 1960s, scientists explained the long time period needed for cancer development as evidence that at least two separate events must occur in the cell before it converts to a cancer cell.

In the early 1970s, Knudson statistically analyzed the patterns of occurrence of retino-



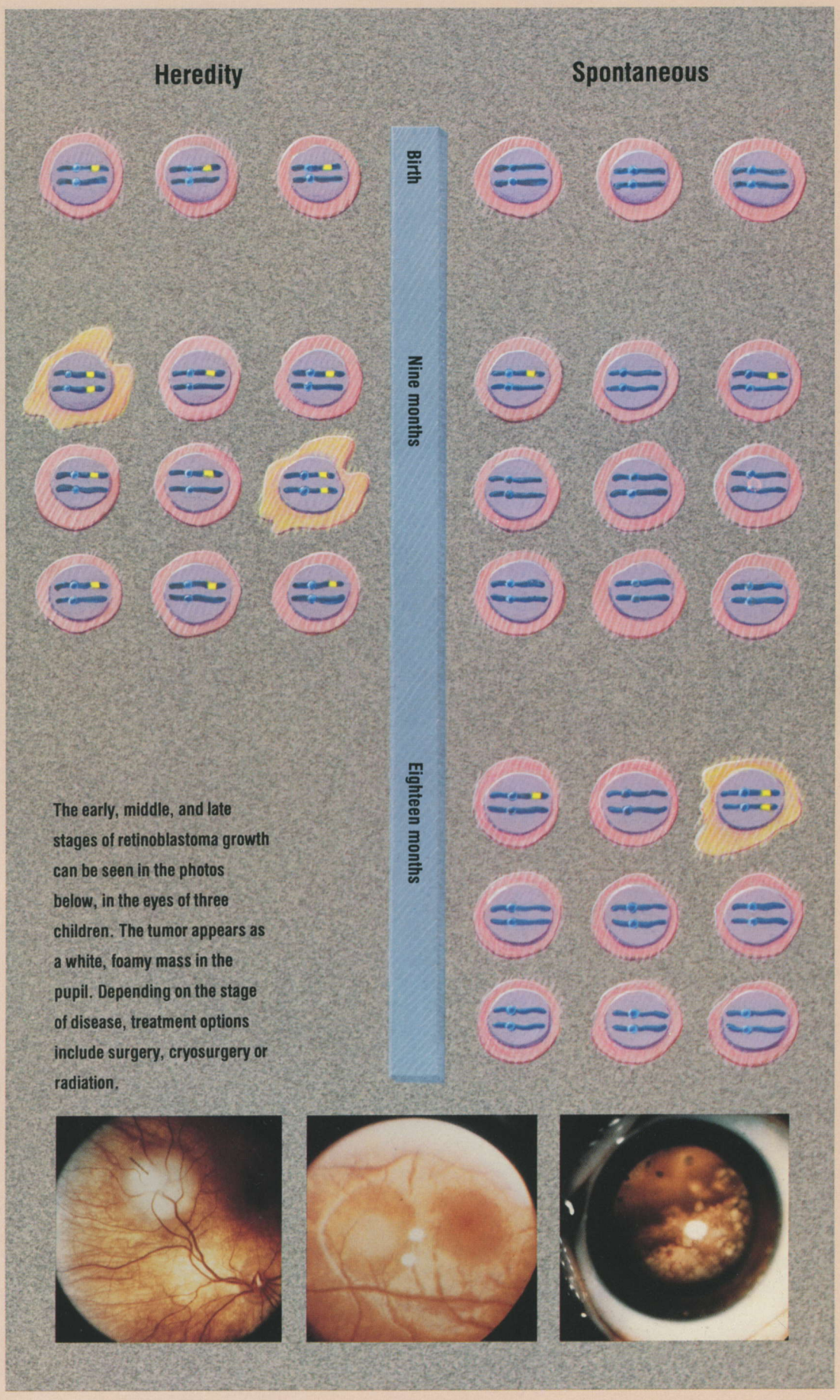
Dr. Alfred G. Knudson was honored in 1988 by the General Motors Cancer Research Foundation for his research to explain how some childhood cancers can result from genetic mistakes.

The Genes of Retinoblastoma

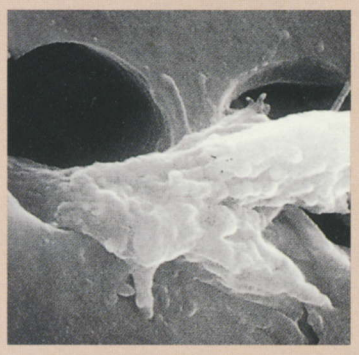
Retinoblastoma, a rare eye cancer of childhood, can be either hereditary or spontaneous. Both forms are caused by the loss of function of genes carried on chromosome 13. Cancer does not arise as long as one copy of chromosome 13 is normal. In the hereditary form (left), the newborn has a copy of chromosome 13 that has missing or damaged genes in the region associated with retinoblastoma. A healthy newborn (right) has two normal copies of the chromosome.

As retinal cells divide during the first nine months of life, random errors cause gene damage in about one of every million cell divisions. In hereditary retinoblastoma, this error may cause tumor growth.

It is very rare that random errors will occur in both copies of the retinoblastoma gene in one cell. Nonetheless, within the first few years of life, in a small number of healthy children, mutations in both genes of a single eye cell cause the cancer. Since their other cells remain unaffected, children with the spontaneous disease, unlike those with the inherited form, will not pass retinoblastoma on to their offspring.



The early, middle, and late stages of retinoblastoma growth can be seen in the photos below, in the eyes of three children. The tumor appears as a white, foamy mass in the pupil. Depending on the stage of disease, treatment options include surgery, cryosurgery or radiation.



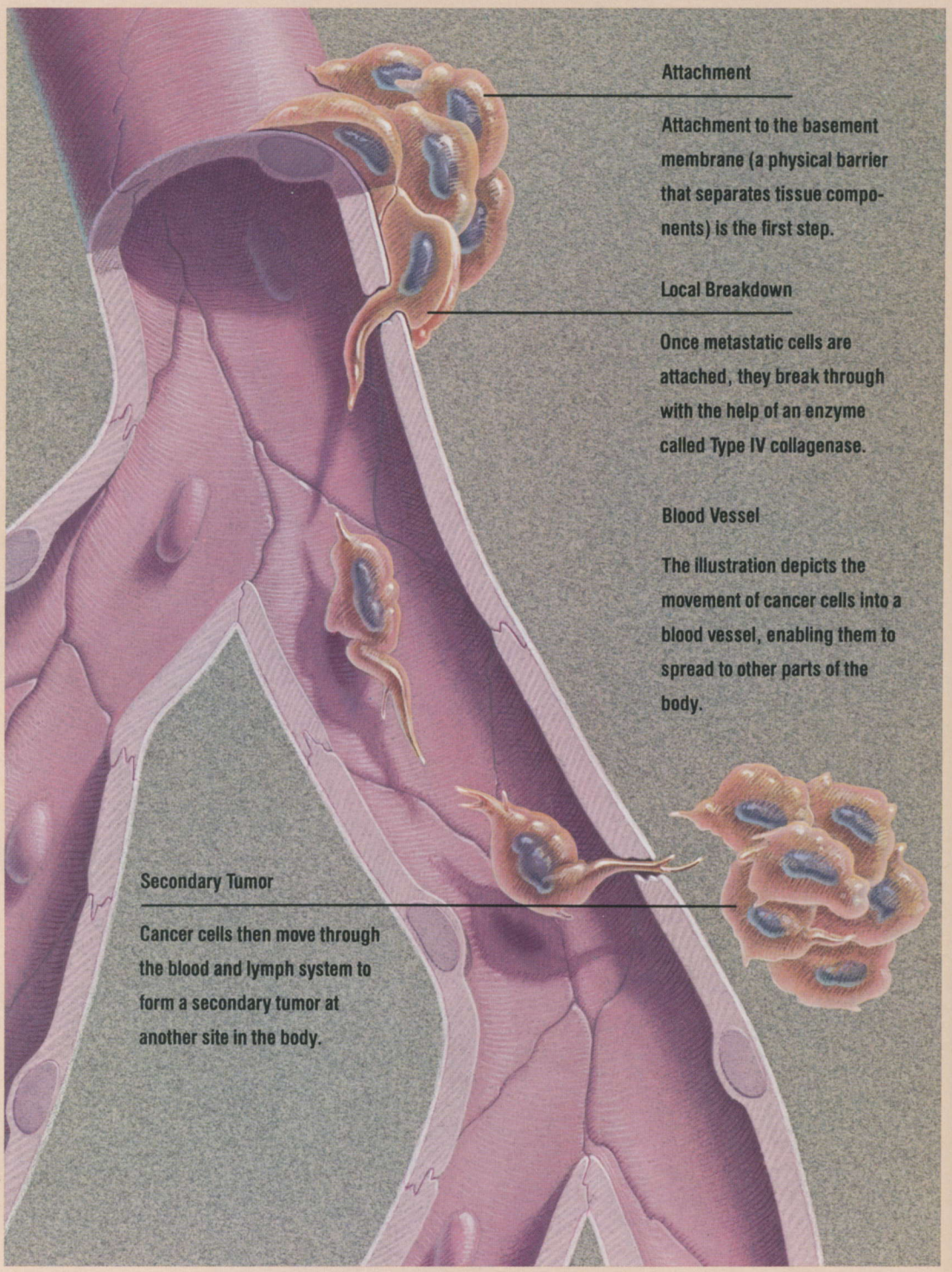
Locomotion is integral to the entire process of metastasis. Scientists have identified a protein, named autocrine motility factor, that causes cancer cells to grow arms or pseudopodia, enabling them to begin to move to other parts of the body.

How Cancer Spreads

Cancer has two distinctive characteristics: disorderly, abnormal cell division, and metastasis, a progressive spread to other parts of the body.

Some cancers spread more aggressively than others. Scientists are locating genes, enzymes and other proteins that help cancer cells break down the linings of organs and capillaries and move to other locations in the body.

Scientists are learning more about the genes and biochemical pathways that govern metastasis, and how to use that knowledge to block metastasis. For example, studies are under way to see if antibodies against autocrine motility factor might keep cancer cells from migrating.



blastoma and proposed his two-hit hypothesis, which suggested that as few as two gene changes could be enough for the cancer to develop. He showed that the hereditary form of the disease occurred in a statistical pattern consistent with an initial mutation occurring in an egg or sperm cell. Retinal cells are continually dividing as the retina develops during pregnancy and early infancy. If, at some point, the second, normal copy of the gene were damaged, cancer could form.

Knudson hypothesized that the spontaneous retinal cancers in people without a hereditary disposition occurred when two chance events damaged both genes in the same retinal cell—a very rare coincidence in the general population.

He then looked at other childhood tumors, including those of the kidney and nervous system, and proposed that they also fit the two-hit scenario.

In the 1970s and early 1980s, newly developed techniques—the products of rapid developments in cell and molecular biology, let researchers study DNA in greater detail and develop ways to examine cells for specific regions that might be responsible for disease.

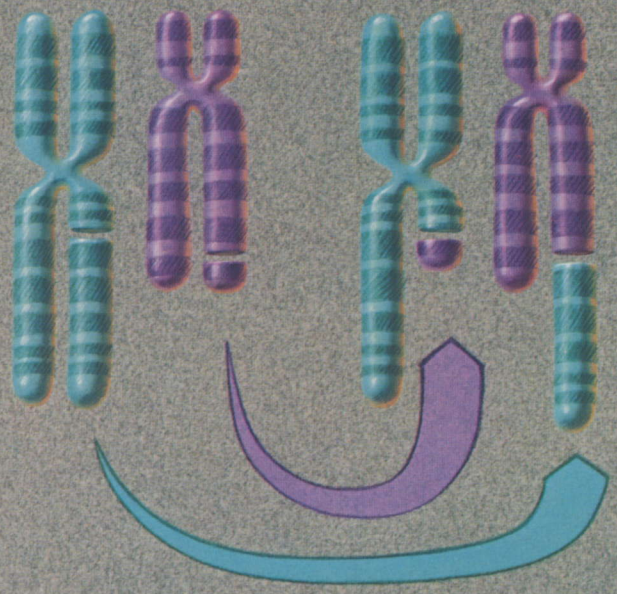
One advance enabled scientists to more clearly examine the organization of human chromosomes, structures in the nucleus of the cell that contain tightly packed bundles of genes. Using dyes, the scientists found that because of the unique banding pattern of each chromosome, specific segments could be numbered for identification.

Banding studies showed that most patients with retinoblastoma, those with the nonhereditary form of the disease, have two normal copies of chromosome 13 in their blood cells, but their cancer cells may be missing the 13q14 region.

In rare retinoblastoma patients, those with mental retardation or other birth defects, even normal blood cells turned out to be missing the 13q14 segment.

Then, scientists discovered that another gene, which directs the production of a readily identifiable enzyme, was also located on 13q14.

Webster K. Cavenee developed probes that identified the chromosomal segment that is missing in retinoblastoma, providing evidence from molecular genetics that the two-hit hypothesis was correct.



Genetic Fingerprints for Cancer

Scientists have found that certain oncogenes are part of the DNA exchange between chromosomes, called translocations (illustrated above for follicular lymphoma) that are common in several cancers. Using special procedures that permit detection of small numbers of specific DNAs, scientists can now probe blood and lymph samples to detect cancers of B-lymphocytes, cells in the blood and lymph that manufacture immunoglobulin (antibody) molecules. Immunoglobulin genes normally undergo rearrangements to enable the body to make antibody molecules capable of recognizing specific protein molecules. Because cancer cells are the descendants of a single wayward cell, scientists can identify the cancer by the unique rearrangement in the immunoglobulin gene of the cancer cells.

For example, in research studies on follicular lymphoma, scientists are using such probes to "fingerprint" an individual patient's cancer, giving physicians a tool to measure precisely whether experimental drug treatments are working, and as a way to detect relapse before it is clinically apparent.

Gene Changes and Cancer Diagnosis

The cancers of thousands of patients are being diagnosed with increased precision by laboratory pathologists, thanks to tests for unique markers that only a few years ago were the exclusive realm of molecular geneticists.

For years, pathologists have routinely tested many patients' leukemia and lymphoma cells for a variety of chromosomal abnormalities. These analyses were made possible in the 1970s by the advent of a new technique, chromosome banding, that enabled scientists to visualize chromosomes clearly.

Some abnormalities became diagnostic, such as in chronic myelogenous leukemia, where appearance of an odd chromosome named the Philadelphia chromosome identifies this cancer. As a result of banding, scientists learned that the Philadelphia chromosome was actually chromosome 22 with a translocation from chromosome 9. In the 1980s, scientists found that a specific gene named c-*abl* was part of the translocated chromosome segment on chromosome 22, where it fused with another gene and made an abnormal product.

Another example is Burkitt's lymphoma, a rare childhood cancer of immune system cells with a characteristic chromosomal translocation. Another specific gene, named c-*myc*, in the 1970s was detected near the translocation breakpoint on chromosome 8, next to a gene for antibody production. Presumably, the *myc* gene is under the same activation control as the antibody gene, and its protein product drives the cell through repeated rounds of cell division. C-*myc* also appears in rearrangements of the chromosomes of lymphoma cells from AIDS patients.

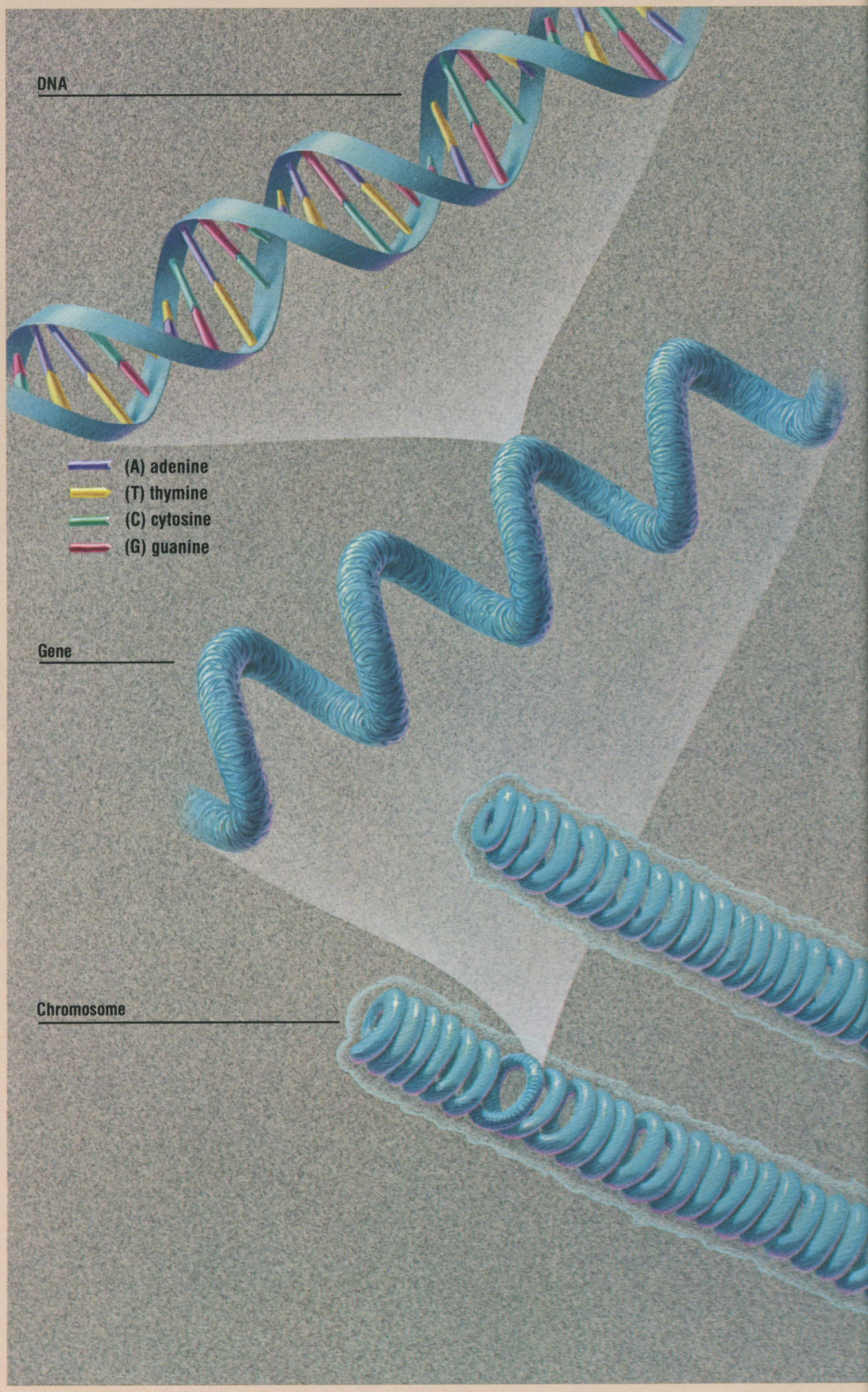
A gene named *bcl-2* by its discoverer, Dr. Carlo Croce of the Wistar Institute, moves from chromosome 18 during a translocation between chromosomes 14 and 18 in follicular lymphoma. In this, the most common lymphoma affecting adults over age forty, the translocation occurs in more than 90 percent of patients. The *bcl-2* gene moves to chromosome 14, where it sits next to another of the antibody-producing genes.

How Cells Package Genetic Information

Several billion nucleotides are packed into the nucleus of each human cell in a precise linear order. There are four types of nucleotides, adenine (A), thymine (T), guanine (G), and cytosine(C), ordered precisely to encode all the genetic information of an individual in DNA (deoxyribonucleic acid). In the laboratory, scientists now selectively break down DNA into smaller segments, determine the precise order of the nucleotides and predict the product.

Genes are segments of DNA that encode a specific protein product. Each gene has two parts, a portion that is copied into RNA, the chemical that carries out the gene's instructions, and a "switch" portion that controls this copying process. Genes are switched "on" or "off" in different tissues at different times.

Each individual cell carries about 50,000 genes, packaged in the cell nucleus into tiny bundles called chromosomes. Except for genes carried by egg and sperm cells, which have only one copy of each gene (to allow the gene mixing that makes each person unique), every cell has two copies, one from each parent. When a cell divides, it must correctly copy every gene and apportion the chromosomes to the daughter cells.



By examining the cells of people within retinoblastoma families, scientists saw that the cancer occurred in family members with a particular enzyme variant, confirming that the predisposing gene was located in that region.

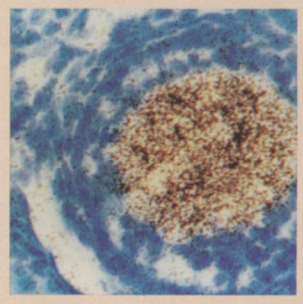
In 1983, while at the University of Utah, Webster K. Cavenee made a series of special probes for precise pieces of the 13q14 region of the chromosome. In collaboration with other scientists in the United States and Canada, he looked for a pattern of hereditary transmission from parents with retinoblastoma to their children. By comparing the patients' normal and cancer cells, he showed that the cancer cells had lost the 13q14 region from the unaffected parent and sometimes instead had duplicate copies of chromosome 13 inherited from the parent that had retinoblastoma as a child. The cancer cells had two mistakes in 13q14, one on each chromosome 13. As a result, no normal copy of the retinal gene remained, allowing the disease to occur.

Several researchers in laboratories throughout the world then began a quest to isolate and clone the specific gene that is missing in retinoblastoma cells. During 1986, researchers at the Massachusetts Eye and Ear Infirmary, led by Dr. Thaddeus Dryja, reported finding a probe within the region of the retinoblastoma gene. Then, Dr. Stephen Friend and coworkers in Dr. Robert Weinberg's laboratory at the Whitehead Institute for Biomedical Research, in collaboration with Dryja's group, cloned the putative retinoblastoma gene. Soon, in California, Wen-Hwa Lee of the University of California at San Diego and Yuen Kai T. Fung of the University of Southern California confirmed and extended these findings.

By isolating the gene and studying the precise order of nucleotides it contains, scientists expect to gain unprecedented insights into how normal genes work and how loss of gene functions leads to some cancers.

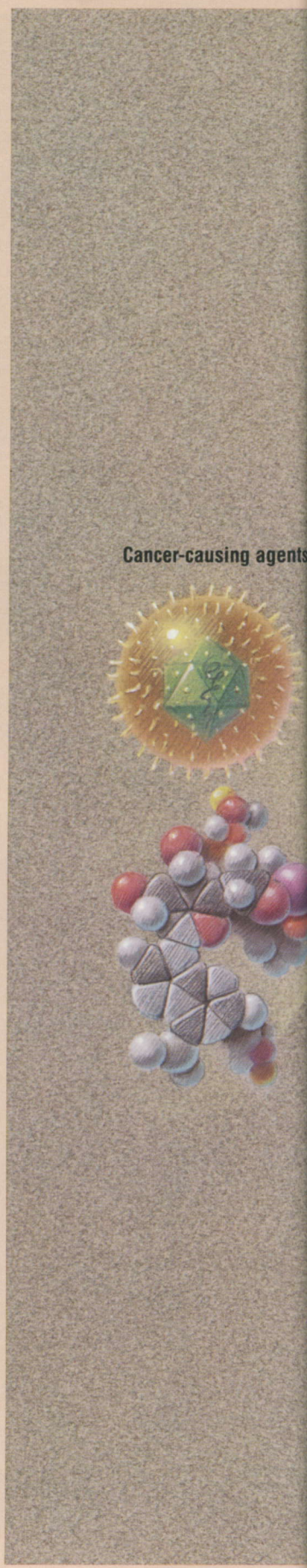
Now director of the Ludwig Institute for Cancer Research in Montreal, Cavenee has used

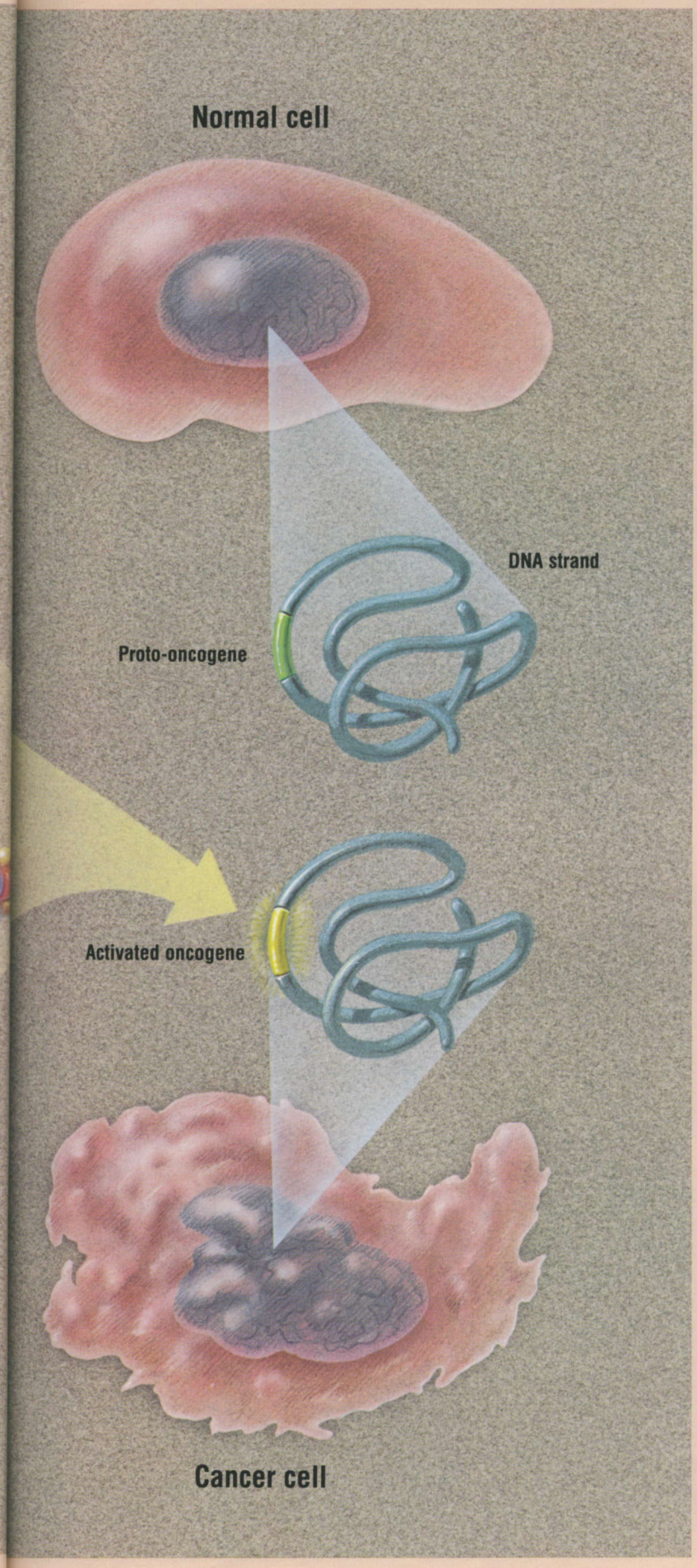
Oncogene Activation and Cancer



A technique called *in situ* hybridization shows whether a gene is actively expressed in cells, and also provides clues to the gene's function. This technique has helped identify activated oncogenes in cancer cells, and their normal counterparts in normal cells, in many different species. In this photograph, a labeled DNA segment (a known oncogene) has been put into a mouse oocyte, a cell that develops into a mature egg cell. The labeled DNA has paired with (or hybridized to) multiple copies of RNA in the mouse oocyte. The presence of this RNA (shown here as black dots inside the nucleus of the immature cell) shows that the normal cellular counterpart of the oncogene is active, suggesting that it is critical for normal germ cell development.

Photo Credit: Basic Research Laboratory, Frederick Cancer Research Facility.





What is an Oncogene?

An oncogene is a specific gene that participates in changing a normal cell into a cancer cell. It is a variant of a normal cell gene.

The first clues to oncogenes came from research on the life cycle of retroviruses, a family of viruses that can cause leukemias and solid tumors. These viruses have been found in reptiles, birds, and mammals, including humans.

During the 1970s, scientists used the new techniques provided by molecular biology to examine the genes in these viruses. They found that some retroviruses contained genes that gave the viruses the ability to stimulate abnormal cell growth, and they named those genes oncogenes.

They also found normal genes that were structurally similar to oncogenes. Certain retroviruses, it turned out, had captured genes from normal cells and had substituted these cellular genes for some of their own genetic information.

Within the retrovirus, the oncogenes are mutated and can spread to new cells by infection. In the normal cell, these genes appear to regulate and influence normal cell growth and cell divison.

Because of this research, scientists are developing greater understanding of normal as well as cancerous cell growth. Some of the more than 50 known oncogenes encode proteins called growth factors that encourage cells to divide, and some make proteins that transmit growth signals inside the cell. Still other gene products stay inside the nucleus of the cell, where they can bind to DNA and control critical processes.

Dr. Michael H. Wigler of the Cold Spring Harbor Laboratory on Long Island has been a leader in research on DNA. He showed that the primitive yeast organism contains a gene needed for normal growth that has structural similarity to a gene in human DNA.

Says Wigler, "If you knock out the gene in yeast and replace it with the human gene, the yeast will grow and divide extremely well. But if you mutate it and insert it into mouse cells, you can transform the mouse cells, causing loss of growth control."

his probes to predict, prenatally, which infants from retinoblastoma families are likely to develop the disease. One infant that Cavenee predicted would develop retinoblastoma was examined at a few weeks of age and found to have two tumors in each eye. Prompt treatment with radiation saved the infant's eyes and sight.

In research studies, other scientists are now using probes like Cavenee's and Friend's in families with retinoblastoma to help identify family members who have inherited a susceptibility to the disease.

The probes also are being used to study survivors of hereditary retinoblastoma, who have a 15 percent chance of developing other cancers, usually osteosarcoma, a bone cancer. Using his molecular probes, Cavenee and coworkers showed that in two of three retinoblastoma patients who subsequently developed osteosarcoma, the osteosarcoma cells had alterations in the 13q14 region of chromosome 13. Osteosarcoma cells from three of four patients with the spontaneous form of the disease (that is, no family history of retinoblastoma) also had the defect. Because the defect was found in the cancer cells of one of the patients prior to cancer drug treatment, the scientists believe that, as in retinoblastoma, the defective region of the chromosome was responsible for both the inherited and spontaneous osteosarcomas.

Other research is looking at other cancers to see if cancer cells show abnormalities in the region of chromosome 13 that is changed in retinoblastoma. Recent work by Friend and colleagues has shown deletions in patients who have never had retinoblastoma, but who have developed certain soft tissue sarcomas.

Cavenee and other scientists have looked for similar gene defects in other, more common, cancers. For example, Cavenee has found alterations on chromosome 13 in ductal breast cancer cells from premenopausal patients. He and other groups have reported a pattern of gene defects, similar to those seen in retinoblastoma, in patients with Wilms' tumor, a childhood kidney cancer, where the deletion occurs on chromosome 11.

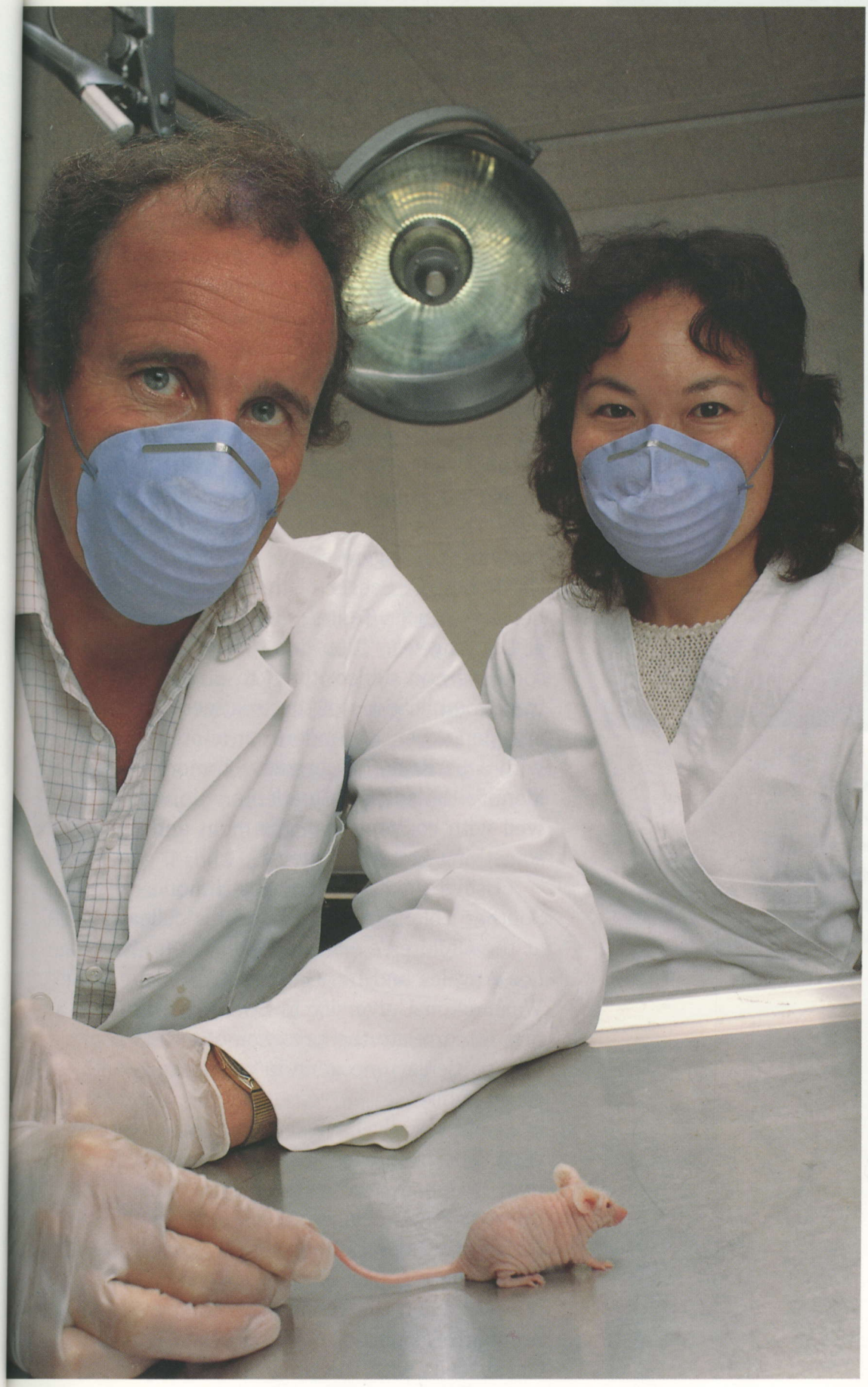
At the Childrens Hospital of Los Angeles and the University of California at Irvine, Dr. Eric J. Stanbridge and coworkers have shown that introducing a single normal human chromosome 11 into laboratory grown Wilms' tumor cells, which are then injected into mice, curtails the ability of the cells to form tumors in the mice. The implication is that the normal chromosome 11 contains a region that, when missing, contributes to the development of cancer, and when present, helps prevent the development of the cancer.

Certain other cancers of children, and other more common cancers of adults, are now being studied by other groups of scientists to see if missing or damaged areas of chromosomes can be identified.

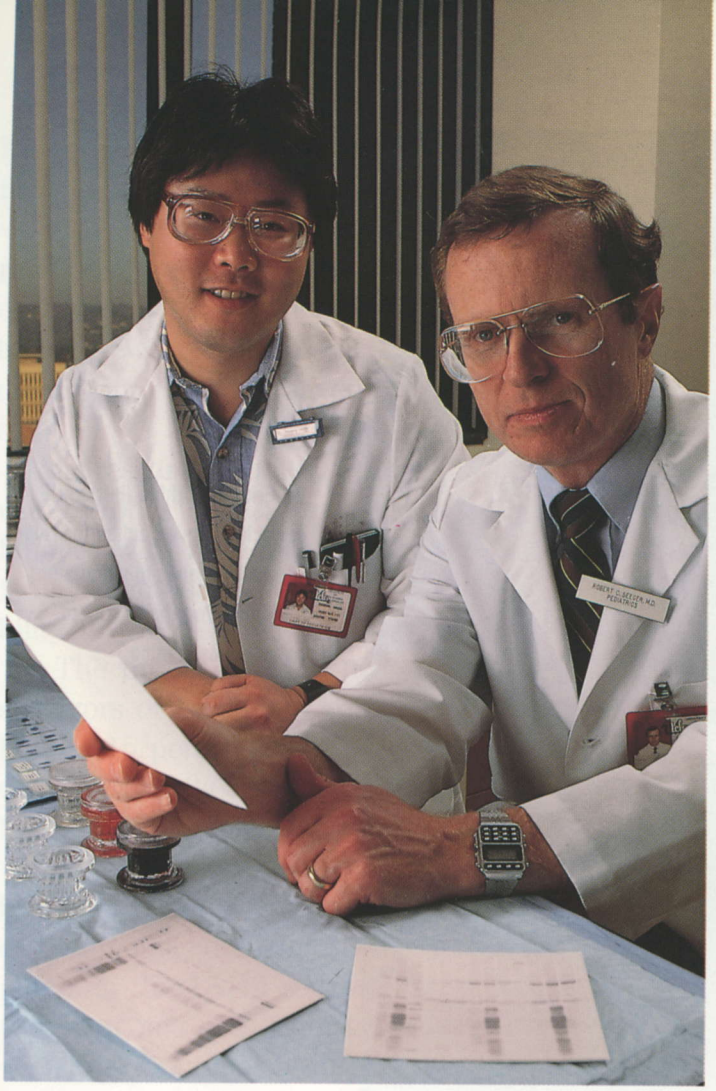
A key finding by Sir Walter Bodmer and Dr. Ellen Solomon and their coworkers at London's Imperial Cancer Research Fund suggests that some colon cancers are due to two-hit mechanism involving an inherited or acquired mutation at a particular site on a chromosome. Their work stems from an individual case report: a portion of chromosome 5 was missing in a patient with familial adenomatous polyposis, a rare hereditary condition that shows up in adolescents. In this disease, the large intestine is carpeted with hundreds of small growths called polyps, and these patients are at high risk of developing colon cancer.

Bodmer and colleagues, using a probe for the missing region of chromosome 5, were able to trace the disease in the polyposis families, demonstrating that the predisposing gene lies in that region. Using another probe for the same chromosome 5 segment, Solomon and her coworkers showed that the segment is missing in the cancer cells of some patients with common, nonhereditary forms of colon cancer. This suggests that cancer occurred as a result of loss of a gene needed for normal cell growth regulation.

While some cancers are caused by damaged or missing genes, other cancers appear to be



Dr. Eric Stanbridge (left) and coworkers have studied the role of specific genes in stimulating and inhibiting the growth of cancer cells in mice.



Dr. Robert C. Seeger (right), and his colleagues use aggressive therapy in neuroblastoma patients whose cancer cells have 10 or more copies of an oncogene.

prompted or rendered more aggressive by the presence of altered or activated genes called oncogenes. Originally discovered in the 1970s in animal cancer viruses, oncogenes have been shown to play a role in a wide range of human cancers, including those of the breast, colon, lung, bladder, nervous system and blood.

In the past several years, scientists have begun to study the role of normal genes related to oncogenes in cell division or differentiation. When altered, these normal genes may play a role in cancer.

Although scientists have yet to learn exactly how oncogenes spur the growth of cancers, their presence in cancer cells may already be useful in predicting which patients should have more aggressive cancer treatment.

"The key treatment issue for cancer is knowing how aggressive a tumor is," says Dr. Robert C. Seeger of the Jonsson Comprehensive Cancer Center, University of California at Los Angeles. "You don't want to overtreat someone and subject them to a risk of dying from complications of the treatment, but you also don't want to undertreat another patient with a particularly aggressive tumor. We try to identify the subset of patients who won't do well with conventional treatment and find something better for them."

Using a gene screening technique called Southern blotting, Seeger and his colleagues at the Children's Cancer Study Group in Los Angeles and Dr. Garrett M. Brodeur of the Washington University in St. Louis were the first to correlate the presence of excess copies of a particular oncogene in cancer cells with the stage of disease.

Cells usually have only two copies of each gene, one from each parent. But when Seeger and Brodeur looked at the cancer cells of children with neuroblastoma, a cancer of the nervous system, they found many of the cells had ten or more copies of an oncogene called *N-myc*. When the researchers compared the number of copies of *N-myc* in each patient's cancer cells with the progress of the patient,

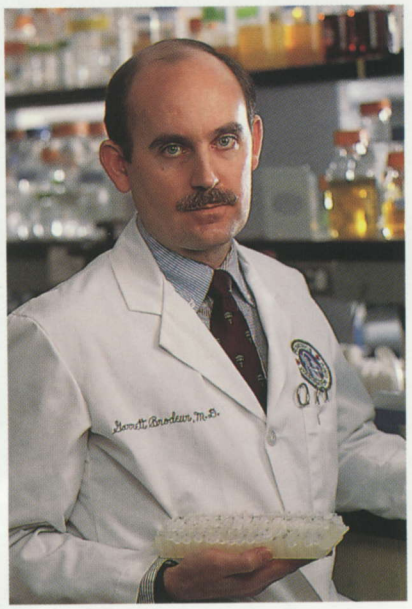
they found that the more copies of the gene, the more rapidly the cancer spread.

The researchers were quick to put these findings into practice. Seeger treats patients who have localized cancers and few or no excess copies of the gene with surgery, conventional chemotherapy, and radiation. But he treats patients who have ten or more copies of *N-myc*—even if their cancer has not spread—with chemotherapy and radiation so intense that it requires bone marrow transplants to restore their blood cells.

Since Seeger and Brodeur made the connection between excess copies of *N-myc* and poor prognosis, their colleague, Dr. Dennis J. Slamon of the University of California at Los Angeles has discovered the same relationship between copies of the oncogene *HER-2/neu/erB-2* and breast cancer. Although Slamon's data are still preliminary, he is encouraged by findings indicating that the more copies of the oncogene in the tumor cells, the more aggressive the cancer. If further studies support his initial findings, doctors may be able to predict which women are most likely to have a recurrence of breast cancer and should be treated with chemotherapy or radiation.

"Even if the *HER-2/neu/erB-2* oncogene doesn't pan out the way we'd like it to," Slamon says, "there are a number of other oncogenes that might prove more prognostic. There must be something going on at the level of the gene that can tell you why some people's cancers are more aggressive than others."

The discovery of such genes could not only refine prognosis, but foster more effective treatments for certain cancers. "If a gene product is important in a disease process, then drugs that block that molecule hold potential for therapy," Slamon says. Echoing Knudson, he adds, "These are exciting times."



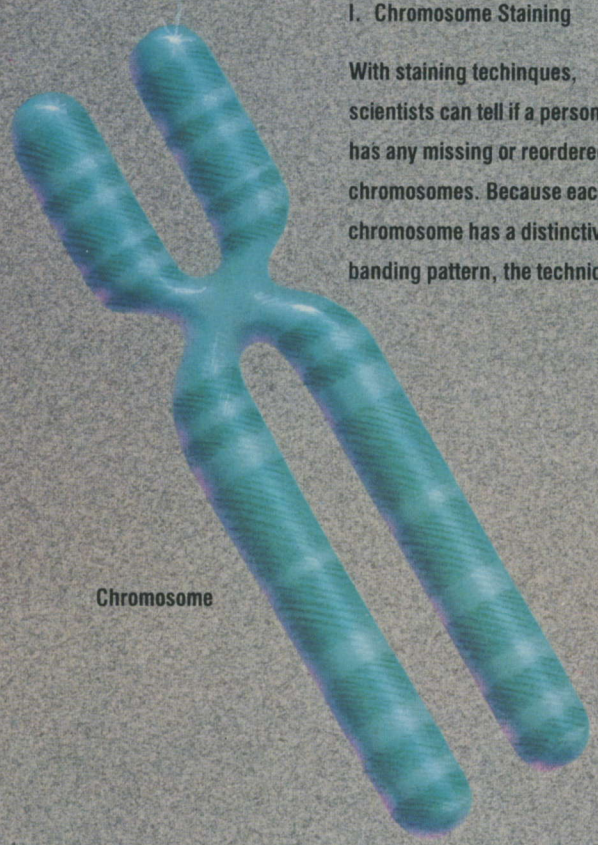
Dr. Garrett M. Brodeur developed oncogene probes and helped show the relationship between oncogene activity and stage of disease in neuroblastoma.

Pinpointing the Genes in Cancer

Scientists can now pinpoint some of the genes associated with cancer, thanks to techniques that allow them to tell chromosomes apart, detect genetic markers for disease susceptibility, and isolate specific genes.

In higher organisms such as humans, a single gene can span hundreds of thousands of bases; chromosomes have hundreds of millions of bases. The complete complement of human DNA comprises three billion base pairs in a precise order. To duplicate the genes and develop a more precise genetic map of human genes and chromosomes, scientists are using recombinant DNA techniques in yeast. Yeast can replicate millions of bases at one time, enough to copy large segments of human DNA. This type of research promises to help scientists understand better how genes are organized on chromosomes. The new insights promised by genetic analysis promise unprecedented progress in understanding diseases such as cancer.

Three Key Techniques



Chromosome

I. Chromosome Staining

With staining techinques, scientists can tell if a person has any missing or reordered chromosomes. Because each chromosome has a distinctive banding pattern, the technique distinguishes between different chromosomes or chromosome segments.

A fluorescent or radioactive dye is added to chromosomes. The dye creates light and dark patterns that identify individual chromosomes and missing, added or translocated segments. Individual bands also serve as markers for the positions of specific genes. Each band contains millions of precisely ordered pairs of bases, about 5 to 10 percent of the DNA in the chromosome.

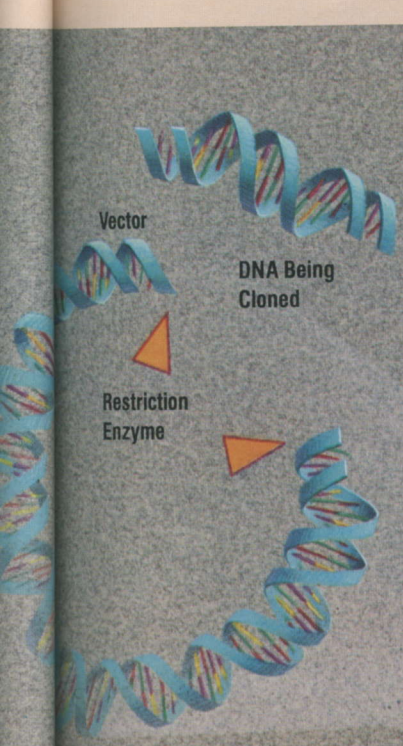
II. Inherited Markers

Two research strategies, when combined, tell scientists where defective genes are located in human DNA. They are: (1) a study of inheritance patterns in families with a specific cancer (such as retinoblastoma) appearing over two or more generations; and (2) sophisticated techniques that identify the precise order of the chemical subunits in DNA. Natural variations in this order, called polymorphisms, make each person unique.

The DNA of blood cells from family members are cut into fragments by restriction enzymes and are separated by size with a technique called a Southern blot. Variations that are inherited over several generations can be detected by comparing the DNA of family members.

In a family with inherited disease, a fragment with a particular DNA variation that is always inherited is a marker if its presence always coincides with disease occurrence. This molecular examination of inheritance is called "RFLP" an-

DNA



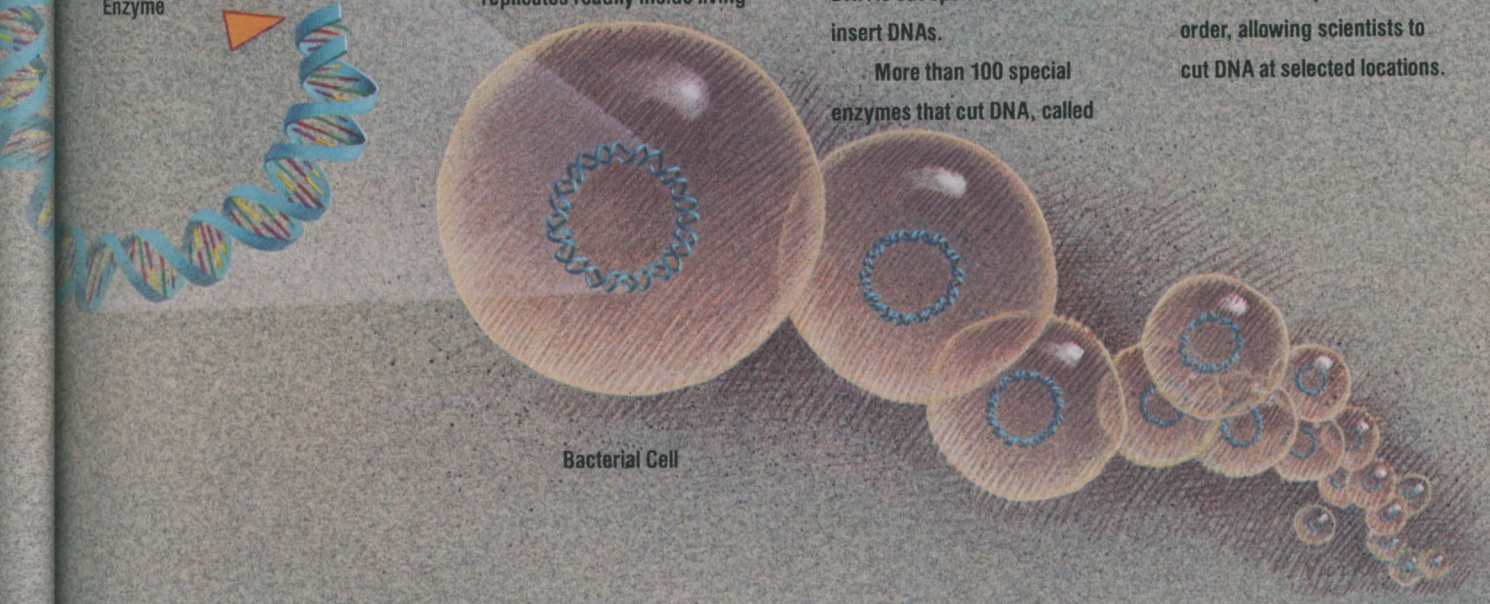
III. DNA Cloning

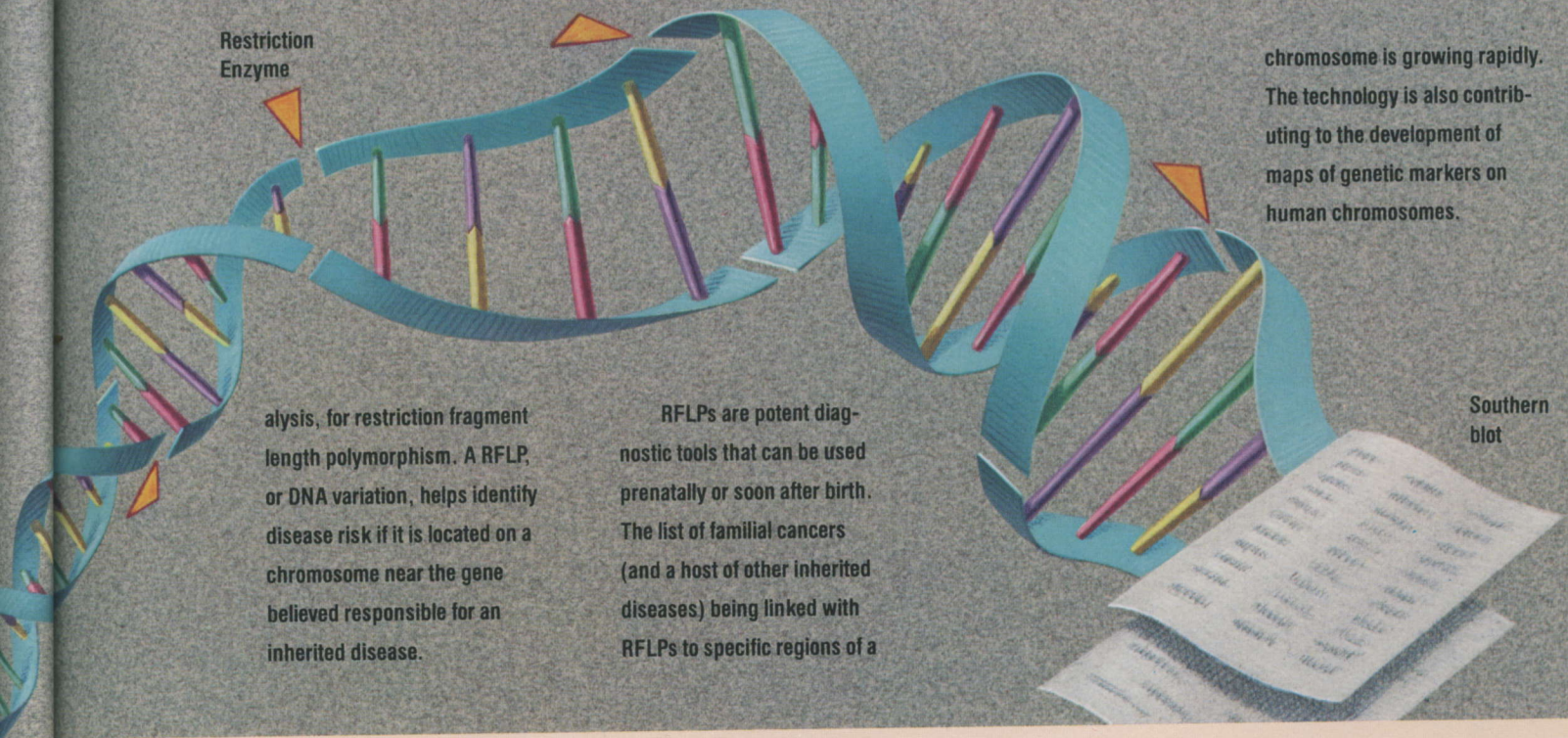
To make the large quantities of a specific DNA fragment needed for testing, scientists clone it.

First, scientists insert the sequence of DNA into a vector—a carrier DNA that replicates readily inside living cells—and insert the vector into bacteria that duplicate the recombined DNA many times when the bacteria replicate.

The vector is then removed from the bacterial cells and the DNA is cut open to release the insert DNAs.

More than 100 special enzymes that cut DNA, called restriction enzymes, are available to scientists for cloning and for a wide range of other tasks in molecular biology. These enzymes recognize small stretches of four to six nucleotide bases in a precise linear order, allowing scientists to cut DNA at selected locations.





alysis, for restriction fragment length polymorphism. A RFLP, or DNA variation, helps identify disease risk if it is located on a chromosome near the gene believed responsible for an inherited disease.

RFLPs are potent diagnostic tools that can be used prenatally or soon after birth. The list of familial cancers (and a host of other inherited diseases) being linked with RFLPs to specific regions of a chromosome is growing rapidly. The technology is also contributing to the development of maps of genetic markers on human chromosomes.