Terminology: 90% of cancers in humans are **carcinomas**; the remaining 10% are **sarcomas** and **leukemias**.

Figure 6: Developmental biology of the early fertilized egg and embryo of the vertebrate. At the developmental stage of gastrulation, the three germ layers, ectoderm, mesoderm and endoderm, are clearly differentiated. Tissues derived from these different layers may give rise to malignant neoplasms with the terminology based on their germ layer of derivation. See text for further details.

Table 2. Examples of Neoplasms Based on the Histogenetic Classification

<table>
<thead>
<tr>
<th>Tissue of Origin</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Epithelial neoplasms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermis</td>
<td>Epidermal papilloma</td>
<td>Epidermal carcinoma</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastric polyp</td>
<td>Gastric carcinoma</td>
</tr>
<tr>
<td>Biliary tree</td>
<td>Cholangioma</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>Adrenal cortex</td>
<td>Adrenocortical adenoma</td>
<td>Adrenocortical carcinoma</td>
</tr>
<tr>
<td><strong>2. Connective tissue neoplasms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrous tissue</td>
<td>Fibroma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Chondroma</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteoma</td>
<td>Osteogenic sarcoma</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipoma</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>Leiomyoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Rhabdomyoma</td>
<td>Rhabdomyosarcoma</td>
</tr>
</tbody>
</table>
Properties of benign versus malignant tumors

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Encapsulated</td>
<td>Non-encapsulated</td>
</tr>
<tr>
<td>2. Noninvasive</td>
<td>Invasive</td>
</tr>
<tr>
<td>3. Highly differentiated</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>4. Slow growth</td>
<td>[Rapid growth]</td>
</tr>
<tr>
<td>5. Little or no anaplasia</td>
<td>Usually anaplastic</td>
</tr>
<tr>
<td>7. No metastasis</td>
<td>METASTASIS !</td>
</tr>
</tbody>
</table>
Benign versus malignant tumors


Figure 23-3. Benign versus malignant tumors. A benign glandular tumor (an adenoma) and a malignant glandular tumor (an adenocarcinoma) appear structurally distinct. There are many forms that such tumors may take; the diagram illustrates types that might be found in the breast.
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 community, 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

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).
count for much of the uncontrolled cell proliferation seen in human cancers. When mutated, proto-oncogenes can become carcinogenic oncoproteins 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.
Fighting Cancer by Attacking Its Blood Supply

By interfering with the expanding network of blood vessels in tumors, researchers hope to cut off the underlying support system.

by Judah Folkman

The tiny blood vessels known as capillaries extend into virtually all the tissues of the body, replenishing nutrients and carrying off waste products. Under most conditions, capillaries do not increase in size or number, because the endothelial cells that line these narrow tubes do not divide. But occasionally—for example, during menstruation or when tissue is damaged—these vessels begin to grow rapidly. This proliferation of new capillaries, called angiogenesis or neovascularization, is typically short-lived, “turning off” after one or two weeks.

But neovascularization can also occur under abnormal conditions: tumor cells can “turn on” angiogenesis. As new blood vessels bring in fresh nutrients and proteins known as growth factors, the tumor mass can expand. In fact, neovascularization appears to be one of the crucial steps in a tumor’s transition from a small, harmless cluster of mutated cells to a large, malignant growth, capable of spreading to other organs throughout the body. Tumor cells are usually unable to stimulate angiogenesis when they first arise in healthy tissue; unless the deranged cells become vascularized, the mass will not become larger than about the size of a pea. Thus, if researchers can determine how mutated cells trigger angiogenesis and, more important for patients, how to interrupt the process, they will have a powerful new anticancer therapy at their disposal. Furthermore, because antiangiogenic drugs stop new growth but do not attack healthy vessels, they should in theory do no harm to blood vessels serving normal tissues. (Angiogenesis inhibitors can stop menstruation or delay wound healing, however.)

Research into the importance of angiogenesis to the progression of cancer has been a vital area of laboratory investigation for several decades—I wrote an early article on the subject in the mid-1970s [see “The Vascularization of Tumors,” by Judah Folkman; SCIENTIFIC AMERICAN, May 1976]. But only in the past seven years has research moved out of the laboratory and into the clinic. In 1989 the first clinical trial of an antiangiogenic agent—interferon alpha—began for the treatment of life-threatening hemangioma (a noncancerous blood vessel tumor found primarily in infants).

By 1992 the first antiangiogenic drug for cancer patients, TNP-470 (a synthetic analogue of the substance fumagillin), entered clinical trials. The first studies were restricted to a few kinds of tumors, but the Food and Drug Administration now allows physicians to administer TNP-470 in clinical trials for a wide variety of cancers in humans. In the past four years, at least seven other angiogenes.
Endothelial cells have receptors for vascular endothelial growth factor (VEGF). Binding of VEGF to these receptors causes the endothelial to proliferate, and form new capillaries growing towards the source of VEGF (the cancer cells).
Metastasis

Metastasis is the process whereby cancer cells detach from the parent tumor and, by entering the vascular or lymphatic system, spread throughout the body and initiate new tumors at distant sites; ie, a tumor is said “to metastasize”. The new tumors are called “metastatic tumors”, or sometimes “metastases”.

Steps in the process of metastasis:

cells grow as a benign tumor in epithelium  break through basal lamina  invade capillary

connective tissue  basal lamina  capillary  travel through bloodstream (less than 1 in 1000 cells will survive to form metastases)

adhere to blood vessel wall in liver  escape from blood vessel (extravasation)  proliferate to form metastasis in liver


Figure 23-15. Steps in the process of metastasis. This example illustrates the spread of a tumor from an organ such as the lung or bladder to the liver. Tumor cells may enter the bloodstream directly by crossing the wall of a blood vessel, as diagrammed here, or, more commonly perhaps, by crossing the wall of a lymphatic vessel that ultimately discharges its contents (lymph) into the bloodstream. Tumor cells that have entered a lymphatic vessel often become trapped in lymph nodes along the way, giving rise to lymph-node metastases. Studies in animals show that typically far less than one in every thousand malignant tumor cells that enter the bloodstream will survive to produce a tumor at a new site.
Patterns of Metastasis

Metastatic cancer cells usually enter capillaries near or in the primary tumor, and end up in the venous circulation. They pass through the heart, and the first capillary bed they then encounter after escaping the primary tumor is usually the lung.

Slower flow rates of blood in a capillary bed facilitates the exit of metastatic cells through the thin walls of these blood vessels and into the neighboring tissue, where an escaped metastatic cell can proliferate to form a new tumor. So the lung is a common site for metastatic tumor growth for many types of cancer (eg, melanoma, breast cancer, etc).
There are some exceptions:

(1) In the case of colorectal cancers, the first capillary bed the metastatic cells encounter is the liver, because venous blood coming from the intestines (containing absorbed food molecules) goes first to the liver. So colorectal cancer often spreads first to the liver.

(2) Sometimes cancer cells carry receptor molecules that are specific for some other cell type. Prostatic cancer cells, for example, often express receptors for adhesion molecules on bone cells, and therefore often metastasize to bone.
PATTERNS OF METASTASIS can be explained in part by the architecture of the circulatory system. Tumors in the skin and many other tissues often colonize the lungs first because the lungs contain the first capillary bed "downstream" of most organs. In contrast, because the intestines send their blood to the liver first, the liver is often the primary site of metastasis for colorectal cancers. Yet circulation is not the only factor: prostate cancer, for example, usually metastasizes to the bones. This tendency may result from an affinity between receptors on prostate tumor cells and molecules in bone tissues (inset).

noteworthy that platelets produce their own rich supply of growth factors, and these may help the cancer cells to which they bind survive in the blood. This may be why, in some experimental systems, drugs that interfere with platelet functions have anticancer effects.)

Physical trapping of cancer cells in the blood vessels at the site of metastasis is not the whole story, however. If it were, cancers would not spread so diversely through the body. Indeed, some types of cancer show a striking preference for organs other than those that receive their venous blood—witness the tendency of metastatic prostate cancer to move into the bones. Once again, the explanation seems to rest with the molecular address system on cell surfaces. A specific affinity between the adhesion molecules on cancer cells and those on the inner linings of blood vessels in the preferred tissues could explain the predilection of the cells to migrate selectively. Different concentrations of growth-promoting factors and hormones in various tissues may also play a part.

Recently, in an elegant piece of work, Ivan Stamenkovic of Harvard Medical School and his colleagues showed that he could direct the metastatic spread of tumor cells: he genetically engineered mice so that their livers displayed a target for an adhesion molecule found on certain tumor cells. As predicted, the tumor cells homed in on the liver. For these experiments, Stamenkovic borrowed receptors and targets from the molecular adhesion system used by white blood cells to leave the circulation and enter tissues. Although this system was artificial, it may be that cancers naturally mimic white blood cells in much this way—cancer cells do often manufacture certain molecules (called Le) important to the mobility of white blood cells in the body.

Finding the Body's Area Codes

If, as seems likely, there is much to be learned by identifying the molecular addresses that white blood cells and tumors use to find particular tissues, a method of doing so that Renata Pasqualini, a postdoctoral fellow in my laboratory, and I have devised should prove helpful. We adapted a technique for isolating biologically active molecules from huge collections, or "libraries," of diverse compounds. The theory behind this approach is that if one screens a sufficiently large number of compounds, one can find a molecule for almost any purpose.

We use a large library of peptides (small pieces of protein) as the source of our compounds. During the 1980s, George Smith, now at the University of Missouri, devised a technique for building such a library that employs a phage, a type of virus that infects bacteria. If a short random piece of DNA is inserted into the phage's gene for a surface protein, the phage will thereafter display on its surface a corresponding random peptide. Applying Smith's method, one can create an entire library of phages carrying a billion different peptides, with each individual phage expressing only one peptide.

Our innovation was to test the affinities of peptides in this library by injecting the diverse viruses into a living ani-