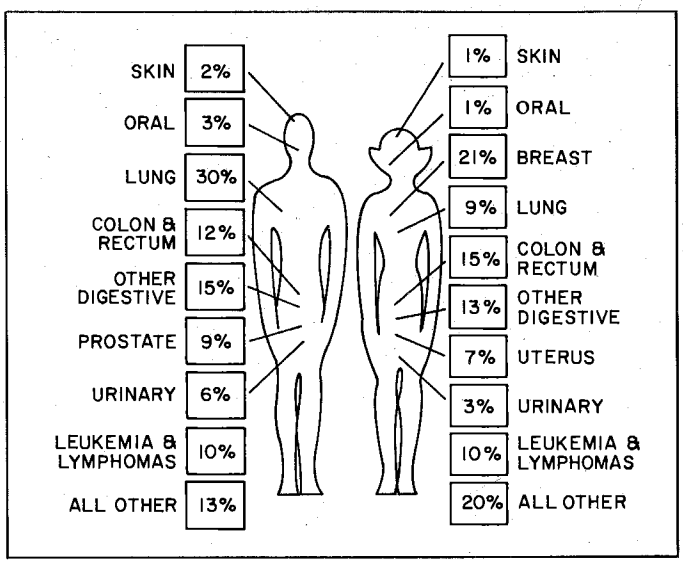
The ABC's of Cancer

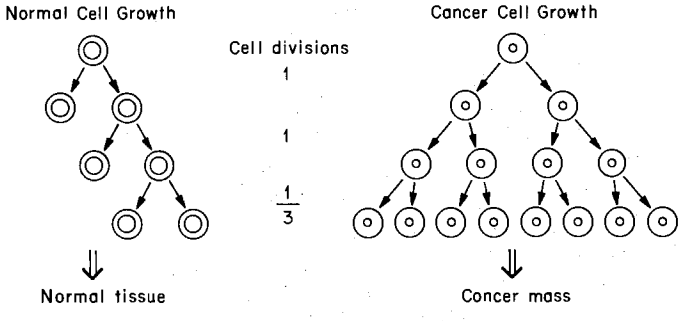
Cancer has had a profound impact on human experience and, accordingly, various segments of society see this disease in different ways. To the physician, cancer is a vexing, frustrating, sometimes tractable, but more often incurable disease. To the research scientist, it is a fascinating enigma which may provide a model for understanding some of the most difficult puzzles of cellular biology. To the layman, it is an unknown, shaped by vague rumors, superstitions, haunting deaths, and most of all by fear.

What Is Cancer?

Cancer is a disease in which cells divide when they should not. Most cancers start as a single abnormal cell which at each step of cell division produces daughter cells that in turn divide to produce additional cancer cells. In contrast, normal cells divide asymmetrically so that only one of the two daughter cells generally has the ability to divide and produce additional daughter cells (below). Thus a single cancer cell divides again and again in an uncontrolled fashion to produce a tumor mass with three general properties that are of clinical importance. First, the tumor mass generally increases rapidly in size. Second, it invades and destroys surrounding normal tissues. Third, clumps of cancer cells can break away from the parent tumor mass, migrate through the blood and lymphatic vessels of the body, and eventually come to rest in distant tissues such as the lungs or the liver to establish secondary tumor foci or metastases. The often explosive seeding and growth of these metastases present the physician with an extremely difficult clinical problem.



CANCER DEATHS BY SITE AND SEX—*It should be noted that the incidence of cancer in a particular tissue can be quite different from the incidence of cancer deaths at that same site. For example, 23 percent of the cancers arising in males occur in the skin, but only 2 percent of cancer deaths are attributable to skin cancer.*



A MODEL FOR NORMAL AND CANCER CELL GROWTH—*In general, each cancer cell can divide to produce two new daughter cells, but normal cells generally undergo an asymmetric cell division that leaves only one daughter cell with the capacity to undergo further cell division. In addition, the growth of normal cells is regulated by a variety of poorly understood mechanisms, while cancer cells divide in an unregulated fashion to produce a tumor mass.*

The prognosis for survival of a particular cancer patient correlates very well with the extent to which the cancer has spread. Patients whose tumor is discretely localized to a single site often have a favorable prognosis. Once the tumor has begun to invade the surrounding tissues the prognosis becomes only fair. Finally, when the tumor begins to metastasize to local and finally to distant sites, the prognosis becomes grave to terminal. Consequently, early cancer detection is an extremely important aspect of the clinical treatment of cancer.

Cancer can arise in any cell type, although it occurs much more frequently in certain tissues (above). In males, lung and colon cancer are major killers; in females, breast and colon cancer predominate. Cancer occurs most commonly in those tissues which cover various organs and are exposed to the external environment (i.e., air and food). Certain environmental agents or carcinogens may cause specific types of cancer.

Cancers of the same tissue may vary markedly in growth rate. For example, two women may each have a small and cancerous breast nodule about a half inch in

by Leroy E. Hood

diameter. After appropriate surgery, one woman will be alive and well 20 years later; in the second, the tumor will already have metastasized and spread throughout her lungs and bones, generally leading to death within a year. Thus the malignancy or the ability of a particular type of cancer to destroy the host varies enormously from one tumor to the next.

Cancer is also a disease that is related to the aging process. More than 50 percent of those cancers that eventually kill the host appear in individuals who are over 65.

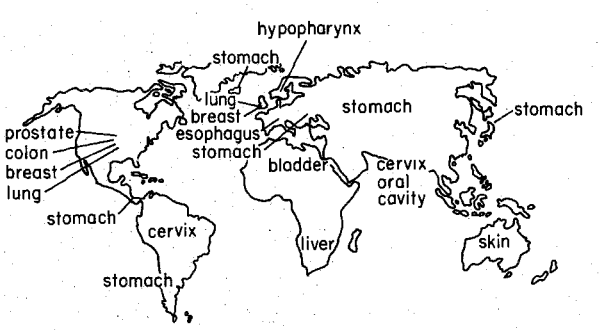
Cancer is the second leading killer in the United States, falling only behind heart disease. Approximately one person in four will contract cancer at some point in his life, and two families in three will be affected by it. In 1973 more than 350,000 Americans will die of cancer.

A Clinical View of Cancer

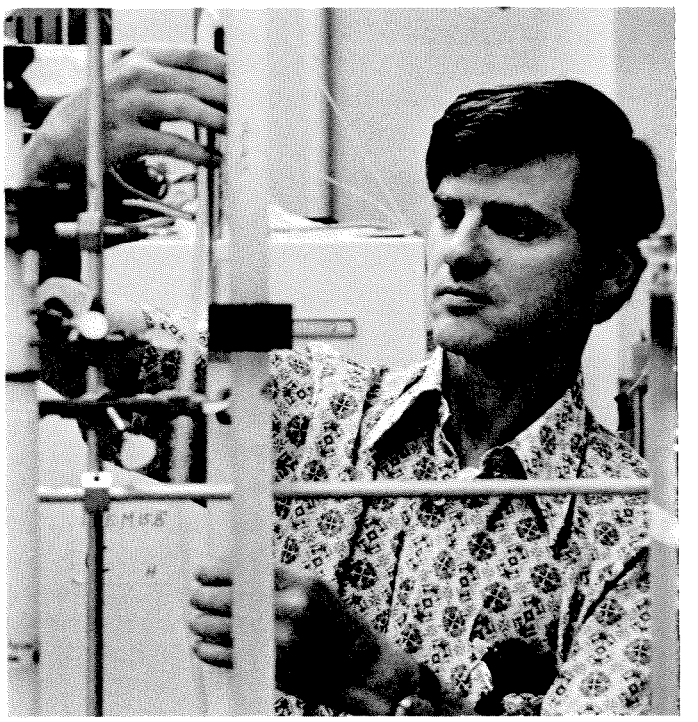
From the clinical viewpoint of the physician there are three aspects to cancer as a disease entity—prevention, diagnosis, and therapy.

Prevention

Environmental agents, or carcinogens, can cause cancer. For example, in 1775 an English surgeon named Percival Pott noted there was an extremely high incidence of cancer of the scrotum in chimney sweeps. His investigations led him to conclude that soot was the causative agent. With the advent of modern heating, the profession of chimney sweep disappeared in England and with it disappeared this particular form of cancer.



THE GEOGRAPHY OF CANCER—*Those forms of cancer with the highest incidence rates are shown for selected regions throughout the world.*



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It was not until 150 years later that a second English physician discovered the carcinogen in soot that was responsible for scrotum cancer. Thus, cancer caused by an environmental agent such as soot can be prevented by avoiding the responsible agent, even though the molecular details of how the carcinogen causes cancer are unknown. This observation also suggests that geographically distinct populations which are presumably exposed to differing carcinogens should vary in their incidence of particular types of cancer. Indeed, the incidence of differing types of cancer in various parts of the world differs markedly from one locale to the next (left). For example, predominant types of cancer in the United States arise in the lung, breast, colon, and prostate; in Japan, in the stomach; in Australia, in the skin; and in Southern Africa, in the liver. One of the most interesting examples of the "geography of cancer" is the incidence of esophageal cancer seen in a narrow belt around the tip of the Caspian Sea in Iran. Within this belt the incidence of esophageal cancer, which is extremely rare throughout the rest of the world, varies more than a hundredfold in regions geographically a short distance apart.

Some cancer experts believe that between 80 and 95 percent of cancer is environmentally caused

This unusual distribution of esophageal cancer might have one of two explanations. First, the people living in the region of high incidence may have a genetic constitution which makes them highly susceptible to this particular kind of cancer. This explanation seems unlikely because migrant populations can move from a region of low cancer incidence to one of high cancer incidence and in time assume the cancer rate of the native population. So, it appears likely that the esophageal cancer seen in Iran is caused by some unknown environmental factor(s).

Cancer Death Rates in Groups of Males Throughout the World*

	High	Low
Mouth	61.3	1.3
Nasopharynx	35.9	0.0
Esophagus	110.5	2.1
Stomach	172.2	6.6
Colon	30.6	0.0
Rectum	23.3	0.0
Pancreas	18.3	0.4
Larynx	15.6	0.7
Lung	154.3	1.9
Prostate	40.8	0.7
Bladder	34.6	1.9
Thyroid	17.0	0.0
Leukemia	15.6	1.3
Total	730.0	17.0

*Average annual death rate per 100,000 for 35-64 age group.

By combining the statistics from Indian oral cancer, Mozambique liver cancer, Chinese nasopharyngeal cancer, Central Asia's esophageal cancer, and so forth, a hypothetical population with an extremely high incidence of cancer can be constructed (above). This hypothetical population would have a cancer incidence rate more than 40 times that of a population constructed from groups with low cancer rates. Is it possible that the incidence of cancer could be markedly reduced by the identification and avoidance of carcinogenic agents in our environment?

Certain cancer experts concluded that between 80 and 95 percent of cancer is environmentally caused and could be prevented by avoiding the responsible carcinogenic agents, which may include viruses, various forms of polycyclic compounds, pesticides, and a variety of other agents present in the environment of contemporary man. Epidemiology, which is the study of the distribution of—and factors that cause—cancer, will certainly be an important aspect of the future control of the disease.

The time factor is extremely important in the understanding of human cancer induction by carcinogenic agents. Cancers develop in man and animals long after the causative agent has been in contact with the target tissue. The time interval, or latent period, can be as long as 20 years or more. For example, in the table below the statistics are given for bladder tumors among 78 men engaged under conditions of heavy exposure in the distillation of 2-naphthylamine and benzidine, two highly carcinogenic dyestuff intermediates. The group of workers who were exposed for only four years did not show a response for the first ten years of observation, but after 20 years their bladder tumor incidence was up to 30 percent, and by 30 years it was as high as 80 percent. For the workers exposed for five years or more the incidence observed in 30 years went up to 94 percent.

Progressive increase of bladder tumors among 78 aromatic amine distillers with increasing length of exposure

Length of latent period in years	Length of exposure in years					
	Up to 1	1	2	3	4	5 & over
	Percentage of workers with tumors					
Up to 5	0	0	0	0	0	0
10	0	0	0	0	0	11
15	0	17	22	0	10	45
20	4	17	22	40	30	69
25	9	17	22	70	70	88
30	9	17	48	70	80	94

Exposures to chemical carcinogens which produce lower levels of tumor incidences would be more difficult to detect, particularly if they were spread throughout the general population. The fact that it may take 20 years to detect the cancers in man due to the exposure to a new chemical carcinogen means that the chemical can be given to people for 20 years under the false appearance of harmlessness. If the effect is then detected and properly attributed to the specific chemical, and this is then removed from the environment, the cancers it induced will continue to appear for the next 20 to 30 years. More effective screening techniques for rapidly detecting possible carcinogens are desperately needed. This, perhaps, should be one of the most important areas of fundamental research in modern cancer biology.

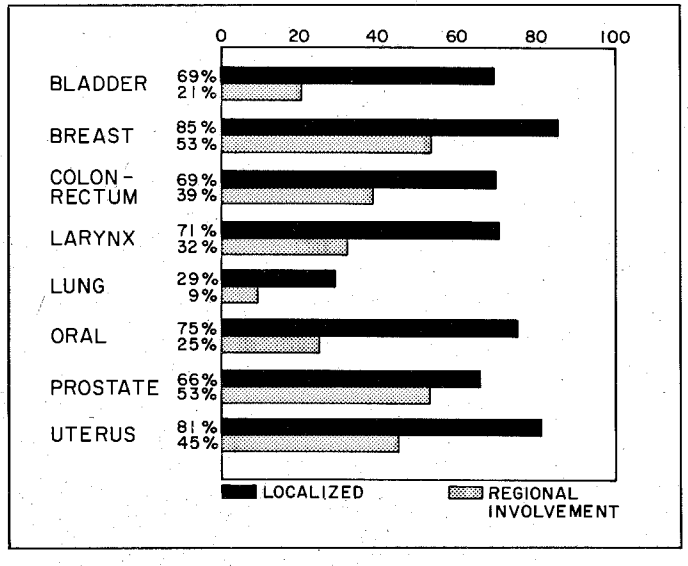
Diagnosis

The prognosis for a particular case of cancer depends primarily on the extent to which it has invaded surrounding tissues and metastasized to distant sites (right). The five-year survival rates can be three times as large in groups of patients with an early as opposed to a late cancer diagnosis. Thus, it is imperative that the earliest possible diagnosis be made. Two individuals play an important role in this early diagnosis—the patient and the doctor.

The patient can approach the problem of early diagnosis through an awareness of the early signs and symptoms of the most common forms of cancer (right). So the patient himself is the most important factor in the early diagnosis of cancer. For example, approximately 95 percent of the cases of breast cancer are detected by patients themselves. Unfortunately, cancer breast nodules can first be detected when they are about one-half inch in diameter, but it is just at this point that many breast cancers begin to metastasize—a fact that underscores the urgency of early diagnosis.

A thorough physical examination should include an inspection of the larynx, inspection of the colon and rectum, and for women a pelvic examination. The chest x-ray is almost the only diagnostic tool that is effective for lung cancer. Various blood and urine tests are also helpful. Most other tests for cancer are expensive, complicated, often ineffective, and to some degree risky for the patient. Indeed, these tests are not carried out unless there are specific indications for their use.

The ideal diagnostic test for cancer should be effective, simple, inexpensive, and relatively safe for the patient. There is at least one test that meets these criteria—the Papanicolau test, or pap smear, which detects cervical cancer by an examination of cells that can easily be scraped from this organ. This simple test has decreased by a factor of three the incidence of cervical cancer, which in the early 1930's was the leading killer of American women. Even today only about 50 percent of American women routinely have pap smears, yet it is obvious that cervical cancer deaths could virtually be eliminated from the American population if the pap smear was a routine, annual procedure for all women. A major effort in contemporary cancer research is directed at developing more of these simple, inexpensive, and routine screening procedures.



FIVE-YEAR SURVIVAL RATES FOR SELECTED CANCER SITES—*"Localized" indicates that the tumor has not yet started to metastasize. "Regional involvement" means that metastases have occurred in the nearby lymphatic system.*

Cancer's Seven Warning Signals

1. **Change in bowel or bladder habits**
2. **A sore that does not heal**
3. **Unusual bleeding or discharge**
4. **Thickening or lump in breast or elsewhere**
5. **Indigestion or difficulty in swallowing**
6. **Obvious changes in wart or mole**
7. **Nagging cough or hoarseness**

Therapy

Cancer patients fall into two classes—those who can be cured and those for whom treatment can merely extend life or alleviate suffering. The physicians' armamentarium contains three general therapeutic tools—surgery, radiation, and chemotherapy.

The oldest therapeutic approach is surgery. The rationale is that the tumor can be completely excised, and this approach is generally successful for well-localized tumors. For example, many skin cancers spread slowly and very high cure rates can be achieved with surgery. However, if the tumor is widely invasive or if it has metastasized, surgery is generally ineffective.

Radiation therapy can be effective for tumors that have started to spread. X-rays and radioisotopes kill rapidly dividing cells more readily than cells that are dividing at a slower rate. In general, cancer cells are rapidly dividing in comparison to most normal tissues and, accordingly, can be more readily killed by radiation. However, radiation therapy must be used carefully with organs which have rapidly dividing normal cells, such as the gastrointestinal tract.

Radiation therapy is useful because local tumor invasion and regional metastases can be destroyed by selecting an appropriately large field for radiation therapy. This type of therapy is probably used on more than 50 percent of the cancer patients treated today. For some types of cancer such as cancer of the cervix and the early stages of Hodgkins disease, the five-year cure rate with radiation is greater than 90 percent. Radiation therapy can, however, fail for a number of reasons. Some tumors are radiation resistant; often the tumor will have spread beyond the field of exposure; and, of course, the patient with widespread metastases is difficult to treat effectively with radiation therapy.

The final tool in the physicians' armamentarium is chemotherapy. The rationale for its use is that of the

Perhaps a "magic bullet" can be designed to kill cancer cells specifically without harming normal cells

"magic bullet." The hope is that a "magic bullet," a chemotherapeutic agent, can be designed to kill cancer cells specifically and not harm normal cells. This idea is based on the enormous success that antibiotics have had in killing the agents responsible for bacterial infections while not harming normal human cells. Unfortunately, cancer cells are derived from normal cells and so they are very similar to normal cells. Once again, chemotherapy depends on the fact that certain chemical agents can kill rapidly dividing cells more effectively than cells which divide at a slower rate. Most chemotherapeutic agents operate by blocking the synthesis of new DNA which, accordingly, blocks the production of new cells. For example, one class of chemotherapeutic agents, the antimetabolites, are compounds which very closely resemble compounds that are used by the body in the normal synthesis of DNA. In some cases the only difference between the two is the positioning of one chemical group about a carbon atom. Yet this subtle difference between antimetabolite and metabolite can render the machinery for DNA synthesis ineffective.

Chemotherapy is generally the only approach effective against disseminated types of cancer, whether due to metastases from solid tumors or to cancer of various types of cells in the blood, such as leukemia, because these agents are injected directly into the bloodstream and, accordingly, distributed throughout the body. Chemotherapy has a high five-year survival rate for a limited number of tumors (below), the most impressive of which is choriocarcinoma—cancer of the placenta, or the organ which attaches the fetus to the mother. This cancer is highly invasive, metastasizes early, and prior to chemotherapy was inevitably fatal; currently the five-year survival rate is greater than 95 percent.

Successful Results with Cancer Chemotherapy

Disease entity	5-year survival rate
Choriocarcinoma	95%
Burkitt lymphoma	75%
Wilm's tumor (kidney)	75%
Acute leukemia of childhood	50%

In the past five to ten years more effective chemotherapeutic approaches have been developed for dealing with one of the most tragic types of cancer, acute leukemia of childhood. The most effective therapies can now achieve a five-year survival rate of approximately 50 percent.

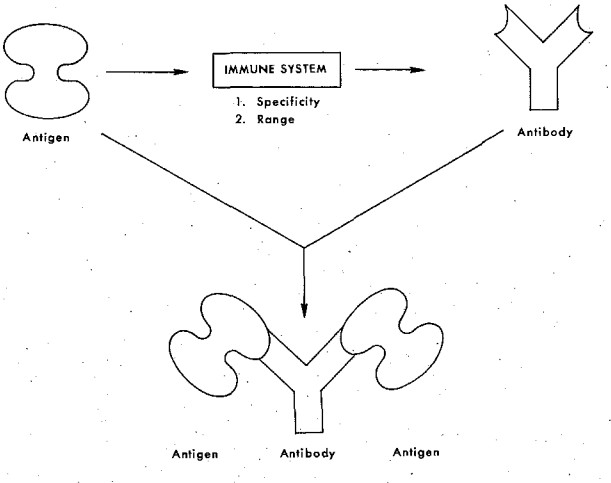
Surgery, radiation, and chemotherapy are now used effectively in various combinations. For example, large tumor masses are often excised, and regional or systemic metastases are countered with radiation or chemotherapy. It is very difficult to determine the optimal treatment for many types of cancer, particularly at the more advanced stages, as this determination requires the statistical analysis of large numbers of patients with appropriate controls. Such studies are rare in clinical cancer research; as a result, there is widespread controversy, even among cancer experts, as to the best therapeutic approach to many types of cancer.

The statistics on cancer survival are dismal. With current diagnostic and therapeutic techniques, for every six individuals who contract cancer, two are saved, one could be saved, and three will die. So new diagnostic or therapeutic techniques are required if the present death rate in cancer patients is to be changed.

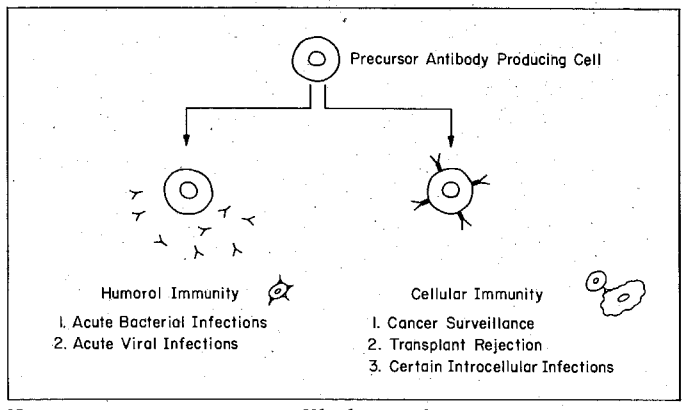
The Immune System

Modern research into the immune system and the role it plays in protecting man against cancer seems to offer enormous promise both with regard to the diagnostic possibilities for early cancer detection and the therapeutic possibilities of more effective cancer treatment.

The immune system is a complex entity comprised of a number of organ systems (such as lymph nodes, spleen, and thymus) and cell types (lymphocytes—or antibody-producing cells—and macrophages). One major function of this system is to defend man against invasive foreign organisms such as bacteria and viruses. This defensive system functions in part through the elaboration of serum proteins called antibody molecules (below). The foreign



A SIMPLE MODEL OF THE IMMUNE RESPONSE—*When a foreign organism or antigen is exposed to man's immune system, the production of specific antibodies is initiated. The immune response has two remarkable features—specificity and range. Each immune response produces antibody molecules specific for the particular antigen that triggered their production. The immune system is capable of an enormous range of responses in that it has the potential of elaborating specific antibody molecules to more than a million different antigens.*



THE TWO IMMUNE SYSTEMS—*The humoral immune system is concerned primarily with acute bacterial and viral infections; and the cellular immune system with the destruction of newly arising cancer cells (cancer surveillance), the control of certain intracellular and parasitic infections, and—more recently—with the rejection of foreign organ transplants. Here, humoral antibodies are shown killing a bacterium, and a cellular lymphocyte is destroying a cancer cell.*

organism, designated an antigen, gains entry into man's body and evokes the production of specific antibody molecules from the immune system. The antibody molecules are specific because they can combine at the molecular level with the particular antigen in a complementary fashion much as a lock and key fit together. This interaction leads to the destruction of the foreign bacteria or virus by a variety of mechanisms. The cells that produce antibodies are called lymphocytes, or antibody-producing cells.

The immune system is actually composed of two components with distinct functions, the humoral immune system and the cellular immune system. The antibody-producing cells of the humoral immune system synthesize specific antibody molecules and secrete them into the blood where they can interact with antigens throughout the entire vascular system and at a distance from the cells which produced them (above). In contrast, the antibody-producing cells of the cellular immune system synthesize specific antibody molecules and place them on their own cell membranes. These membrane-bound antibody molecules interact with antigens, and this juxtaposition of lymphocytes and the foreign entity leads to the destruction of that entity.

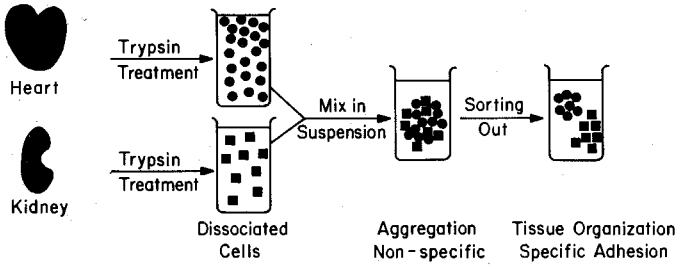
The cellular immune system plays an important role in the protection of vertebrate organisms against cancer. Man is a complex creature constructed of perhaps 10^{14} cells. He is continually exposed to a variety of environmental carcinogens which can transform one or more of those 10^{14} normal cells into cancer cells. One function of the cellular immune system, cancer surveillance, is to recognize cancerous cells and destroy them as they appear.

An impressive array of experimental evidence has been mustered to support the contention that the cellular immune system is involved in cancer surveillance. First, in patients who are to receive an organ transplant, immunosuppressive agents are often used to destroy the cellular immune system so that the foreign graft will not be rejected (left). In these "immunosuppressed" patients the incidence of cancer is approximately 100 times that of normal individuals. In fact, these patients exhibit extremely malignant forms of cancer which spread very rapidly. However, once the immunosuppressive agents are stopped, the patient's cellular immune system is regenerated, and these malignant cancers are rapidly destroyed. Second, the ability of patients to survive cancer depends on the effectiveness of their cellular immune system, and a simple skin test can determine that. Ninety-five percent of those patients surviving cancer surgery beyond two years do have a good cellular immune response, whereas 95 percent of those failing to survive cancer surgery have a poor cellular immune system. Third, the incidence of cancer increases with aging. In normal individuals, beginning at about 30 or 35 years of age the efficiency of the cellular immune system drops off in approximately a linear fashion; at this same time the incidence of cancer starts to increase. In each case the incidence increases when the efficiency of the cellular immune system is compromised.

Biochemical Properties of the Cancer Cell

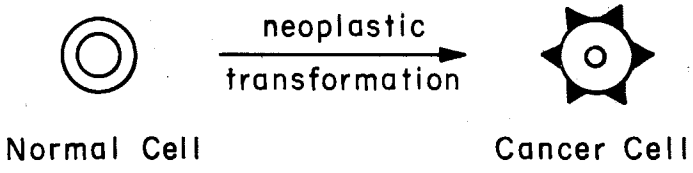
How does the cellular immune system recognize cancer cells as being different from normal cells so that it can initiate the appropriate immune response and tumor cell destruction?

Cancer cells appear to have three biochemical properties—each related to the cell membrane—which can explain at least in part the general clinical properties of a growing tumor. First, cancer cells can no longer receive signals from nearby neighbor cells which regulate the rate of cell division. Consequently, cancer cells grow in an unchecked fashion, and there is no regulation on the size of the tumor mass that is produced. Second, normal cells derived from the kidney, for example, will clump together in a tissue-specific fashion (below). In



SPECIFIC ADHESION OF CELLS FROM THE SAME TISSUE—*Normal organs such as the heart or kidney can be dissociated into single cells by appropriate chemical and enzymatic treatments. When dissociated cells from two normal organs are mixed together, at first they form nonspecific aggregates and later sort out into tissue-specific clumps. Tumor cells lose their ability to adhere in a tissue-specific fashion and form nonspecific aggregates when mixed with normal cells. Perhaps the loss of tissue-specific adhesion in cancer cells is due to the appearance of new molecules on their cell surfaces.*

"Cancer molecules" provide an opportunity for developing simple, safe, and early diagnostic tests for cancer



A SCHEMATIC OF THE "CANCER MOLECULES" ON A TUMOR CELL—*When a normal cell is transformed into a cancer cell, new molecules appear on the membrane surface which are here designated "cancer molecules."*

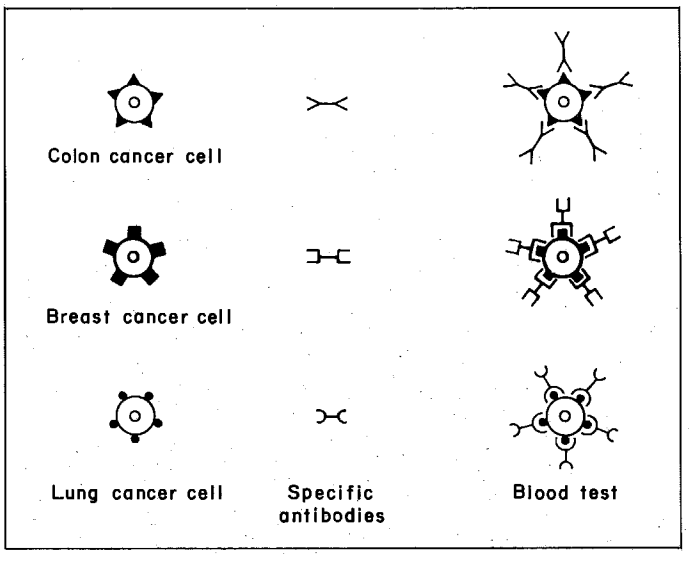
contrast, cancer cells can readily break apart from their nearby neighbors, and it is perhaps this property which often leads tumors to metastasize to distant regions of the body. Finally, cancer cells appear to have molecules on their surface that are not present on normal cell surfaces (above). These "cancer molecules" are foreign, and the cellular immune system mounts a response against them which leads to the eventual destruction of the cancer cell.

Immunodiagnosis

"Cancer molecules" provide an opportunity for the development of simple, safe, and early diagnostic tests for cancer. An example of this was demonstrated in 1965 by a young physician in Montreal named Philip Gold, who decided to undertake the study of cancer as part of a PhD thesis project. He chose human colon cancer as a model system because of its prevalence in man. Dr. Gold examined the differences between normal and cancer cells by injecting the tumor tissue into rabbits to raise antibodies against the colon "cancer molecules." Then he removed that fraction of the antibodies reacting with normal cellular components by absorption with normal tissue. Thus he was able to produce antibodies that could react with cancer cells and not with normal cells, and these antibodies appeared to be specific for the "cancer molecules" on the surface of the colon cancer cells (right). Gold then demonstrated that the colon cancer sheds its "cancer molecules" to the blood. He examined the blood from 35 patients with colon cancer using the antibodies specific to the colon cancer cells. In 97 percent of the patients the blood gave a positive reaction with the specific cancer antibodies, indicating that antibodies raised against "cancer molecules" may serve as a specific immunodiagnostic reagent for cancer detection.

The importance of such an early diagnostic test, once again, must be stressed, for in 1972 approximately 79,000 Americans contracted colon cancer. Of these, 47,000 died, and it is estimated that with early diagnostic techniques more than three-quarters of them could have been saved. In other words, if the simple and inexpensive immunodiagnostic test described above were specific and could be made a part of the general physical examination for all adults, approximately 35,000 deaths from colon cancer could be avoided every year. The future diagnostic potential for these immunodiagnostic techniques is even more exciting when we consider that six of the most common types of cancer cause approximately 60 percent of the cancer deaths seen in the United States. If simple immunodiagnostic tests could be devised for each of these six types of cancer, a tremendous saving of life would be possible (below).

Unfortunately, subsequent research has indicated that this kind of simple immunodiagnostic test has some difficulties. For example, the sera from patients with certain other types of cancer—and indeed that from certain patients with other types of disease—also react with the antibody molecules raised against the colon "cancer molecules." I think that eventually antibodies specific for a particular kind of cancer can be produced in one of two ways: through the use of sophisticated purification techniques to obtain homogeneous preparations of specific



A SCHEMATIC OF THREE TYPES OF CANCER CELLS WITH THEIR SPECIFIC "CANCER MOLECULES"—*It appears likely that most types of cancer have "cancer molecules" that are different from those of other cancers. Thus if specific antibodies can be produced against each type of "cancer molecule," they could be used as diagnostic reagents for the detection of cancer cells (or "cancer molecules") in the patient's blood. Since these antibody reactions are specific and very sensitive, very small quantities of "cancer molecules" can be specifically detected. When perfected, these immunodiagnostic tests will be ideal for the early diagnosis of cancer.*

"cancer molecules," or through the use of complicated immunologic procedures to absorb out undesired reactivities. Each of these approaches will require a great deal of additional fundamental research, and the problem does not appear to be at a stage now where expensive mission-oriented research efforts will yield fruitful results.

The immunodiagnostic technique developed by Dr. Gold for colon cancer is extremely useful in one regard at present. It can be used to follow cancer patients postoperatively after surgery. The level of "cancer molecules" in the blood following cancer surgery drops and remains at a low level unless there is a recurrence of cancer. Thus, this specific immunodiagnostic technique can be used to detect early recurrences, and appropriate action can be initiated immediately.

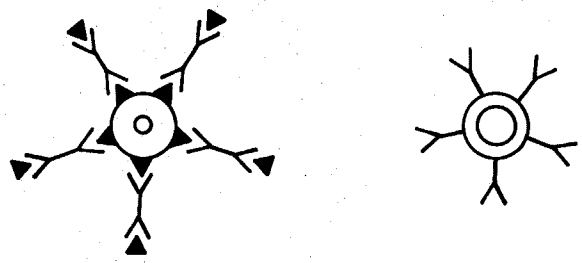
Immunodiagnosis promises to yield a real breakthrough into the early diagnosis of cancer in the future. But it is clear that a great deal of fundamental research remains to be done before this tool can be employed effectively.

Immunotherapy

The rationale for immunotherapy is similar to that for generating immunity against specific bacterial or viral pathogens. For example, cancer cells of a particular type might be killed and then used to immunize an appropriate host. In this fashion cellular immunity could be generated against the specific "cancer molecules," and this immunity could protect the host from that type of cancer. In practice, this type of approach can fail for a number of different reasons. One in particular is interesting because it demonstrates that under certain circumstances the two immune systems can oppose one another.

A husband and wife cancer research team in Seattle, the Hellstroms, made a series of interesting observations on a type of brain cancer found in small children, the neuroblastoma. Tumor cells were taken from a child in whom the tumor was actively growing, and they were cultured in a small petri dish. Since this tumor was growing in the child, the Hellstroms predicted that lymphocytes, or antibody-producing cells, taken from that same child and placed in the petri dish with the tumor cells would fail to kill the cancer cells. To their surprise, however, the lymphocytes from the tumor patient were very effective in killing the tumor cells—as long as these antibody-producing cells were removed from the patient's own blood. Why could the lymphocytes kill the patient's tumor cells in the petri dish, but not in his body? Because cancer cells shed their cancer molecules into the blood and stimulate the production of a specific type of humoral antibody which combines with the specific cancer molecule to form what is termed "blocking factor." Blocking factor, as its name indicates, apparently blocks the cellular immune system from effectively destroying cancer cells.

One possible mechanistic explanation for the behavior



ONE POSSIBLE MECHANISM BY WHICH BLOCKING FACTOR PROTECTS CANCER CELLS FROM IMMUNOSURVEILLANCE—*Blocking factor, a combination of a humoral antibody molecule and a specific "cancer molecule," may enhance tumor growth by shielding it from the cellular immune system.*

of blocking factor is that it can cover the "cancer molecules" and prevent lymphocytes from the cellular immune system from interacting with cancer cells (above). The blocking factor seems to form a protective coat around cancer cells, which then grow even in the presence of lymphocytes that are capable of destroying them once the blocking antibodies are removed. Thus, the effects of the two immune systems can oppose one another.

The neuroblastoma of childhood is also interesting because it undergoes spontaneous remissions at the rate of 1 to 2 percent; that is, tumors occasionally disappear in relatively short periods of time. These spontaneous remissions appear to be an immunologic phenomenon in which a second type of humoral antibody appears that has the ability to remove the blocking factor. Appropriately enough, this second type of antibody is called "unblocking factor," and in its presence the cancer cells can once again be killed by lymphocytes, even in the presence of blocking factor.

The existence of unblocking factor raises some interesting possibilities with regard to cancer therapy. They are illustrated by the clinical history of a young doctor from New York State. He came from a family with a history of hypernephroma, a kidney tumor. Hypernephromas are, like neuroblastomas, tumors that occasionally undergo spontaneous regression. This young physician contracted a hypernephroma which was presumed to be successfully removed by surgery. But six months later it was learned that the hypernephroma had metastasized to his lungs. A second surgical procedure removed most but not all of the tumor from the lungs. The prognosis was grave.

The young physician, however, was aware of an uncle who had some years earlier contracted a hypernephroma which later underwent a spontaneous regression. Knowing of the Hellstroms' work, he reasoned that unblocking factors must be present in the serum of his uncle, so he underwent a bimonthly series of serum transfusions from his uncle for a period of more than two years. Now, some four years later, the young physician is completely free of

cancer. The Hellstroms checked the serum from this young physician and were able to demonstrate blocking factors and unblocking factors at appropriate times throughout the clinical course of his disease. Of course, the young physician's tumor may have actually undergone a spontaneous remission just as did the tumor of his uncle in the past. We will never know whether the uncle's unblocking factor really contributed to the young physician's recovery, but this clinical course points out one exciting possibility for immunotherapy.

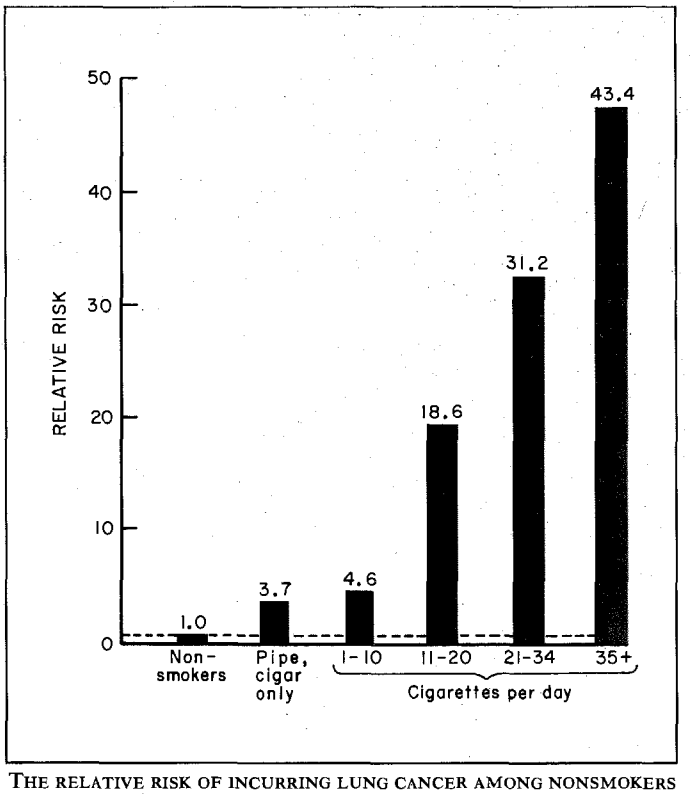
The general problem with regard to immunotherapy is to learn how to manipulate the two immune systems independently of one another. How can we immunize individuals so that blocking factor is not produced? How can the cellular immune system be specifically stimulated to provide immunity against various types of cancer? These are difficult questions which will require concerted efforts in fundamental research before immunotherapy will be an effective and safe tool for the physician. Immunotherapy offers enormous possibilities for a cancer cure, but that cure will not come in the near future.

Some Social and Ethical Aspects of the Cancer Problem

There is an undeniable statistical correlation which links cigarette smoking and lung cancer (right). In the past, smoking has been a matter of personal choice and, indeed, it has been viewed as a fundamental right by many. These attitudes may have to change in the future because it is clear that cigarette smoke is just as harmful to people who do not smoke as to those who do. Since this is so, those who have sat on a plane for four or five hours inhaling someone else's cigarette smoke may feel that their basic rights are being infringed.

This question of the infringement of rights has much broader sociologic implications. For example, suppose that smog is carcinogenic. Can a certain subset of the population, perhaps a majority, choose to risk an increased incidence of cancer in order to have unlimited use of cars and other concomitants of smog? Can this majority force a minority to accept environmental conditions that are unhealthy? This question can also be posed for those environmental carcinogens, such as DDT, which are economically beneficial but dangerous. Society is going to have to identify these environmental carcinogens and balance the economics and convenience of their use against their potential risk as carcinogenic agents.

Euthanasia or mercy-killing is an ethical consideration which relates to the problem of cancer in at least two regards. First, most of us have seen at least one example of the agony and suffering of terminal cancer patients where in certain cases even the most powerful drugs fail



THE RELATIVE RISK OF INCURRING LUNG CANCER AMONG NONSMOKERS AND VARIOUS GROUPS OF SMOKERS—*Those who smoke more than 35 cigarettes per day, for example, are more than 43 times as likely to develop cancer as those who do not smoke.*

to alleviate suffering. The response to this suffering can be extreme. For example, in August of 1967 a young man was arrested because he had killed his mother. She was dying of leukemia and had for three weeks begged him to end her life because of the agony and hopelessness of the terminal stages of this disease. How should society view this crime? Should an individual be able to choose to terminate his life under such circumstances? Second, the extremely sophisticated life-support systems that physicians now have make it possible to keep terminal cancer patients alive for protracted periods of time. In the future these life-support systems will become more sophisticated, and patients could be kept alive for even longer periods of time —prolonging the suffering and agony that families must go through, as well as incurring enormous expenses. Clearly the question of euthanasia is an issue that society—laymen and physicians alike—must deal with in the near future.

Cancer is a disease entity which poses complex social and ethical questions as well as challenging clinical problems and exciting opportunities for probing the innermost workings of the human cell. The future for the eventual control of cancer is very promising, but a great deal of fundamental research is still required. Do not expect too much too soon. □