Immunity, Disease, and Cancer
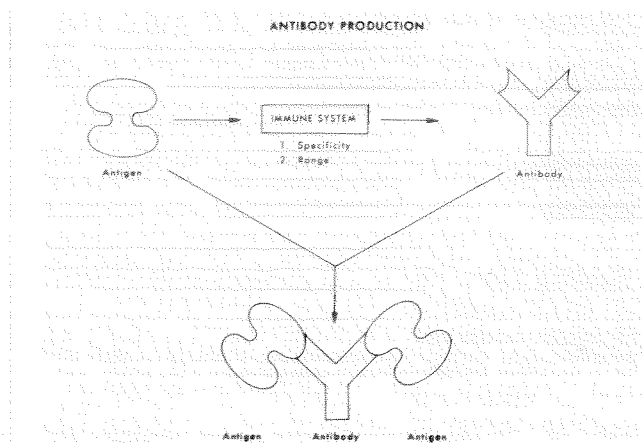
by Leroy E. Hood

The immune system plays a central role in protecting vertebrate organisms against disease. Indeed, immunology, the study of the immune sustem, has played a fundamental role in many striking advances of modern medicine. This discipline relates to a variety of disease states including infections, allergies, autoimmune conditions, organ transplantation, and cancer. Here I would like to discuss two aspects of immunity — how the immune system functions, and the interrelationship between immunity and two general categories of disease, infections and cancer.
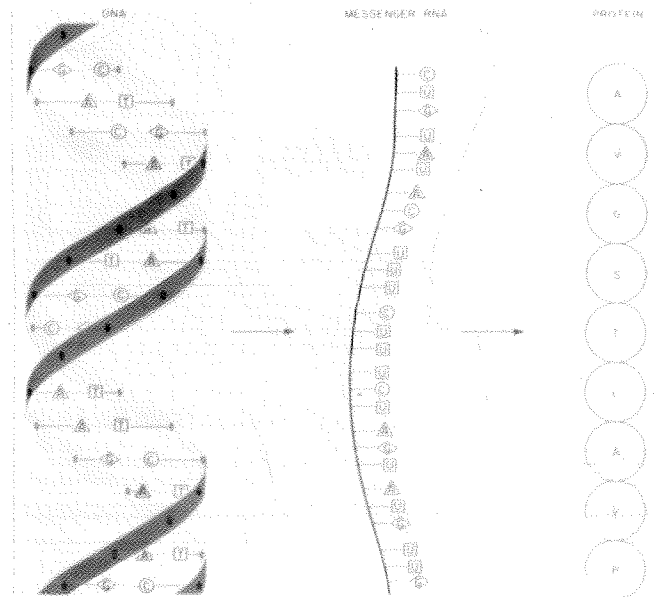
THE IMMUNE SYSTEM

Immunity and foreign patterns. The immune system has evolved to recognize foreign molecular patterns. These foreign molecular configurations may lie on viruses, bacteria, or even cancer cells. Accordingly, the function of the immune system is to recognize and destroy, or eliminate, any molecular patterns that are different from those contained within the organism itself.

How does the immune system function? Let us consider the vertebrate immune system as a black box (below). When a bacteria (antigen) invades the organism, its foreign

The synthesis of proteins. The linear information of a gene (DNA) is transcribed into messenger RNA which finally is translated into a linear protein.

A black box model of the immune response. The immune system responds to foreign molecular patterns (antigen) with the production of specific antibodies.

patterns stimulate the immune system to synthesize antibody molecules which are then released into the bloodstream. These antibody (protein) molecules have two special features. First, they can combine with the antigen that elicited their synthesis in a highly precise and specific manner. These precise molecular interactions ultimately lead to the destruction or elimination of the antigen. Second, the immune system can respond to millions of different antigens with the synthesis of specific antibodies for each. Thus the specificity and range of the immune response are virtually unlimited.

Antibodies and molecular complementarity. How is it possible for antibody molecules to recognize any one of millions of different antigens? The chromosomes are blueprint repositories containing all of the information necessary to construct an organism (above). Individual

units of information on each chromosome are called genes. The vertebrate organism has many genes encoding antibody molecules. The information in a particular gene is converted into a specific protein by a complex cellular process called protein synthesis. A protein is a linear polymer comprised of 20 different subunits termed amino acids. The precise linear order of amino acids in a protein is dictated by the gene. Proteins are the building blocks from which living organisms are constructed. How then is the linear one-dimensional information of the gene and the protein translated into the three-dimensional information that allows proteins to carry out their various functions? The individual amino acid subunits have different sizes, electrical charges, and shapes. The particular order of amino acid residues causes a protein to fold into a precise three-dimensional shape. Accordingly, the specificity of an antibody molecule arises from the fact that it folds into a three-dimensional pattern that exhibits molecular complementarity for its corresponding foreign pattern, much as a key fits into a lock (below).

The fundamental unit of function in the immune system is the antibody molecule. The range of vertebrate immunity arises because each organism can synthesize a million or more different antibody molecules, each of which exhibits a unique three-dimensional configuration that permits it to recognize and bind a unique foreign antigenic pattern. Moreover, the antibody molecule is an extremely sophisticated molecular machine that carries out two inter-related types of functions. One portion is involved in pattern recognition, and the second triggers the elimination or destruction of the antigen. Let us now consider the cells that synthesize antibody molecules and the two distinct ways in which they are employed.
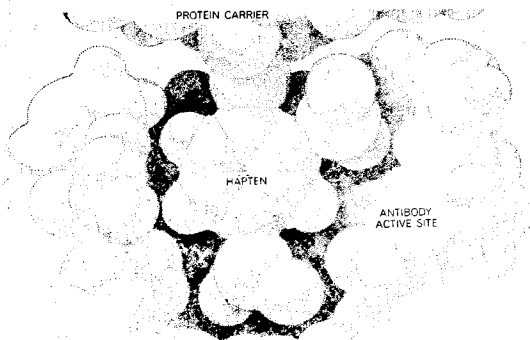
A hypothetical example of the molecular complementarity an antibody exhibits for its corresponding foreign pattern or hapten.
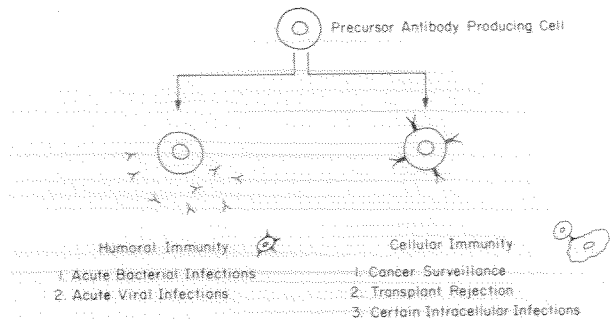

The humoral and cellular branches of the immune system

Humoral and cellular immunity. The immune system has two distinct functional branches which utilize antibody molecules differently (above). Antibody molecules are synthesized by cells designated lymphocytes which are morphologically indistinguishable for both branches. Lymphocytes of the humoral immune system secrete antibody molecules directly into the blood. Thus humoral antibody molecules can meet and destroy antigen at great distances from the lymphocyte that synthesized them. In contrast, lymphocytes of the cellular immune system place antibody-like molecules on their cell surfaces. These cell-surface antibodies serve to juxtapose the corresponding lymphocyte next to a cell that has a foreign molecular pattern, such as a cancer cell, and the lymphocyte itself mediates the killing of the foreign cell. Clinically, the humoral and cellular immune systems carry out distinct functions. The humoral immune system is concerned with fighting acute bacterial and viral infections for which the pathogenic organisms are found mainly in the blood. In contrast, the cellular system is involved with a variety of intracellular infections such as tuberculosis and many parasitic infections, and with cancer. Evidence for the discrete nature of these two branches of the immune system is provided by those rare individuals who lack either a cellular or humoral function. Let us now consider the anatomy of the immune system.

Anatomy of immunity. Lymphocytes in adults arise in the marrow of the bones (page 8). Lymphocytes from both the humoral and cellular systems arise from a single stem or progenitor cell. How then do these lymphocytes acquire their two very different sets of characteristics? Precursor cells of the cellular system arise in the bone marrow and migrate to the thymus where they undergo a diffentiation process that includes the acquisition of many new cell-surface molecules (page 8). After this maturational process, lymphocytes migrate into the blood circulation and are

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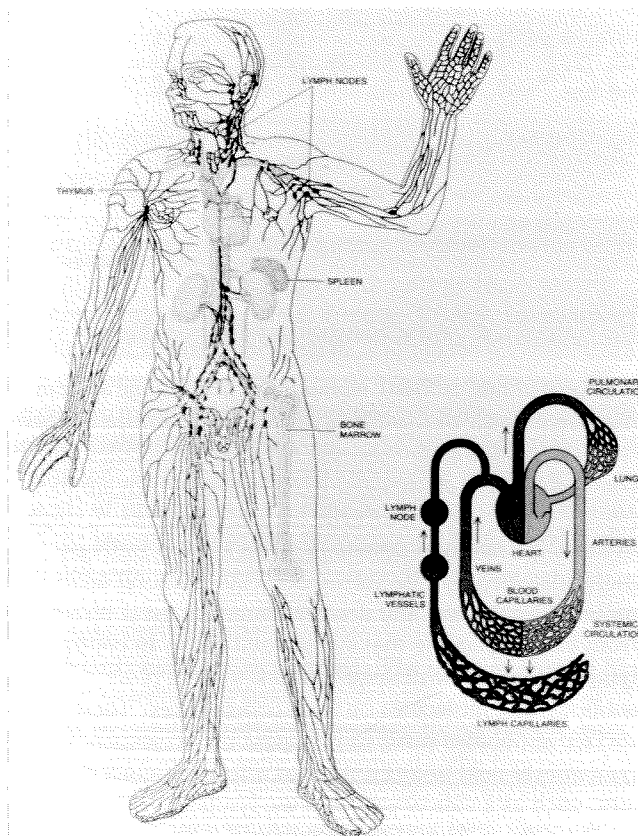
The organs and circulatory pathways of immunity

then capable of recognizing and destroying foreign patterns. Conversely, precursor lymphocytes of the humoral system mature in the bone marrow itself and then migrate into the circulation.

How do lymphocytes patrol the entire body and protect it against disease-causing or pathogenic organisms? Lymphocytes can circulate throughout either of two circulatory systems which pervade the entire body (above). The blood circulation is a closed system including the arteries, capillaries, veins, and its pump — the heart. Lymphocytes can migrate through the walls of certain blood vessels into the lymphatic system, which is comprised of thin-walled vessels and one-way valves. The pumping of the lymphatic fluid is carried out by the movement of nearby muscles. The blood and lymphatic systems have biological filters — the spleen and lymph nodes, respectively — where antigens are trapped and interact with lymphocytes to induce the immune response. For example, the swelling and soreness of nodules in the elbow in response to an infection of

the hand represents an immune response occurring in that particular lymph node. These two circulatory systems extend throughout the entire human organism and permit the ever-circulating lymphocytes to patrol most of our body in their never-ending search for foreign patterns.

Immunization and clonal expansion. The immune system is capable of generating an enormous amount of information in the form of antibody molecules, which it employs to recognize and destroy millions of different foreign patterns. How then does the immune system express this information in an orderly and controlled fashion? How does it turn on the synthesis of those particular antibodies needed to respond to an individual pathogenic organism, and at the same time fail to turn on the synthesis of hundreds of useless antibody molecules?

The answer to these questions is contained in two observations about the immune system. First, each lymphocyte is capable of synthesizing just a single type of antibody molecule (below). Some of these antibody molecules are placed on the surface of the lymphocyte and, upon interaction with a complementary antigen, they trigger the cell to divide and generate 1,000 to 10,000 daughter cells with identical antibody-synthesizing capacities (below). The functionally identical progeny of a single lymphocyte are termed a clone. Thus, exposure to an antigen — which is called immunization or vaccination — causes a 1,000-fold expansion of the lymphocytes that can respond to that particular antigen. Clonal expansion, then, is the cellular basis for the enhanced immunological responses that come with immunizations for smallpox, measles, or influenza. Second, the human organism has about 10^{12} lymphocytes that
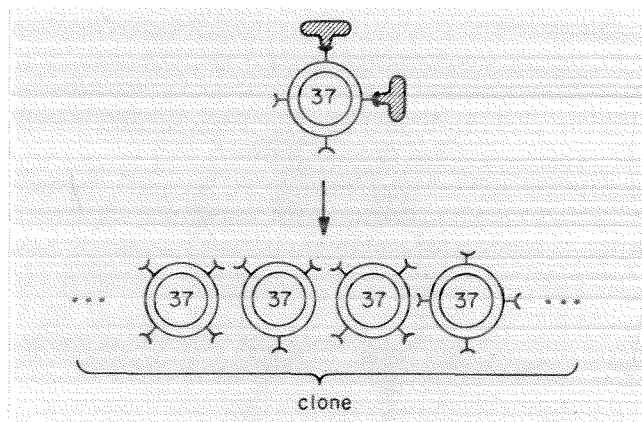
Clonal expansion of a lymphocyte by antigen. The shaded entity denotes an antigen. The $\curlyvee$ designates a cell-surface receptor antibody. The number 37 indicates that each of each of these lymphocytes synthesizes the same type of antibody molecule.

are capable of responding to virtually all foreign patterns. So different antigens will cause distinct lymphocytes — those synthesizing complementary antibodies — to undergo clonal expansion. Thus humans have a vast library of lymphocytes poised and ready to react with a multitude of different foreign patterns.

In brief summary, the antibody molecule is responsible for the specificity of the immune system. Humans can synthesize perhaps a million different antibody molecules that collectively can respond to most foreign patterns. Clonal expansion allows the immune system to respond effectively to invasions by foreign organisms. Let us now consider infectious disease and immunity.

INFECTIONS AND IMMUNITY

Infectious diseases are caused by the invasion of disease-producing micro-organisms such as bacteria or viruses. The foreign organism may be pathogenic because it produces a toxic substance which, for example, may paralyze the heart or destroy certain cells of the brain. Alternatively, the organism may directly invade and destroy specific tissues such as the lung or kidney. Let us consider the immunology of two infectious diseases.

The eradication of smallpox. Immunology as a science began with a partial understanding of the immunology of smallpox. It is estimated that this disease killed between 10 and 20 percent of the English population in the 17th and 18th centuries. A surgeon, Edward Jenner, noted in 1796 that one group among the English population — milkmaids — remained free of the pox marks characteristic of the nonlethal form of smallpox. Jenner reasoned that the milkmaids' protection was in some manner derived from their early exposure to cowpox, a related but much milder pox-like disease. He then immunized an 8-year-old with pus from a cowpox infection and later demonstrated that the boy was totally resistant to subsequent infection by smallpox. The general acceptance of this medical advance was slow to come, however, and it was not until the 20th century that smallpox vaccinations were widely employed as a public health measure.

In 1967 approximately 10 to 15 million cases of smallpox were distributed throughout 42 countries of the world. At this time the World Health Organization (WHO) established a program to eradicate smallpox within 10 years. Several factors led to this first optimistic proposal to eliminate one of mankind's major diseases. First, the virus that causes smallpox has but a single host — man. Moreover, smallpox infections within an individual are of limited duration, and therefore the virus must move to a
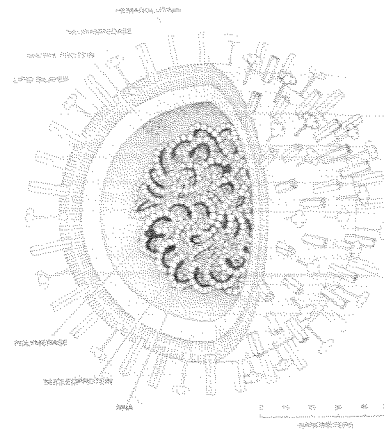
The structure of the influenza virus with a portion of the shell removed to reveal its inner proteins (polymerase and nucleoprotein) and genes (RNA).

new host or die. Second, immunization prevents the smallpox virus from living in the vaccinated host. Accordingly, once a case of smallpox is identified and those people around the diseased host are vaccinated, the smallpox virus dies out because it has no unprotected host into which it can spread. Once the WHO program was initiated, the number of countries reporting smallpox infections dropped rapidly from 42 to 16, then to 5, and, finally, in 1978 smallpox was totally eradicated as a disease — certainly a major triumph in the annals of modern medicine. Unfortunately, this elegant approach cannot be applied to most other infectious diseases. Let us consider a second example, the viral infection influenza.

Influenza – cyclic and recurrent infections. The structure of the influenza virus is shown above. Basically the eight small chromosomes that encode this virus are surrounded by a membrane shell which has several types of spikes projecting from the virus. These spikes carry the foreign antigenic patterns against which the human immune system reacts. Two factors explain the cyclic and recurrent infections of influenza throughout human populations. First, when two influenza viruses with distinct foreign patterns infect the same host, the small chromosomes may exchange (recombine) genetic information to generate entirely new foreign patterns heretofore unseen by human hosts. Accordingly, there is a continual race between the human immune system that immunizes one against the foreign patterns of particular influenza viruses and the ability of these viruses to undergo recombination and generate entirely new foreign patterns. Second, the influenza virus can live in a wide spectrum of hosts including many domestic animals and birds. Hence there are enormous animal reservoirs from which influenza viruses with new and distinct foreign patterns may emerge. What marks

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each of the great pandemics of influenza that mankind has suffered in the last 50 years is the emergence of entirely new types of foreign patterns for the antigenic spikes. As rapidly as the human immune system develops antibodies that react against an established influenza pattern, a new type of influenza virus emerges to reinfect mankind.

Resistant infections. Certain infectious diseases have been notoriously resistant to the immunological approach. For example, the gonococcus, a bacterial organism causing veneral disease in approximately 10 percent of the juvenile population of California, has resisted all attempts to generate effective immunization procedures. This failure underscores the need to understand the fundamental aspects of the immune response and the means by which difficult antigens like the gonococcus may be rendered more immunogenic. These kinds of fundamental studies are under way in many laboratories throughout the world.

Let us now turn to cancer and consider the biology of this complex disease before considering how immunology may be employed to fight cancer.
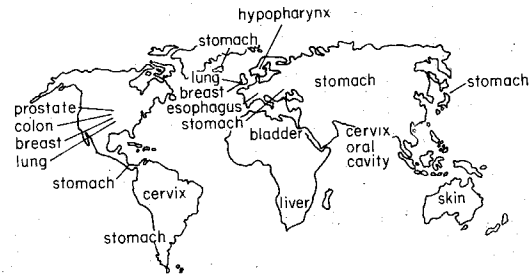
CANCER

Cancer biology. The statistics of cancer are awesome. Last year more than 400,000 United States citizens died of cancer. Cancer will kill every fifth American. A very high percentage of those who acquire this disease will eventually die from it.

Cancer is not a single disease; rather, it is a spectrum of different but related diseases. Cancer may arise in virtually any tissue or cell type. Cancerous cells lose their ability to control their rate of cell division, and they divide again and again in an unchecked fashion. Thus a large cancerous mass or tumor is generated. A fundamental property of cancerous or neoplastic cells is that they acquire the ability to invade surrounding tissues. Often cancer cells separate from the main tumor and pass via the blood or lymphatic systems to seed new tumors in distant parts of the body. These secondary cancer foci are termed metastases, and they probably result in the majority of cancer deaths by destroying the functions of vital organs.

There are three general categories of cancer. Carcinomas are cancers that arise in the tissue coverings of the body — the skin, the gastrointestinal tract, the respiratory tract, and the ducts of various glands. Sarcomas arise in the connective tissues of the organism. Leukemias and lymphomas are tumors of the blood cells — the lymphocytes, red blood cells, and white blood cells.

Many cancer biologists believe that the majority of cancers — perhaps as many as 90 percent — arise because of


The geography of cancer. The types of cancer most frequently found in specific areas are indicated.

exposure to environmental cancer-causing (carcinogenic) agents. This is consistent with the observation that the vast majority of cancers are carcinomas that arise in those tissues most directly exposed to the environment — the body coverings. Let us now consider the case for environmental carcinogens.

Environmental cancer. There is a distinct geographical distribution to certain types of cancer; that is, distinct types of cancer are prevalent in different countries (above). For example, in Japan cancer of the stomach is prevalent, whereas in the United States more than 50 percent of cancer deaths are caused by three types of cancer — lung, breast, and colon.

There are two possible explanations for these distinct geographical distributions of tumors. Obviously humans may be exposed to different environmental carcinogens in different environments. Particular carcinogens will cause specific types of cancer. Alternatively, perhaps different gene pools lead to the tendency of different types of cancer to arise in various countries. Careful analysis of this latter possibility suggests that genetic differences are an unlikely explanation for the asymmetric geographic distributions of
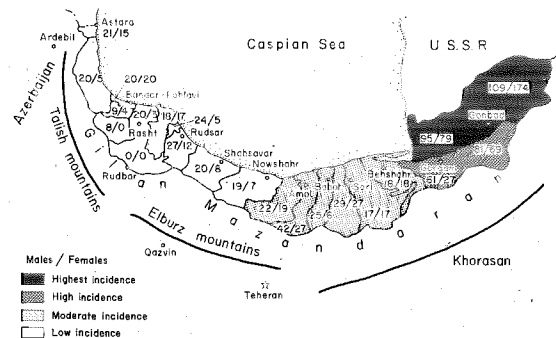
Incidence rates of esophageal cancer in the Caspian Littoral of Iran. Numbers indicate the cancer rate per 100,000 individuals, with male incidence on the left and female on the right.

cancer. For example, portions of Iran have an extremely high incidence of cancer of the esophagus (below left). Other regions have a very low incidence of this same cancer. When migrants move from an area of low to high cancer incidence, their children acquire the high incidence of esophageal cancer characteristic of the new area. The inverse also is true. Hence genetic factors do not control the rate of this cancer; rather, there appears to be some unknown environmental carcinogen that causes a high incidence of esophageal cancer in certain areas of Iran.

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 35-54 age group.

A fundamental feature of environmental cancers is that they appear to have a long latent period between the time of first exposure to the carcinogen and the acquisition of this disease. For example, the incidence of smoking among men in the United States increased exponentially during the early 1900's. After a lag period of about 20 years, the incidence of lung cancer also rose in an identical exponential fashion. Indeed, a significant increase in smoking among women 15 to 20 years ago is just now being followed by a corresponding increase in lung cancer among women smokers. The latent period in the acquisition of environmental cancers obviously makes it difficult to trace the causes of particular cancers and to predict what effect a new widely distributed potential carcinogen might eventually have.

The highest and lowest rates of specific types of cancer in various countries are shown above. If one could assemble the ideal environment from each of those countries with the lowest rate of cancer, the cancer incidence would be roughly 40 times less frequent than for countries with the higher incidences. Indeed, individuals belonging to the Seventh Day Adventists have roughly half the incidence of

cancer of the average American population, a statistic probably related to the Adventists' strict views on smoking, eating, and drinking. These observations raise provocative questions. Once potent environmental carcinogens are identified, how can we deal with them? For example, virtually all lung cancers in the United States are directly caused by cigarette smoking. The elimination of cigarette smoking would save more lives than the abolition of all other forms of cancer put together. Does the government have a responsibility to control more effectively this unequivocal environmental carcinogen? These same arguments will be raised for other carcinogens as we identify them.

Once an individual has acquired cancer, how is it treated?

Cancer therapy. There are three classic treatments for cancer — surgery, irradiation, and chemotherapy. Highly localized tumors are excised by surgery. Tumors that have invaded surrounding tissues may be treated with irradiation. Widely disseminated cancers such as leukemias must be treated by anticancer agents injected into the blood (chemotherapy). Each of these three forms of treatment is nonspecific in nature; that is, these approaches kill or destroy normal as well as cancerous cells. Immunology offers the hope of eventually being able to develop cancer therapies that are highly specific only for the cancer cells.

Immunology of cancer. A cancer cell is distinguished from its normal counterpart by the presence of special cancer antigens on the surface of the cancer cell (below). All types of tumor cells appear to acquire these new cancer antigens. Hence cancer antigens appear to be an inevitable consequence of the neoplastic transformation of individual cells.

Some immunologists believe that the immune system evolved in complex and multicelled organisms in order to destroy continually arising cancer cells. This line of reasoning suggests that in any complex organism, normal cells such as those of the intestine or bone marrow are con-
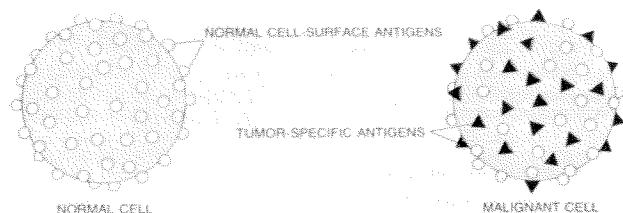
Cancer antigens. A cancer cell is distinguished from its normal counterpart by virtue of newly acquired cell-surface molecules called tumor (cancer) antigens.

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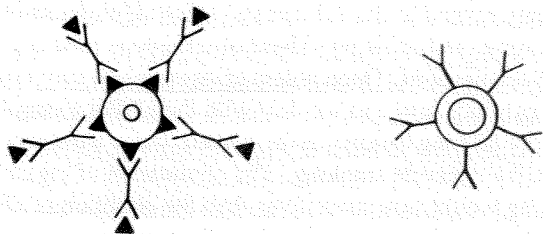
Humoral antibody molecules may shield a tumor cell (left) from destruction by the cellular immune system (right).

tinually dividing. Occasionally neoplastic cells arise from these dividing cells and express foreign cell-surface antigens. The cellular immune system can then destroy these newly emerging cancer cells by recognizing the foreign nature of their cancer antigens. By this view, the immune system evolved as a surveillance system for destroying neoplastic cells before they proliferate and destroy the organism. Accordingly, clinically diagnosable cancers must in some fashion escape this surveillance system.

The rationale for immunotherapy is that the immune system of one individual may be activated to attack the particular type of cancer he has acquired. In principle, the humoral and cellular immune systems could be immunized or activated against a particular cancer. In practice, immunotherapy has not been successful to date for several reasons. First, immunizations against cancer antigens have not been very effective for a variety of technical reasons. Second, most cancers are not susceptible to destruction by humoral antibodies. Indeed, humoral antibodies may "block" the beneficial effects of the cellular immune response to tumors by covering up the foreign antigenic patterns on the surface of the cancer cell (above) and thus preventing the cellular lymphocytes from attacking the cancer cells. Accordingly, successful cancer therapy in the future will require the fundamental understanding of two general problem areas. First, how can tumor antigens be isolated and rendered more immunogenic? Second, how can the cellular but not the humoral immune response be stimulated by immunization with cancer antigens?

It is now possible to make antibodies that detect certain types of cancer antigens. These antibodies can be used as diagnostic reagents to search for very low levels of cancer antigens in the blood of apparently normal individuals. A future goal is to make specific antibodies for each of the major types of human cancer and to use these antibodies as routine diagnostic agents to detect cancer at its very earliest stage — for the early detection of cancer often leads to its successful cure (right). Perhaps in the future these

diagnostic cancer antibodies will be a routine part of the periodic medical examinations that older individuals should undergo.

Immunotherapy and immunodiagnosis offer exciting future prospects for dealing with the cancer problem. However, additional fundamental research is required before these techniques can be effectively and widely applied. We must not expect too much too soon.

CALTECH'S MEDICAL SCIENCES PROGRAM

Caltech has initiated a new program termed the Medical Sciences Program. This program will entail the appointment of three new professors and the construction of a new building — the Braun Laboratories of Cell Biology and Chemistry. The focus of this program will be immunology, a discipline which, as you can now appreciate, interfaces beautifully with fundamental and clinical research. The newly recruited professors also are to be interdisciplinary; they will be outstanding fundamental researchers as well as individuals with medical backgrounds. One hope is that fundamental discoveries can be rapidly translated into the applied realm of medicine.

Caltech offers a unique environment for this new program with its small size, its scientific excellence, its superb students, its access to the high technology of the Jet Propulsion Laboratory, and its close relationships with several local medical institutions, including the Huntington Memorial Hospital and the City of Hope. This program insures that Caltech will remain at the cutting edge of fundamental biology and medicine for years to come. □
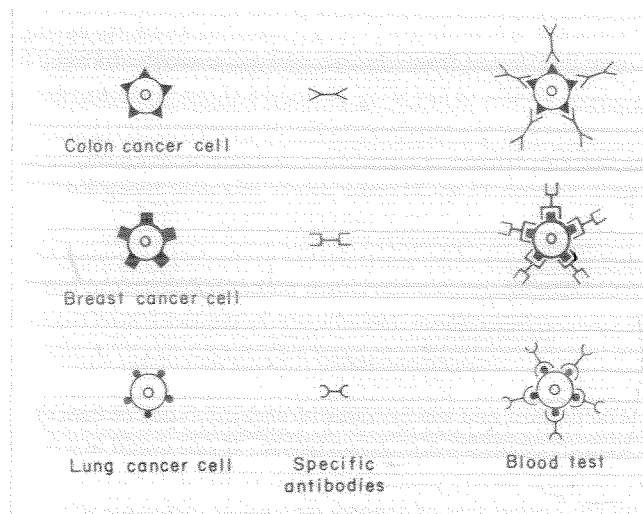
Immunodiagnostic reagents. In the future, specific antibody reagents may become available for blood tests to detect particular types of cancer at their very earliest stages.