confirm, as many geophysicists believe, that the technique has considerable potential for earthquake studies.

Other research presented at the AGU meeting included theoretical studies of the properties of dilatant rocks, models of dilatant phenomena, and more field studies. There is by no means agreement on the details of the dilatancy-diffusion model or on the extent to which it can be applied to widely varying geophysical situations. Many geophysicists, for example, question the accuracy of predictions based on any model that is not based on the measured properties of the rock in a particular location, and others believe that dilatancy on the scale necessary for a major earthquake is not likely. (In this regard the report by M. Wyss of the University of Colorado of *P*-wave velocity variations before a magnitude-7 earthquake in New Zealand, where the dilatant region was approximately 300 kilometers across, is of interest.) Nonetheless, it seems clear that most investigators are taking the model seriously and directing their research along lines indicated by it. The prospects for a better understanding of earthquake mechanisms and for earthquake predictions that may be of social and economic value both appear to be excellent, and it is correspondingly a time of considerable excitement for geophysicists.

—ALLEN L. HAMMOND

Tumor Immunology (I): The Host's Response to Cancer

No one worries about the growth of cancer cells in culture systems or in test tubes. Only when they grow in the living — human—organism is there cause for alarm. Culture systems are valuable for studying the basic mechanisms of oncogenesis, but it is the response of the whole individual to his disease that is of prime importance because this interaction between host and disease determines the patient's prognosis. Many investigators think that the immune system is a major component of an individual's response to cancer. They are now seeking the answers to two questions of fundamental importance: What is the role played by the immune system in the initiation and growth of tumors? And, how may the immune system be manipulated to cure or control cancers in humans?

Since deficiencies in the immune responses of cancer patients are well documented, there is little doubt that the immune system is somehow involved in oncogenesis. The uncertainty concerns its role—whether the deficiencies are the cause or effect of the disease and whether the immune system hinders or promotes tumor growth. Determining the nature of immune system involvement in cancer development is thus critically important for devising strategies for immunotherapy.

Immunotherapy—the manipulation of immune responses for cancer treatment—is considered by some investigators to hold the greatest promise for a cancer cure. Techniques employing surgery and radiation are restricted in application. They can eliminate the primary cancer but are of little value in controlling metastasis, the spread of cancer throughout the body. Chemotherapy, which aims to kill all cancer cells regardless of their location, has proved successful in controlling certain kinds of relatively rare cancers like Hodgkin's disease and some leukemias, but not for more common cancers like those of the lung and colon. Consequently, many investigators are turning to immunotherapeutic techniques. Some of their early clinical trials—and they emphasize the preliminary, experimental nature of the studies—have produced results that have encouraged them to proceed, but with caution.

The caution stems from observations that in some studies with animals, and possibly with humans, stimulation of the immune system produced enhancement, not inhibition, of tumor growth. Complexity appears to be the rule for cancer research, and tumor immunology is no exception. Immune responses require a number of components, including several different cell types and an assortment of "factors," which may or may not interact with one another. Thus, despite recent progress, immune response mechanisms are incompletely understood, and there is still uncertainty about how they can best be manipulated for the cancer patient's benefit.

The early history of tumor immunology research was inauspicious. Investigations at the beginning of this century purported to show that animals immunized with material prepared from a transplantable tumor resisted tumor growth when they were subsequently challenged with live tumor cells. The tumor cells grew and formed tumors in nonimmunized animals. The experiments suffered from a major flaw, however; at that time, there were no inbred strains of animals. Resistance to the tumor challenge was due, not to recognition and rejection of specific tumor antigens, but to an immune response directed against normal tissue antigens from a genetically dissimilar animal.

All cells carry genetically determined antigens. (Antigens are any substances that stimulate an immune response; most are chemically complex materials like proteins or nucleic acids.) An individual does not normally mount an immune attack on antigens of his own tissues, but cells with different antigens from another individual are recognized as foreign and attacked by the immune system. Identical twins can tolerate each other's cells because they are genetically the same. This is also true for members of the same inbred strain of laboratory animals, which have very similar, if not identical, genetic compositions. Development and use of these strains has greatly facilitated immunological research.

Scientists now think that most (but not all) tumor cells carry membrane antigens called tumor-associated antigens that do differ from those of the host's normal cells. Proving that these antigens are absolutely tumor-specific (found only in tumors and not in normal cells at any time during development) is extremely difficult and remains a major problem of tumor immunology. Investigators have established, in both in vivo and in vitro systems, that animals can mount an immune response against tumor cells. For example, after a chemically induced tumor is surgically removed from a mouse, the animal can resist tumor growth when viable cells of that same tumor are injected. It cannot

resist the growth of a tumor induced by another chemical and carrying antigens different from those of the first tumor. These experiments demonstrate that when an animal has once been exposed to tumor antigens they can be recognized on subsequent exposure and tumor growth resisted; that is, the animal can be immunized against the tumor. In addition, numerous investigators have shown that effector cells ("killer" cells or small lymphocytes) of the immune system can recognize and destroy cultured tumor cells.

Both of these concepts—tumor-associated antigenicity and the capacity of the host to make an effective immune response to tumor antigens—underlie the theory of immunological surveillance now favored by a majority of tumor immunologists. According to this theory, tumor cells constantly arise in complex organisms such as man, but because of their "foreignness," they are efficiently eliminated by the immune system of most individuals. Occasionally, however, tumor cells escape the immune system's surveillance. They can then proliferate—and cancer results.

Evidence supporting the immune surveillance theory includes observations that the cancer incidence is higher in people with less effective immune systems than in those with strong responses. The immune system is thought to deteriorate with increasing age, and the incidence of cancer is known to be higher in the elderly. Cancer afflicts up to 10 percent of patients with certain genetic immunodeficiency diseases, according to Robert Good of Memorial Sloan Kettering Cancer Center, New York, Thomas Waldman of the National Cancer Institute, Bethesda, Maryland, and others who have investigated these diseases. Since many of these patients are young, their cancer incidence is far higher than that of normal individuals of the same age.

Patients who have undergone immunosuppressive therapy for the treatment of disease—including cancer—or to prevent rejection of organ transplants are also prone to a higher cancer incidence. Israel Penn and his colleagues at the University of Colorado, Denver, found that patients with kidney transplants had an incidence of cancer approximately 100 times greater than that of the general population in the same age range. The chemicals used for treating cancer also suppress immune responses. These observations have led to the suggestion that intermittent chemotherapeutic regimes that allow recovery of the patient's immune response may be more beneficial to the patient than continuous administration of the drugs.

Graft or transplant rejection and tumor surveillance are thought to be effected by the same components of the immune system. The immune system consists of two major functional branches—cell-mediated and humoral immunity. Cell-mediated immunity is the province of T or thymus-dependent lymphocytes that act directly to destroy foreign antigens. They are involved in transplant rejection and immune surveillance, and also in delayed hypersensitivity reactions and resistance to viral infections. An example of a delayed hypersensitivity reaction is the skin response of redness and swelling that may occur 24 to 48 hours after antigens are injected subcutaneously. Such skin tests are frequently employed to assess the immunocompetence (the ability to respond to antigens) of cancer patients.

Humoral Immunity

Humoral immunity depends on the production of soluble antibodies by plasma cells. Plasma cells differentiate from B (for bone marrow) lymphocytes when they are stimulated by an antigen. Antibodies circulate in the blood and are required for resistance to a number of bacterial infections. They combine with antigens and make them more susceptible to destruction.

Needless to say, the situation is more complex than indicated by this brief explanation. The two branches of the immune system interact in a manner not completely understood at present. Numerous "factors" elaborated by lymphoid cells also participate in the responses. In addition, a third cell type, the macrophage, may be important for tumor cell destruction. Macrophages are large mobile cells, produced by the organs (including the liver and spleen) of the reticuloendothelial system, that can engulf and destroy particulate matter, including other cells.

If the immune surveillance theory is assumed to be correct, researchers must then explain how cancer cells can escape surveillance and produce tumors in normal people, that is, in people with no known immune deficiencies. A number of theories have been proposed. They need not be mutually exclusive; a system as complex as the immune system might malfunction in several different ways, each of which leads to the same result—tumor growth.

One escape mechanism thought to play a role in oncogenesis involves the presence of "blocking factors" in the blood serums of individuals with tumors. Ingegerd Hellström and Karl Erik Hellström of the University of Washington School of Medicine, Seattle, proposed this mechanism on the basis of results obtained with in vitro assays of cell-mediated immunity. These assays measure the cytotoxic effects—cell destruction or inhibition of cell division—of lymphocytes on target cells in culture. In order for lymphocytes to exert their cytotoxic effects, they must first be sensitized to antigens present on the target cells. This requires prior exposure, either in vivo or in vitro, of the lymphocytes to tumor cell antigens. Such sensitized lymphocytes are also called immune lymphocytes.

The Hellströms showed that lymphocytes taken from mice with growing sarcomas that had been induced with Moloney sarcoma virus were cytotoxic to Moloney sarcoma cells in culture. If the sarcoma cells were incubated with serum from animals with growing tumors before the lymphocytes were added (the serum was removed before lymphocyte addition), the lymphocytes no longer attacked the tumor cells. Incubation with serums from normal animals or animals with tumors unrelated to Moloney sarcoma had no effect on lymphocyte cytotoxicity. Neither did serum from animals whose tumors had regressed. The Hellströms interpreted these results as showing that mice with growing tumors produced "blocking factors" that prevented their lymphocytes from attacking tumor cells even though the lymphocytes had the capacity to do so. Blocking activity has since been detected in serums from several animal species with different tumors and also in serums from human cancer patients.

Whenever in vitro assays are used, there is always the problem of whether the results are truly applicable to the situation in vivo. Here the question is whether the blocking activity demonstrated in vitro enables tumor cells to escape from immune surveillance in vivo. A number of investigators, including S. C. Bansal of the Medical College of Pennsylvania in Philadelphia and H. O. Sjögren of the University of Lund, Sweden, have shown that serums that block the cytotoxic activity of lymphocytes on cultured tumor cells

also enhance the growth of tumors of the corresponding type that have been transplanted into animals.

Additional evidence for the importance of blocking factors in cancer etiology has been obtained by the Hellströms. They found that patients with primary melanoma that had not metastasized no longer had blocking activity in their serum after their tumors were removed surgically. Patients with progressive metastatic melanoma did have the activity. Finally, in patients who had been in remission from the disease and subsequently relapsed, blocking factor reappeared in the serum 2 to 6 months before their relapses were clinically detectable. Although these and other studies indicate that blocking factors may play a role in promoting or permitting tumor growth in vivo, the case has not yet been definitively proved. At the very least, however, knowledge of an individual's blocking factor status may be of diagnostic or prognostic value.

The biochemical nature of blocking factor is still uncertain. The Hellströms originally thought that it was antibody against tumor antigens. Such antibody could block by binding to antigen on tumor cell membranes and preventing attack by sensitized lymphocytes. If this were true, stimulation of the immune system as an immunotherapeutic strategy could do more harm than good if humoral immunity—and thus the production of blocking antibody—were stimulated in addition to cell-mediated immunity.

More recent evidence supports the hypothesis that blocking factor is either a complex of antibody with tumor antigen or is tumor antigen itself. The Hellströms, with Sjögren and Bansal, found that they could separate blocking factor into two fractions. One contained components, including antibodies, with molecular weights greater than 100,000; the other contained substances with lower molecular weights and included antigens. Under the standard conditions employed by the Hellströms for their in vitro assay system (incubation of cultured tumor cells with the material to be tested for blocking activity and removal of that material before addition of lymphocytes), both fractions were required for blocking activity. Antigen alone prevented the cytotoxic effects of lymphocytes but only when it remained with the lymphocytes throughout the entire test. Antigen may act directly on the lymphocytes rather than on the tumor cells.

Robert Baldwin and his associates at the University of Nottingham, England, have additional evidence that complexes of tumor antigens with antibody cause blocking. They isolated tumor-associated antigens from hepatoma cells. (A hepatoma is a liver tumor.) Serum taken from rats following surgical removal of their hepatomas contains antibody against tumor antigens but it does not block the cytotoxic effect of lymphocytes on cultured hepatoma cells. Baldwin and his colleagues could restore blocking activity by adding isolated antigen to the serum. Blocking occurred only when the proper ratio of antigen to antibody was attained. Addition of either too

Lithium Primary Cells: Serendipitous Search

Another piece of evidence in the ongoing debate between those who advocate that scientific research be directed toward solving specific practical problems and those who believe that practical benefits can flow from undirected research has been contributed over the last 2 years in the form of the discovery of a new primary cell (battery) based on lithium and liquid chlorine compounds by scientists at the GTE Laboratories, Waltham, Massachusetts (*1*), and by researchers at the Army Electronics Command, Fort Monmouth, New Jersey (*2*).

Primary cells, as distinguished from the secondary cells which make up storage batteries, cannot be recharged, but still find wide application as power supplies for items as mundane as flashlights and transistor radios and as sophisticated as heart pacemakers and aerospace electronics.

The name of the game in battery research is to find an electrochemical system that can be made to deliver a high specific energy, usually expressed in watt-hours per kilogram (1 watt-hour = 3600 joules), in a small volume. Not infrequently, the batteries in a piece of electronic equipment take up the largest part of its volume. For some applications requiring a rapid battery discharge, a high specific power (watts per kilogram) is desirable. A long shelf life (the time the battery sits unused) is also needed. But most importantly, the whole package must be inexpensive.

For years, battery researchers have been fascinated with the prospect of using lithium as the anode material in batteries, because of its light weight and extremely electropositive character. Because of the reactivity of lithium with water, however, most such cells have required (for room temperature operation) an organic solvent to contain the electrolyte, or molten salt electrolytes which operate at high temperatures. In recent years, for example, a room temperature lithium primary cell has been developed which uses sulfur dioxide (SO_2) dissolved in an organic solvent (along with a lithium halide electrolyte) as the active cathode reactant. The sulfur dioxide cells, now manufactured by at least two battery companies, demonstrated the principle that the soluble cathode reactant can contact the lithium in the cell without reacting with it. Instead, a passivating layer of reaction products inhibits the reaction.

The new primary cell under development by GTE Laboratories and the Army differs from the sulfur dioxide cell in that the cathode reactant [liquid oxyhalides, such as thionyl chloride ($SOCl_2$) or sulfuryl chloride (SO_2Cl_2)] also serves as the sole solvent for the electrolyte [usually lithium tetrachloroaluminate ($LiAlCl_4$)]. As in the sulfur dioxide cell, a low weight, high surface area carbon positive electrode acts as a catalyst for the reduction of the cathode reactants, thus permitting the cell reaction to proceed. Since the solvent acts as the "fuel" for the cell, there is no need for a separate supply of cathode reactants, and the attendant result is a greatly reduced cell weight and increased specific energy.

Curiously enough, the GTE scientists did not start by

little or too much antigen to the serum produced no blocking activity. Baldwin thinks that large complexes of antibody with antigen, which can bind to tumor cells through the antibody moiety, block the access of lymphocytes to tumor cells more effectively than antibody alone. Alternatively, the antigen portion may have a specific role in preventing lymphocyte activity on tumor cells.

In addition to blocking factor, the population of factors involved in tumor immunology includes "unblocking factor." According to the Hellströms' definition, "unblocking" simply means that one serum can abrogate the blocking activity of another. For example, serum taken from mice whose Moloney sarcomas have spontaneously regressed nullifies the blocking activity of serum from mice with growing tumors. Baldwin found similar results with serum from mice whose hepatomas had been excised and serum from mice with growing tumors. Although the evidence is not yet conclusive, unblocking factor may be free antibody. This would be consistent with Baldwin's finding that blocking does not occur in the presence of excess free antibody.

Other investigators, including Graham Currie of the Chester Beatty Institute in London and Charles McKhann of the University of Minnesota Medical School, Minneapolis, have focused on the role of tumor antigens in oncogenesis. McKhann points out that tumors may have evolved the capacity to shed large quantities of antigen as a defense mechanism against immune surveillance. McKhann and Currie think that antigens shed by tumor cells permit tumor growth by binding to receptors on lymphocytes and preventing them from attacking tumor cells. Antigen could thus inhibit immune surveillance by binding directly to lymphocytes or by forming blocking complexes with antibody, or both. The effect would be to saturate and overwhelm the immune response. This suggestion is consistent with observations that animals that have been immunized against a particular tumor can resist challenges with small doses of tumor cells but not with large ones. The immune system apparently does have a limit to its capacity to respond to antigens.

Pinning down the roles of antigen and antibody in tumor growth should facilitate rational design of immunotherapeutic approaches. Strategies to remove antigen by increasing its breakdown or to prevent its release from tumor cells might be feasible. So might strategies to increase cell-mediated or even humoral immunity. Current approaches to immunotherapy will be surveyed in the next article of this series.

One of the few investigators to challenge the current view of immune surveillance is Richmond Prehn of the Fox Chase Center for Cancer and Medical Sciences, Philadelphia, Pennsylvania. According to Prehn, weak immune responses, such as those that might occur in the initial stages of tumor growth when only a few aberrant cells are present, stimulate tumor growth rather than inhibiting it. The immune system does function as a defense against cancer, but, in Prehn's

for a New Laser Leads to an Advanced Battery

seeking a better battery, according to Adam Heller of GTE Laboratories. Rather they were evaluating the oxyhalide solvents, such as phosphorous oxychloride ($POCl_3$), as potential hosts for rare earth ions in liquid laser systems. (Rare earth ions are well known for their application in phosphors for, among other things, color television sets.) In a second generation of experiments, they attempted and succeeded in observing light emitted as a current was passed through the ion containing oxyhalide solution. In these experiments, the researchers observed that rare earth metal was being plated out onto the anode and that chlorine gas was evolved at the cathode. Recognizing they had the makings of an electrochemical cell, they tried lithium chloride and other more soluble salts, and obtained a lithium-chlorine cell which operated at room temperature in an inorganic solution. The GTE workers then began exploring other possible constituents for a lithium battery.

At this point, both the GTE researchers and the scientists at the Army Electronics Command began exploring the possibility of eliminating the use of chlorine gas as the cathode reactant by trying solid reactants, such as graphite fluoride. But the discovery that more energy was obtained from these cells than could be accounted for from the solid reactants alone led to the realization that the solvent itself was acting as a cathode reactant. Present batteries are the result of the development of a high performance carbon cathode electrode that efficiently promotes the reduction of the solvent.

Current laboratory versions of the lithium-thionyl chloride cell exhibit specific energies of the order of 500 watt-hours per kilogram, more than 50 percent higher than previous lithium–sulfur dioxide cells and more than eight times higher than the common flashlight battery. Other features include improved low temperature operation (down to $-45°C$) and voltage stability. However, Sol Gilman, one of the Army scientists working on the lithium battery, points out that problems of cell storage life and safety engineering (a lot of energy is packed into a small volume) are still to be solved to complete satisfaction.

Observers agree that the new lithium battery amounts to a significant development that could have a considerable effect in reducing the size and weight of a wide variety of electronics packages. Work is in progress at GTE and other laboratories directed toward production of commercial cells, and, although projected materials costs are low (*3*), other researchers in the battery field caution that, often, developing a manufacturable version of a battery with a low cost presents the most formidable problem of all.—ARTHUR L. ROBINSON

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view, it acts too late and too inefficiently to be of much value for surveillance. He does think, however, that stimulating the immune system could still be useful for cancer therapy.

Prehn contends that there are alternate interpretations, consistent with his theory of immunostimulation of oncogenesis, that can be made of data already cited as evidence in favor of immune surveillance. For example, 50 percent or more of the cancers found in patients with immunodeficiency diseases or undergoing immunosuppressive treatments are leukemias, lymphomas, or other tumors of the lymphoreticular system. Immunosuppression and immune deficiency diseases directly affect this system. Thus, the increased malignancies may result from intrinsic or induced abnormalities in the lymphoid system rather than from impaired surveillance. The weakened immune response of the patients may even stimulate tumor growth.

In at least one animal model, lack of cell-mediated immunity does not appear to increase the incidence of tumors. Osias Stutman of Memorial Sloan-Kettering Cancer Center, New York, used a chemical carcinogen to induce cancer in nude mice lacking thymus glands and in nude mice having the glands. There were no differences between the two groups either in the length of time before tumors appeared or in tumor incidence. Yet athymic mice do not have active T lymphocytes or cell-mediated immunity.

Not all tumors can stimulate a strong immune response that inhibits tumor growth, according to Prehn. Most of the tumors studied in the laboratory that have this capacity are induced by viruses or chemicals and may be laboratory artifacts. On the other hand, many "spontaneous" tumors have this capability to a slight degree, if at all. They would not be likely targets for immune surveillance and might elicit only a weak—possibly stimulating—immune response. This argument is double-edged, however. Immune surveillance might be a selective force that favors tumors of low antigenicity by destroying those of higher antigenicity.

Under some conditions, sensitized cells of the lymphoreticular system can stimulate tumor cell division both in vivo and in vitro. In order to cripple the immune responses of mice used for an in vivo study, Prehn first removed their thymus glands and irradiated the animals. Then, he injected them subcutaneously with constant amounts of tumor cells mixed with varying numbers of spleen cells. Large quantities of spleen cells that had been sensitized to the tumor antigens inhibited tumor growth. But small quantities of sensitized cells stimulated tumor growth.

Working in Prehn's laboratory, H. F. Jeejeebhoy injected mice with tumor cells. Lymphocytes taken from the animals before tumors were detectable stimulated division of the corresponding tumor cells in culture. Lymphocytes collected after tumors became detectable inhibited cultured tumor cell division. These results support Prehn's hypothesis that, early in tumorigenesis, a weak immune response is stimulatory while a later, stronger response is inhibitory to tumor growth.

Although Prehn concedes that he is swimming against the tide of opinion about immunosurveillance, he is not alone. Isaiah Fidler of the University of Pennsylvania School of Dental Medicine, Philadelphia, found that small numbers of immune lymphocytes stimulated the growth of cultured tumor cells while a large number of lymphocytes were cytotoxic. The usual in vitro assays, which regularly show cytotoxic effects of lymphocytes, employ high ratios of lymphocytes to tumor cells.

Role of Macrophages

Results from Fidler's laboratory, and from several others, indicate that macrophages may participate in the host's defenses against cancer. Macrophages from mice that had been immunized against melanoma were cytotoxic to cultured melanoma cells whereas macrophages from normal mice or from mice with growing tumors were not. Fidler could activate macrophages from mice with tumors, however, by incubating them with supernatants from cultures containing both immune lymphocytes and melanoma cells. (Lymphocytes are known to produce factors that activate and attract macrophages.) Fidler thinks macrophage function may be defective in mice with growing tumors. The fact that the defect can be remedied by an in vitro technique suggests another approach to immunotherapy.

In order to act, macrophages must be able to recognize foreign matter. Such recognition depends on the presence of yet another factor—this one called recognition factor. Nicholas DiLuzio and his colleagues at Tulane University, New Orleans, suggest that a failure in recognition mechanisms may contribute to tumor growth and development. They found that carcinoma patients had less recognition factor activity in their serums than did healthy individuals or patients with a number of nonmalignant diseases. Patients with advanced metastatic carcinoma had the lowest levels of all. Recognition factor activity increased following treatment of the carcinoma by surgery or radiation.

DiLuzio thinks that combination of tumor cells with recognition factor may be the first step required for recognition and subsequent attack by macrophages. When he injected leukemic cells into rats, recognition factor activity in serum declined almost 70 percent within 30 minutes, which suggested that the factor had combined with the cells. No decline occurred when normal leukocytes were infused into rats. DiLuzio hypothesizes that failure of recognition mechanisms might permit tumor cells to go undetected by the macrophages and escape destruction.

The Tulane group has isolated and partially characterized recognition factor. It is a protein, an alphaglobulin. DiLuzio, with Peter Mansell, also at Tulane Medical School, initiated clinical trials of the use of recognition factor. It is a protein, an alphaglobulin. with recognition factor decreased in size. They contained large macrophage populations not seen in uninjected tumors. These observations, although preliminary, support the hypotheses that macrophages and recognition factor are important components of the host's response to tumors.

Not all of the pieces of the tumor immunology puzzle have been fitted together. Some are even missing. There are, for example, uncertainties about the specificity of tumor-associated antigens, and about the relation of in vitro assays to in vivo situations. These are more than just technical details, because their interpretation will influence not only the hypotheses formulated about the role of the immune system in oncogenesis but also the strategies devised for immunotherapy. Nevertheless, progress has been made, and investigators are hopeful that the picture is forming.—JEAN L. MARX