Cancer: The Great Challenge for Immunology

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The existence of immunity to cancer was postulated by the eminent scientists who helped to establish the discipline of immunology. In 1907 Clowes suggested that human resistance to cancer resulted from what we today call "immune surveillance."[1,2] During the ensuing 70 years the results obtained from experimental animal cancers and human cancers have greatly influenced the palatability of tumor-immunity theories.[3,4] Early optimism that immunity to cancer could be specifically induced waned and almost disappeared when it was demonstrated that the rejection of cancer transplants resulted from transplantation immunity and not tumor immunity. A sustained wave of enthusiasm for immunity to cancer appeared after demonstrations that inbred animals could be immunized to cancers arising in the inbred strain.[5,6]

The objective of this paper is to try to reexamine many aspects of cancer immunology and to shift the emphasis currently placed on some of these aspects into other areas with greater potential for clinical application. This is not meant to be one of the numerous reviews of cancer immunology but rather a balanced presentation of alternative viewpoints which will ultimately tilt toward my viewpoint.

The plan for the paper is as follows: (1) the types of contributions immunology has made to mankind will be briefly reviewed; (2) a general theory describing cancer immunity with some supporting evidence will be presented not once but twice; (3) finally the current status of immunotherapy of human cancer will be briefly mentioned.

Contributions of Immunology.

A review of the major contributions of immunology to humanity should offer a preview of what can reasonably be expected from future contributions of this field to the understanding and control of cancer. The trademark of immunology is prevention of disease by immunization. With the discovery of antibiotics and their use in tissue cultures, a fresh attack upon many viral infections became possible. In the past two decades, the cultivation of viruses in vitro has resulted in the elimination of epidemics of poliomyelitis; infection with measles virus is less common. Where the human is the sole host and reservoir of an infection, immunization may lead to the eradication of a disease. This appears to be the attainable goal in smallpox where we are at the threshold of its eradication by intensive immunization and epidemiologic field work.

While the trademark is immunization, the work horse of immunology is serology. Its use in diagnosis and blood banking alone are of critical importance to the functioning of our hospitals. A strike of all technicians doing serologic tests would paralyze our health care system. In addition to its diagnostic contributions, immunology provides an important understanding of the pathogenesis of disease.

A relatively new but potentially major contribution is in predicting susceptibility to disease. The association of certain transplantation antigens with specific disease states may be the forerunner of serologic identification of disease-risk factors.

When one turns to the role of immunology in therapy, the work seems harder and the results hardly optimal. This view is not meant to belittle the value of replacement therapy in certain immune deficiency diseases, or of immunosuppressive therapy in preventing transplant rejection; rather it is intended to point out that cancer immunology is much, much more than immunotherapy.

General Features of Immunity to Cancer.

All cancer immunology is inextricably linked to the existence of an antigenic difference between the

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cancer cell and its closest normal "relative" cells. Without such a difference, immunology has no entry into the cancer field.

The transformation of a normal cell to a cancer cell is probably accompanied by an antigenic change. This transformation may occur frequently in all of us. With a properly functioning immune system, the antigenic change or changes in the cancer cells are recognized and following recognition an effective anticancer cell immune response destroys the malignant cells. Appearance of clinical cancer is thus considered to be a prima facie case of a failure of normally operating immunologic mechanisms.

Evidence Supporting Immune Surveillance.

Origins for cancer antigens are not hard to find. Oncogenic viruses are obvious sources of extraneous antigenic material incorporated into cancer cells. While no human oncogenic virus has been clearly identified, several viruses are viewed with suspicion. Chemical compounds play an important role in the initiation of human cancer, and for many years these carcinogens included many compounds that are also mutagens. Recently a bacterial test for detecting chemical mutagens has shown that almost every known chemical carcinogen is either a mutagenic agent or is metabolized to a mutagen.[7] Chemical carcinogen-induced changes in the bases of deoxyribonucleic acid (DNA) can result in the synthesis of abnormal, that is, antigenic, proteins. Similarly, physical agents such as ultraviolet and x-irradiation are also known carcinogens and mutagens.

Amongst the wide variety of human cancers, an impressive list of cancer-associated "time and place" antigens have been detected.[8-10] The carcinoembryonic antigen of the gastrointestinal tract, alpha-fetoprotein, chorionic gonadotropin, antidiuretic hormone, and parathormone are examples of normal products made by cancers that are either abnormal for postnatal life or for that type of cell.

As we move to consider the evidence for the existence of immune cancer-rejection systems, we need to rely on negative observations. It is impossible to demonstrate that we are cancer-free as a result of active recognition and destruction of small clones of cancer cells, but strong circumstantial evidence points to such immune mechanisms. Patients who are recipients of organ transplants have a high risk of subsequently developing a malignant disease[11,12]; these patients are estimated to be at least 25 times more likely to develop cancer than the normal population.

An additional group of patients at high risk for developing cancer are those individuals with immunodeficiency diseases. From 5% to 10% of patients with sex-linked agammaglobulinemia, combined immunodeficiency disease, Wiskott-Aldrich, or ataxia telangiectasia will develop clinical malignant disease. Further but less definite indications that we are protected by immune mechanisms include the observations that chemical carcinogens may be immunosuppressive,[14] the claims of cutaneous anergy in patients with neoplastic disease,[15-17] and the frequently stated view that patients with cancer have an increased susceptibility to infection.[18]

The last element to be considered in the construction of an immunologic lattice for the containment of cancer is the alteration of the course of cancer by immunologic methods—immunotherapy. Attempts to stimulate a specific immune response[19] and to stimulate the entire immune response by agents like bacille Calmette Guérin (BCG)[20] have been extensively performed. In 1971, a comprehensive review was published by Yashpie,[21] and the report of a conference entitled, "Immunotherapy of Cancer: Present Status of Trials in Man," held in Washington in October, 1976, is to be published.

How effective is immunotherapy for human cancer? It is important to realize that the concept of the "proof of the pudding is in the eating" is as much determined by how hungry one is as by the quality of the pudding. Rather than enthuse about immunotherapy, I prefer to accept its present meagre results as a challenge to reexamine our entire position. I will also consider immunology with respect to prevention, pathogenesis, early diagnosis, treatment monitoring aids, and immunotherapy.

Prevention of Human Cancer by Vaccines.

An extensive review of the possibilities in this area was recently published.[23] At least two major obstacles need to be overcome before vaccines for human cancer become a reality. First and foremost the link between a human virus and the cancer it causes needs to be firmly established. Then the virus can be developed into a vaccine—living, killed, or subunit. The second problem is to determine who should receive the vaccine. Since the incidence of any one kind of carcinoma is relatively low, methods are needed to identify the high-risk groups. Where the prevalence of a carcinoma may be 5 to 10 persons per 100,000, it would be unacceptable to try to immunize the whole population.

Where a viral-associated neoplasm behaves like

a communicable infectious disease, a vaccine could be very helpful. Such a situation exists in the poultry industry. A DNA herpes-like virus (Marek's disease virus) is manufactured into a fully infectious form in the feather follicle of the chicken. In addition this virus spreads within the chicken and causes a fatal lymphoreticular disease; it also spreads amongst chickens and can wipe out a flock. An effective vaccine has been prepared from an apparently harmless herpes virus of turkeys. This vaccine protects the chickens against Marek's disease.[23]

The Pathogenesis of Cancer.

Immunologists searching for human cancer antigens have made an astounding, although largely ignored, contribution to our understanding of the pathogenesis of cancer. Despite years of search by numerous competent investigators, a cancer-specific antigen has not been isolated for any human cancer. Although the search for cancer-specific antigens is too important to be abandoned, the possibility that specific cancer antigens do not exist must be faced. Instead of cancer-specific antigens, cancer-associated antigens have been found. Some of these antigens are considered time antigens. A cancer cell makes fetal alkaline phosphatase, or a fetal pyruvate kinase isozyme, or embryonic antigens, or structures such as alpha-fetoproteins; place antigens also are made. Thus a variety of normal hormones are made by malignant cells derived from cells that have ceased making these products. Frequently these hormones produce symptoms in the patient, a paraneoplastic syndrome. Were we to have the full catalog of normal gene products made from conception to maturity, it is possible that a time or place antigen or both could be associated with every human cancer. The finding of time and place cancer-associated antigens instead of cancer-specific antigens fits in with an intriguing new concept of the pathogenesis of cancer,[24] which as its essential feature regards cancer as a programming error. Carcinogenesis is not a mutation to new structures but rather a reactivation of genetic programs that were terminated a long time ago. In this view viruses, chemicals, and physical agents act by going into the "old book" section of the cell's DNA library and activating something long dormant.

It is possible to estimate the percent of the informational DNA that is being actively transcribed by cells. There is no difference in the amount of DNA active in the blastula phase, the gastrula phase, or the adult cells. About 3% of the DNA is being used, but the 3% used in the gastrula phase cells is not identical to the 3% used by the blastula cells. Thus normal development consists of the orderly and sequential production and elimination of portions of the DNA program.

Can programs be initiated? Dr. Ruddy referred to androgen treatment of hereditary angioedema. The administration of an androgen leads to synthesis of a significant amount of a protein necessary to inhibit spontaneous activation of the complement system; other examples exist, perhaps the best being the reactivation of the information locked up within a cell nucleus as reported by Gurdon.[25] Transplantation of organelles produced striking results when the nucleus of a fertilized frog ovum was removed and replaced by the nucleus of a mature frog muscle cell. The microsurgically treated cell was then restored to its proper environment, and development of the ovum resulted in the formation of a tadpole. All the information for this development was uncovered in an orderly fashion from the mature nucleus of a differentiated cell. Similar results have been obtained when the nucleus from a mature frog lymphocyte was transplanted into an enucleated fertilized frog ovum.

Our society seems to have more difficulty in formulating the correct questions than it does in providing the answers to these questions. The finding of several cancer-associated antigens emphasizes that cancer immunologists must continue to examine serologically the early stages of development with the objective of identifying additional tumor-associated antigens that in turn may be critical in establishing valid early diagnostic tests for cancer.

The Nature of the Immune Defect in Cancer.

The failure to demonstrate an effective immunotherapeutic method requires that the defects in the immune surveillance and rejection system be examined again with respect to cancer.

Does the patient who develops a carcinoma of the lung, or breast, or stomach or other organs have a defect that is applicable to the recognition and reaction to many antigens or is the defect confined to the antigen or antigens associated with that particular cancer? This is not a trivial question since the direction for future immunotherapy depends on the answer. Arguments in favor of a broad defect are the high incidence of neoplasm in transplant patients and in those with immune deficiency diseases, but the interpretation of this evidence is not decisive. Cytotoxic immunotherapy is not exclusively immunosuppressive. It may interfere with DNA repair mech-

anisms which if unchecked could cause malignancy as seen in xeroderma pigmentosa.[26] These patients have a very high incidence of neoplasms of the skin, and severe impairment of the ability to repair the damage in DNA caused by ultraviolet irradiation. Many of the drugs used in immunosuppression may also interfere with DNA repair mechanisms.

The evidence suggesting that there is no broad immune defect in cancer patients is drawn from the incidence of infection in patients with solid neoplasms. Since the earliest days of immunology, infection has pointed to the areas where immune defects exist, and it is unusual to see clinically significant immune defects without concomitant frequent infection. Indeed the defects may be so subtle, as in sickle cell disease, that increased susceptibility to infection is recognized long before the nature of the immune defect is discovered.

Contrary to general opinion, infection is not a common problem in the patient with solid cancers, although infection certainly occurs when large masses obstruct a passageway or become necrotic. If extensive chemotherapy renders the patient granulocytopenic, or if large doses of steroids are given, infection occurs, but under other circumstances, infection in a non-terminal cancer patient is rare. Accounts of infection in cancer patients are predominantly those of patients with leukemia, lymphoma, and myeloma. Of 93 patients with aspergillosis, only 14 had solid tumors.[27] Of these, 11 were receiving steroids and nine were receiving cytotoxic drugs. Another recent report[28] shows that 31 of 35 patients treated for infection with sulfamethoxazole-trimethoprim had hematologic malignancies; so it goes with all reports of infection in cancer patients.

It appears to me unlikely that the overwhelming majority of patients with solid tumors have a large blind spot in their immune system. Skin testing for anergy, counting T and B lymphocytes, and stimulating lymphocytes with mitogens can probably be safely discontinued or replaced by looking for the real defect in the immune system in cancer patients.

This leads to the second question. How does an antigenic cancer escape detection? The answer to this question is beset with technical difficulties. The reports of two workshops[29,30] designed to evaluate the results of in vitro cytotoxicity tests for cancer cells are gloomy. More emphasis needs to be placed upon technical improvements in the culturing of cancer cells and in determining their in vitro susceptibility to antibody and to lymphocytes and macrophages.

Our understanding of this area is intimately tied to our efforts in human cancer immunotherapy. An outline of how a cancer breaks through or may break through is of value even though it is purely speculative. Early studies in malignant melanoma[31] stressed the importance of humoral antibodies. Patients with localized melanoma were reported to have antibody which reacted with melanoma cells while patients with disseminated melanoma generally lacked these antibodies. Using in vitro techniques, the Hellstroms demonstrated a more complex Trojan Horse type of immunologic arrangement[32] in which lymphocytes from a cancer patient could destroy in vitro cancer cells removed from that patient. This cellular immune reaction could be inhibited by antibody present in the serum of that cancer patient and from these observations a dual immune system was formulated—antibody could protect the cancer, and cellular immunity could destroy the cancer. Further modifications have been made in both the serum and cellular aspects, but the basic premise remains that the destruction or growth of a cancer depends upon the relative strengths of two types of immune reactions. This point should be returned to in considering the results of immunotherapy.

Immunology and Early Diagnosis of Cancer.

Early diagnosis implies identification of the presence and location of malignant cells at a time when curative treatment can be performed. Today none of the immunologic tests for cancer-associated antigens are sensitive and specific enough to meet this requirement.

The nature of the immunologic tests for cancer-associated antigens is qualitatively different from tests measuring levels of liver enzymes or bone enzymes. In the latter tests, it is unlikely that a small mass could raise the level of normally present enzymes to an abnormal level; that is, there is a high background of normal activity that obscures the similar activity of the neoplastic cells. In the immunologic tests, the search is for fetal antigens in which the background levels should be low. This is an area in which future progress may produce valuable results.

Immunologic Treatment Monitoring Aids.

Three radioimmunoassay tests are currently of great value in the management of patients with cancer.

The carcinoembryonic antigen (CEA) test is of great assistance in management of some patients with colorectal carcinoma. Where the level is elevated preoperatively, the postoperative levels are useful in as-

sessing the recurrence of disease and the response to therapy. We are not recommending adjuvant postoperative chemotherapy, but an elevation in the CEA is one indication to search for the location of the recurrence and for initiation of therapy.

Radioimmunoassay of chorionic gonadotropins has long been known to be essential in planning the treatment of choriocarcinoma. The radioimmunoassays for alpha-fetoprotein and for the B-subunit of chorionic gonadotropin add a major new dimension to our management of patients with testicular cancer. Decisions about starting chemotherapy and the selection of the chemotherapy drugs used are greatly influenced by the results of these immunologic tests.

Immunotherapy of Cancer.

I have not allotted much space to the analysis of cancer immunotherapy. Many techniques—some simple, some complex, and some very ingenious—are being used to either treat human cancer or to prevent its recurrence.

The experimental studies of BCG immunization in the guinea pig[33] illustrate the potential value and the limitations of immunotherapy. In this system, injection of living *Mycobacterium bovis* BCG into the tumor residing in an animal capable of developing cellular reactivity to BCG, *and* at a time when the tumor is small, results in a marked decrease in the number of tumor-transplantation takes. Many experimental animal systems carefully designed to demonstrate an effect of immunotherapy have been published. The literature on human cancer immunotherapy trials is enormous; its abundance makes it difficult to discount. In my view the effectiveness of any immunotherapeutic procedure in human cancer has yet to be demonstrated. There is great interest in studying the results reported at the conference "Immunotherapy of Cancer: Present Status of Trials in Man."

Predicting the future course of immunotherapists is hazardous. The mood or moving spirit seems to indicate a great disenchantment with BCG and its allied products. A shift to *Corynebacterium parvulum* is underway, but it is probably too toxic to gain wide acceptance. The newest bacterial entry is the pseudomonas vaccine. The direction seems to be to go through Bergey's Manual, a task that could involve generations.

Ironically BCG is being rejected as uncritically as it was accepted. If we are to be able to interpret an immunotherapy trial properly, we need to know more than the change in size of a cancer mass or the duration of survival. We need measurements of the changes in the levels of antitumor blocking antibody, unblocking antibody, and cellular cytotoxicity and cellular suppression. With this information we can learn how to stimulate selectively the portion of the immune response that destroys cancer without stimulating the immune response that aids cancer.

Conclusions.

Immunology provides a valuable tool as a treatment monitoring aid in many cancers.

The likelihood of an effective cancer vaccine is remote and requires identification of both an oncogenic virus and a susceptible subgroup.

The failure to find cancer antigens and the abundance of cancer-associated antigens suggest that cancer may be a programming error and potentially reversible.

Immunology is likely to provide better and effective early diagnostic tests.

The major need in immunotherapy is laboratory support to measure the effects of therapy upon antitumor immune response.

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