Cancer Immunotherapy:
Facts and Fancy

E. Benjamini, Ph.D.
D. M. Rennick, M.D.

Although the possibility of immunological intervention in cancer was conceptualized almost one hundred years ago,1-3 immunotherapy has been in the limelight for only the past two decades. Much has been written about the subject and numerous opinions have been expressed in many review articles. Understandably, the subject of immunotherapy has been an emotional one, with wishful thinking interwoven with hard experimental findings. This article will highlight some of the various approaches to immunological intervention in cancer. It is not meant to rehash old ideas, but rather to present examples of some up-to-date experimental and clinical results, to stimulate the reader to realistically evaluate the present status and the potential of cancer immunotherapy. It is important to point out from the start that this article is not meant to deal with the broad and exciting area of the application of immunological tools to the diagnosis and prophylaxis of cancer, but rather to focus exclusively on tumor immunotherapy, i.e., the use of immunology for the cure of cancer.

Immunotherapy, whether of cancer or of infectious diseases, can be broadly categorized into the following major modalities:

(a) Nonspecific—immunotherapy through the activation of the immune response by nonspecific means.
(b) Specific—immunotherapy through the activation of the immune response directed specifically against a given antigen.

In both of these modalities, the immune response can be conferred by active immunization or by passive immunization, utilizing immune serum or immune cells or their products (the latter is referred to as adoptive immunization).

Attempts to use these modalities for cancer immunotherapy are numerous and will be briefly discussed below. Most of the trials, whether experimental or clinical, have yielded disappointing results. Therefore, to date, immunotherapeutic modalities have not proved to be the treatment of choice, or for that matter even an effective treatment of cancer. This is true not only when immunotherapy is the sole form of treatment, but also when it is an adjunct to other forms of cancer therapy such as chemotherapy, radiotherapy or surgery. In describing the various modalities of immunotherapy, we hope to point out some of their underlying mechanisms and possible shortcomings.

Dr. Benjamini is Professor of Immunology, Department of Medical Microbiology, University of California School of Medicine, Davis, California.

Dr. Rennick is a Postdoctoral Fellow, Department of Medical Microbiology, University of California School of Medicine, Davis, California.
Immunotherapy Using Nonspecific Stimulation of the Immune Response

It was observed by Coley\textsuperscript{1,2} and others almost 100 years ago that a variety of bacterial infections in some cancer patients led to the regression of their tumors. Accordingly, Coley used mixed bacterial toxins in an attempt to induce tumor regressions. This approach to tumor therapy was not pursued by others, undoubtedly due to its unpredictability. Although the mechanisms behind Coley's observations were not understood at that time, we know today that many bacterial products, including their toxins, possess the capacity to stimulate and enhance the immune response. Although the immune response induced by a bacterial product is specific to that antigen, it also sets into motion antigen-specific components and leads to the accumulation of a multitude of leukocytic cells and their products and to the stimulation of biologically active components at the vicinity of the antigen. The accumulation of these substances adjacent to the antigen will result in damage to cells in that area. In fact, such tissue damage is the basis for antigen-specific hypersensitivity reactions. It is easy to realize that if cells—whether microorganisms, normal cells, or tumor cells—are present at the vicinity of such a reaction, they will be damaged, as innocent bystanders, near an antigen-specific immune response. It is probably such a mechanism that would account, at least in part, for Coley's observations.

This rationale was employed some 50 years later by Klein, who produced an intense delayed hypersensitivity reaction by applying potent contact sensitizers (such as dinitrochlorobenzene) on several skin tumors.\textsuperscript{4} The delayed hypersensitivity reaction, specific to the contact sensitizing agent, involved activated inflammatory components that damaged cancerous tissue as well as normal tissue. Again, the specificity of the immune reaction was against the contact sensitizers but there was damage to all cells in the immediate vicinity of the reaction. However, the normal tissue regenerated, whereas in many instances the tumors were destroyed and did not reappear.

The concept of killing tumors as innocent bystanders in inflammatory immune reactions has been modified to include the intralesional treatment of tumors with a variety of agents, such as contact sensitizers and Bacillus Calmette-Guerin (BCG).\textsuperscript{4-8} By and large, this form of immunotherapy has resulted in tumor regression provided the malignant lesion was small and localized, and the patient was immunologically competent. However, there is no clear-cut evidence that such treatment is effective in metastatic disease. Moreover even when the treatment is limited to the skin there is a question as to its efficacy. As summarized recently by Terry, "It is alleged that patients with disease limited to the skin survive longer as a result of intralesional therapy, but there has not yet been a study to critically test this clinical impression. Until such a study is performed, intralesional therapy must be considered local therapy not known to be superior to surgery or to other local forms of treatment in terms of patient survival."\textsuperscript{9} This conclusion certainly cannot be disputed.

Nonspecific stimulation of the immune response, which is used in cancer immunotherapy, particularly in the disseminated form of the disease, is also achieved by the use of numerous substances that act as immunopotentiators. Although their mechanism of action is not clearly understood, it is known that the administration of these substances into the body enhances, in a nonspecific manner, the entire immune response, including the immune response to the tumor.\textsuperscript{10-12} BCG, Corynebacterium parvum, several polynucleotides, levamisole and lately, interferon, have all been used as immunopotentiators, either alone or in combination with other, conventional forms of therapy. They have been applied to such cancers as malignant melanoma, lymphoid neoplasia, mammary and bronchial carcinomas and others.\textsuperscript{13,14}

Several of these immunopotentiators have been very much in the limelight in the past decade. In fact, the "promising
results" obtained with some of these substances, notably BCG, have been so heavily publicized as to give the impression that cancer immunotherapy has come of age as a major modality among cancer therapies. Although there occasionally have been documented successes in some clinical trials, the results of the majority of those trials were, unfortunately, marginal. Moreover, many of the trials were so poorly designed that the results cannot be properly evaluated. Although there is no question that the immunopotentiators enhance the generalized immune response, the complicated immunological interrelationship between the host and the tumor suggests that even in the immunocompetent host the immune response has a finite capacity to counteract the antigen, be it a toxin, a microorganism or a tumor. It is thus doubtful that immunopotentiation will result in an immunological capacity heightened sufficiently to significantly alter the growth of a tumor or affect metastases. After more than a decade of marginal results using BCG and similar immunopotentiators, it is difficult to believe that simply altering the methodology and experimental design of clinical trials will significantly alter the conclusion that their efficacy is better than marginal.

Numerous attempts at cancer immunotherapy have been made by either conferring or augmenting generalized immune competence via the transfer of nontumor-specific immunity. Since most (but not all) forms of immunity depend on immunocompetent thymus-derived cells (T lymphocytes), attempts have been made to evaluate the effect of the enhancement of T lymphocytes and their products by thymic hormones in primary immunodeficiency diseases and in cancer immunotherapy.15-17 The results of many clinical trials have indicated a beneficial effect of thymic hormone treatment in cases of known immunological deficiency diseases, and it is such positive results that have prompted interest in the potential of this form of therapy for cancer treatment. In cases where tumor-bearing individuals demonstrated depressed T cell function, administration of thymic hormone enhanced T cell activity and prolonged the disease-free interval. However, the mortality rate was unaffected. Immunotherapy of cancer by adoptive transfer of nontumor-specific components such as bone marrow has been employed in the therapy of murine and human leukemias in combination with chemotherapy or radiotherapy.18-21 The results of these studies indicate some beneficial effect of the combination therapy over the chemotherapy or the chemoradiotherapy alone. However, the beneficial effect could be attributed to the restoration of hematopoiesis after the heavy dosages used in the chemotherapy or chemoradiotherapy rather than to the antitumor activity of the transferred marrow.

Tumor-Specific Immunotherapy

Inherent in the approach of activating an immune response that is directed specifically to the tumor is the assumption that tumor cells express tumor-specific antigens. Although such tumor-specific (or tumor-associated) antigens have been demonstrated for numerous experimentally induced tumors, the existence of tumor-specific antigens in most "spontaneous" tumors seen in clinical situations awaits definitive demonstration. Moreover, it is conceivable that the tumor cells, either experimentally induced or spontaneously occurring, would express only a limited number of tumor-specific antigens and that the immunogenicity of such tumor cells would therefore be low. Although a tumor cell may express tumor-specific antigens on its membrane, the majority of the membrane surface is recognized by the immune system as "self." This is in contrast to such strong immunogens as bacteria or foreign grafts, in which cases the cell surface consists of numerous foreign entities. This association of tumor-specific antigens with cell components that are recognized as self may lead to restrictions
in mounting an effective immune response against the tumor. Nevertheless, tumor-specific immune responses have been demonstrated in many tumor-bearing individuals, including those carrying spontaneous tumors.

Tumor-specific immunotherapy, as discussed in several articles,\textsuperscript{14,22-25} has been attempted by active and passive immunizations. The following is a summary of these modalities.

**Active Immunization**

Various preparations have been used as immunogens (vaccines) through active immunization. These preparations included autochthonous, syngeneic or allogeneic tumor cells of the same histological type whose replication has been blocked by one of a variety of ways (e.g., x-irradiation and mitomycin C treatment). Because these vaccines have usually been ineffective or marginal,\textsuperscript{14,23,26-28} and in view of some of the considerations discussed earlier (e.g., relatively low immunogenicity of tumor-specific antigens), attempts were made to prepare vaccines with increased immunogenicity for tumor-specific antigens. Tumor cells have been treated with the enzyme neuraminidase, which removes the normal component, sialic acid, from the cell surface and appears to increase the immunogenicity of these cells.\textsuperscript{29} Immunization with neuraminidase-treated tumor cells has been demonstrated to result in a modest regression of tumors in experimental animals.\textsuperscript{30,31} However, the beneficial results have been apparent only under special circumstances, such as in the treatment of relatively small tumor masses, or after first reducing tumor mass with surgery and incorporating the vaccines with BCG treatment.

Neuraminidase-treated tumor cells have also been tested in clinical trials of immunotherapy of various tumors.\textsuperscript{31-33} The results of these trials, some of which are still in progress, indicate that the immunogenicity of neuraminidase-treated cells (especially with regard to enhancing cell-mediated immunity) is enhanced and that immunotherapy of some human cancers with neuraminidase-treated cells, although not an effective cure, appears to prolong remission periods and to enhance survival. Other attempts at active specific immunotherapy have been made with tumor cells or tumor cell extracts that have undergone a variety of chemical modifications.\textsuperscript{34-36} The results of these attempts are, for the most part, disappointing, especially in view of the fact that some preparations exhibited a remarkably high immunogenicity capable of protecting experimental animals against supralethal dosages of transplanted tumor cells; despite their high prophylactic efficacy, these vaccines were largely ineffective in immunotherapy of tumor-bearing animals as exemplified by murine leukemia vaccines.\textsuperscript{27} Only marginal efficacy of these vaccines was apparent when they were used in combination with other forms of therapy.\textsuperscript{14}

**Passive Immunization**

"Passive immunization" is used here in its broadest sense: to denote the transfer of specific antitumor antibodies or tumor-immune cells or their products from an immunized individual to a nonimmune individual and the use of antitumor antibodies to "deliver" drugs or radiation specifically to tumor cells that carry the tumor-specific antigens. The term "serotherapy" is appropriately applied to the practice of using antiserum as the therapeutic agent. Serotherapy is predicated on several major requirements: the antibodies must be specific to the antigen; the titer of the antibodies must be sufficiently high to be effective; the antibody must reach its target and, either alone or in combination with other factors (e.g., complement or phagocytic cells), must exert its effect upon its target, be it a microorganism or a tumor cell. There are many examples of serotherapy of infectious diseases.\textsuperscript{37} It is therefore reasonable to expect that serotherapy may be of use in cancer therapy, and in fact, attempts at this form of cancer therapy
are documented from as early as 1895, and the history of cancer serotherapy has been recently summarized. Although numerous successes have been reported in several animal models, and although several reports of “successful” tumor serotherapy of human cancers have been reported, the status of serotherapy, as summarized recently by Pressman, indicates that “In spite of glowing reports a general (sero)therapy of cancer did not develop,” probably because the requirements for successful serotherapy mentioned above were not fulfilled.

As previously stated, the rationale for using antitumor antibodies is not confined to the use of these antibodies for purposes of serotherapy only, but in fact extends to the use of tumor-specific antibodies as “missiles” to specifically deliver drugs or radiation preferentially to the tumor. Since all currently available antitumor agents are toxic not only to tumor cells but also to normal cells, their general toxicity prohibits their administration in high concentrations. However, their attachment to the specific antitumor antibodies might enable their specific delivery to the tumor at a high concentration, minimizing their harmful effect on normal tissue. Indeed, such approaches have been used with varying successes and have recently been summarized. Drugs such as methotrexate, chlorambucil and others, as well as radionuclides, have been coupled to antitumor antibodies and assessed for their immunotherapeutic effect. Again, this treatment requires large quantities of highly specific antitumor antibodies and delivery of an effective drug or radionuclide dose to the tumors.

It is tempting to speculate that one of the reasons cancer serotherapy or tumor-specific antibody “missiles” have not become a major modality of cancer therapy is due, in part, to the great difficulties in obtaining sufficient quantities of high-titer tumor-specific antibodies. However, recent developments in cell biology and immunology have brought forth a very important technical advance that allows the potential production of large quantities of tumor-specific antibodies, justifying a reassessment of the use of tumor serotherapy by passive immunization or the delivery of antitumor agents by antibody “missiles.” A case in point is the recent development of hybridoma lines for the production of homogeneous antibodies of a desired specificity. The technique is based on the fact that genetic information of a cell that produces antibodies of a given specificity is incorporated into a myeloma cell line. Under appropriate conditions, a continuous cell line is formed that synthesizes homogeneous antibodies of the specificity present in the original antibody-producing cells. By this technology, the availability of large quantities of highly specific antitumor antibodies is becoming a reality. Renewed interest in the potential use of such antibodies in cancer therapy is forthcoming. We are still rather pessimistic about the efficacy of tumor serotherapy using such hybridoma antibodies, because of the difficulties in meeting the aforementioned criteria for successful serotherapy. However, we are less pessimistic about their potential use as carriers of antitumor agents, particularly in situations where tumor mass is minimal.

Another form of passive immunization is the adoptive transfer of immunocompetent cells, their precursors, or the products of such cells from an immune to a nonimmune individual. The subject has been reviewed. In general, the success of such adoptive tumor-specific immunotherapy among syngeneic animals depends upon the number of transferred cells and upon the tumor mass of the recipient. Thus, it is apparent that the higher the number of transferred cells, the higher is their therapeutic efficacy. There are situations in which the tumor mass of the recipient is of such magnitude that the transfer of a sufficient number of cells to cope with the tumor mass becomes logistically impossible. In such cases, attempts at immunotherapy following the reduction of the tumor mass were much more rewarding.
theless, such attempts are not always successful, a variety of factors in the tumor bearer of that preclude effective immunotherapy by adoptive transfer. Some of these factors are nonimmunological in nature (such as blocking antibodies or antigen-antibody complexes, excessive circulating antigen, and suppressor factors).

In contrast to adoptive cell transfer between syngeneic individuals, immunotherapy by adoptive transfer of immune cells between individuals who are not matched for histocompatibility is much more problematic and less promising. Adoptive immunotherapy using allogeneic cells will remain problematic until techniques are developed for successful tissue transplant between nonidentical individuals.

To overcome the problems of rejection in adoptive immunotherapy between nonidentical individuals, attempts have been made to transfer the products of cells specifically immune to the tumor rather than whole cells that bear the transplantation antigens. Since the discovery by Lawrence\(^43\) that delayed type hypersensitivity could be transferred from one human to another via an extract of leukocytes from the sensitized donor to the nonsensitive recipient, much interest has been focused on the activity and characterization of the "transfer factor." To date, both the activity and the physicochemical characteristics of transfer factor are still controversial, although there are reports of successful treatment of several immune deficiency diseases and several infectious diseases with transfer.\(^44\)-\(^46\) Clinical trials using transfer factor in cancer immunotherapy are in progress, but are not yet evaluable.\(^9\) There are, however, two major stumbling blocks in the use of transfer factor in cancer immunotherapy, one practical and one conceptual. The first concerns the amounts of transfer factor required for reasonable therapeutic regimens, the result being that, generally, transfer factor must be pooled from many different donors. This leads to the second problem, namely, whether nonspecific transfer factor will be sufficient or whether effective therapy will require transfer factor from tumor immune individuals. A requirement for the latter would put severe restrictions on the use of this form of therapy.

Another form of adoptive immunotherapy with cell products is the administration of immune RNA from lymphoid organs of immune individuals to the tumor-bearing individuals. It has been claimed that immune RNA can effectively transfer immunity not only between syngeneic or allogeneic individuals but even between xenogeneic individuals. The various attempts at immunotherapy with immune RNA have been summarized.\(^47\) In general, the mode of action of immune RNA in transferring immunity from an immune to a nonimmune individual is still obscure. There have been several encouraging reports of augmentation of tumor-specific immune responses by immune RNA, as well as indications of some beneficial effects in tumor patients.\(^47\)-\(^51\) However, the results are primarily marginal. Additional clinical trials using immune RNA are in progress, but data are not yet evaluable.\(^9\)

Present and Future Status of Immunotherapy

The foregoing gave a brief overview of past and present approaches to the immunotherapy of cancer. Since the realization that the immune response may be recruited for the therapy of tumor, numerous attempts—some of which now seem naive and others ingenious—have been directed toward cancer therapy. By and large, it is fair to state that so far these attempts have been disappointing. As expressed by Terry in his summary of the present status and future direction for cancer immunotherapy, "All current immunotherapy is experimental...there is no example of an immunotherapeutic treatment that can be considered as the treatment of choice for any cancer."\(^9\) There are probably numerous reasons...
for this assertion. It is clear that in many instances strong tumor-specific antigens have been demonstrated under experimental conditions. Such antigens constituted powerful vaccines that could protect experimentally immunized animals against supralethal dosages of tumor cells. In fact, the literature is replete with examples of successful immunophylaxis of experimental animals to virally and chemically induced tumors. Yet, despite the ability of these vaccines to protect animals against cancer implants, they were largely ineffective in the treatment of established tumors. Such vaccines had either no effect or a marginal effect upon the progression of the disease.

Although it is generally expected that immunological manipulation benefits the host, there are studies that indicate that there are instances where immunological manipulation is in fact detrimental to the host and may actually lead to tumor enhancement rather than to tumor destruction. Tumor enhancement may be due to the induction of tumor-specific and/or generalized suppression of the immune system; this may be due to the induction of antibodies that may bind to tumor cells without destroying them, and thereby protect the tumor from destruction by tumor-specific cytotoxic cells or by other cytotoxic antibodies. These are but a few examples for several postulated mechanisms underlying tumor enhancement due to immunological interventions.\textsuperscript{52-54} Accordingly, it is possible that immunological intervention in neoplasia may be more detrimental than beneficial.

Even if tumor enhancement is not a factor, it is becoming clear that the failure of immunotherapy may be due to a multitude of other factors that must be considered when immunotherapy is attempted. For example, the immune response has a finite capacity. Thus, it cannot be expected to be effective against a large tumor mass. Consequently, attempts at immunotherapy should be made only following tumor reduction by surgery, chemotherapy, and other means. Moreover, the individual on which immunotherapy is attempted should be immunologically competent if attempts are made to augment his own immune response. Additionally, if adoptive immunotherapy is attempted, it is essential to ascertain that the recipient does not possess factors that are capable of interfering with the transferred response. Even the optimistic methodology that deals with the delivery of antitumor drugs or radiation by specific antitumor antibodies has practical problems: large amounts of circulating tumor antigens could combine with the antitumor antibodies and prevent the antibodies from reaching their target—the tumor cell. Moreover, it is still not clear what would be the fate of such drug-antibody complexes or radiation-carrying antibodies following their action on the tumor cells. Would the resulting immune complexes and the accompanying drug or radiation trigger immunopathological conditions?

In short, the logistics of tumor immunotherapy are monumental and require a great deal of experimental research. As elegantly summarized by Terry,\textsuperscript{9} "The real future of immunotherapy is impossible to predict. It is my speculation that in five to 10 years some form of immunotherapy will play a significant role in the treatment of some cancers, either alone or in combination with other forms of cancer therapy. Converting that speculation into reality will take considerable intelligence, hard work, and a certain amount of good luck." We could not agree more with these conclusions.

It is perhaps worthwhile to compare tumor immunotherapy with immunotherapy of infectious diseases. It is safe to state that the hallmark of immunology is the prophylactic capacity of the immune response against infection with microorganisms. This appears to be similar to the demonstrated prophylactic capacity of the immune response against transplanted tumors. Usually, infection with microorganisms results in disease followed by recovery with residual specific immunity. With more virulent microorganisms infection could result in
death in spite of high immunogenicity and antigenicity of the microorganisms. Except for the cases of serotherapy, there are only a handful of examples of successful immunotherapy of infectious diseases. Prior to the advent of successful therapy of infectious diseases by antibiotics, many attempts were made at immunotherapy of infectious diseases, but these were largely unsuccessful, a situation that led to the development of chemotherapy and antibiotics. Justifiably or not, the advent of antibiotics made further investigations into immunotherapy of infectious diseases of secondary importance, so that to date we do not understand the reasons for its failure. In the absence of successful cancer therapy, much hope has been placed in immuno-
therapy. Unfortunately, to date, cancer immunotherapy's lack of success probably parallels that of immunotherapy of infectious diseases prior to the advent of antibiotics. Just like the many different mechanisms that influence the host-parasite relationship, the host-tumor relationship is complex and differs from one tumor system to another. With our present understanding of the tumor-host relationship, in particular their immunological aspects, the expectation of successful cancer immunotherapy is premature. It is imperative to elucidate the interrelationship of the host and the tumor, including the immunological aspects. Thereafter, hopefully we will be able to intelligently manipulate the relationship in favor of the host.

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