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IMMUNOLOGIC ASPECTS OF CANCER CHEMOTHERAPY

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INTRODUCTION

Most human and animal tumors bear antigens which may be classified as tumor specific or as tumor associated (1–4). Many scientists believe that the immune response to these antigens constitutes a critical host defense against cancer, and there are numerous reports in which immune manipulation has been utilized as a treatment for cancer (5–8). Clearly, lymphocytes from animals and human patients cured of tumors may destroy cultivated cells from their respective neoplasms; however, this may also be true when the lymphocyte donors have a growing tumor mass (9–10). Even with sophisticated immunologic testing, the majority of patients with early cancer appear to have normal immunologic function (11). Moreover, in many cases the best treatment for these patients is with drugs that can depress immunologic function, and cure or long-term control is nevertheless possible (12).

Because of these conflicting facts, physicians are faced with a serious question: what is the risk to benefit ratio of cancer chemotherapy as it relates to the immune system? This review focuses on the relationship between cancer chemotherapy and the immune system. Initially, I consider the immune response to cancer and immunologic function in patients with cancer. I then review the immune suppression which can be seen with both single-agent chemotherapy and combination chemotherapy and conclude with a discussion of immunotherapy and chemoimmunotherapy as current approaches to the amelioration of immune defects in patients with cancer. This review does not consider the use of immunosuppressive drugs in human transplantation or as treatment in a wide variety of "autoimmune" diseases.

THE IMMUNE RESPONSE IN CANCER

The normal immune response involves an exceedingly complex interaction between cellular and humoral factors (2, 6, 10, 13, 14). A simplified version of the immune system as it relates to cancer is shown in Figure 1, which distinguishes between

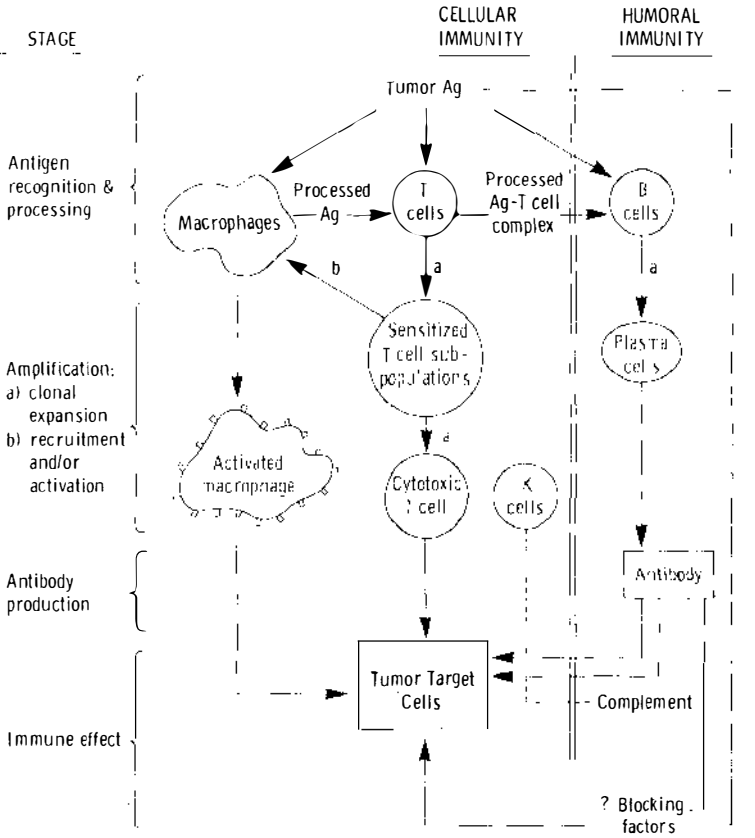

Figure 1 Diagrammatic representation of the immune response to a tumor antigen (Ag). The successive stages of the immune response are depicted on the left side of the diagram. Abbreviations: a, clonal expansion; b, recruitment and/or activation; T cell, thymus-dependent lymphocyte; B cell, bursa or bone marrow—derived lymphocyte; K cell, a lymphocyte population that has neither T- nor B-cell markers.

events involving humoral immunity and those involving cellular immunity. It does not distinguish between the primary and secondary responses to an antigen.

The initial stages of antigen recognition and processing may occur with macrophages, thymus-dependent lymphocytes (T cells), or bursa or bone marrow–dependent lymphocytes (B cells). Interactions between these cell lines are also possible, and subsequent amplification mechanisms follow. Amplification of the immune system may occur by clonal expansion, in which lymphocyte blastogenesis occurs with a proliferation of selected cell populations. Recruitment and/or activation of other cell lines may also occur; for example, it is known that macrophages can be activated by sensitizing T-cell subpopulations through the elaboration of macrophage activat-

ing factor (14). The final stage of immune effect involves a complex interaction of one or more of these elements. Activated macrophages are capable of killing tumor cells directly, and cytotoxic T cells can also act independently. A newly described lymphocyte population referred to as K cells (15), which bear neither T nor B lymphocyte surface characteristics, can kill tumor cells in the presence of specific antitumor antibody. Antibody, in the presence of complement, is also capable of killing tumor cells, and recently polymorphonuclear leukocytes in the presence of antibody have been shown to have cytotoxic effects (16).

These components of the immune system are considered critical to the process of killing tumor cells bearing tumor antigens. It is generally assumed that the cellular component of this effect is dominant, with humoral immunity playing a lesser role. Indeed, there is evidence that humoral immunity, through the formation of blocking factors (probable antigen-antibody complexes), may act to abrogate the ability of the cellular immune system to kill these cells (9, 10). Other cellular and humoral immune suppressors and stimulators have also been postulated (6, 17–20).

A diagram such as Figure 1 cannot convey the variety of responses to individual tumors that may occur. Differing levels of immunogenicity (1, 2, 21), changes in immunogenicity developing during the course of tumor dissemination and metastasis (22, 23), nonuniform responses in cell-mediated and humoral immune systems (4, 6, 10), the functional capacity of amplification factors, the importance of host abnormalities in antigen processing such as may occur with inadequate lymphocyte "trapping" in some sites of the body (24), prior antigenic experience, the functional status of the nervous system as it relates to humoral immunity (25), and genetic factors (26) may all serve to individualize the balance within the immune system and between tumor and host.

Many abnormalities in immunologic function have been documented during the course of malignant disease in patients with many different kinds of cancers. There is, however, considerable controversy whether such abnormalities are the result of cancer or represent an important causal factor. Many scientists believe that the immune response is the principal defense against neoplastic cells. This view was formulated by Thomas (27), and subsequently Burnet (28) elaborated on the concept and called it *immunologic surveillance.* They reasoned that the immune response destroyed cancer cells while they were still in the incipient stages of tumor formation, a possible function similar to graft rejection of foreign cells. This theory predicts that impaired immunity would inevitably increase susceptibility to cancer and suggests that immunity against a variety of neoplasms would exist in all normal adults. A tremendous amount of experimental work ensued to define the relationship between oncogenesis and the immunologic status of the host. Results often have been contradictory (29, 30). Many studies demonstrated tumor-specific antigens on human and animal cancer cells, facilitated carcinogenesis by immunosuppression (31), and increased incidence of malignancy in immunosuppressed or immunodeficient patients (14, 32–34). On the other hand, it is clear that some tumors do not seem to be antigenic (29, 30), and other studies failed to demonstrate enhanced carcinogenesis with immunosuppressive treatment (35).

In a critical review of the theory of immunologic surveillance, Schwartz (29) proposed that defective immunity may lead to cancer, not through surveillance against neoplastic cells, but by failure to terminate lymphoproliferation triggered by an antigen. He concluded that it may be unrealistic to expect the enormous complexities of cancer to crystallize within the confines of a single theory. Some neoplasms may well arise as a result of spontaneous mutation, while others may be induced by viruses, chemical carcinogens, X rays, or hormonal stimulation. Some may be eliminated by an immune response, whereas others may actually require an immune response for their development. Clearly, the latter situation has been well documented by Prehn (36), where the initial effect of the immune system on a developing tumor was stimulation of tumor growth at very small tumor cell numbers. A corollary of this is seen in some animal tumors, where manipulation of the immune system has resulted in a marked increase in the rate of tumor growth (37, 38).

Ritts & Neel (4) have provided yet another perspective on the role of the immune system in cancer. Drawing from the work of Voisin (39), they point out that current concepts of the immune system appear to neglect the well-founded physiologic importance of homeostasis. The very vocabulary of immunology with its traditional martial posture of attack versus defense (using such terms as *invader, surveillance, front line of defense, recruitment, escape*) is antithetical to homeostasis. As articulated by Voisin, a posture of dynamic equilibrium is more sensible. In essence, he postulates a dynamic spectrum of immune reaction, which ranges from host rejection to enhancement, allowing one to visualize a finely tuned balance, with both rejection and enhancement utilizing the components of the immune system outlined in Figure 1. This concept considers the facilitation or enhancement of cellular growth equal in importance to the rejection of cells; facilitation represents the necessary counterpart of the rejection reaction to prevent the autodestruction of the individual.

Although immunologic theories of cancer appear to be in a state of crisis, physicians treating patients with cancer must carefully consider both the impact of the tumor on immune function and the impact of treatment on the immunologic status of the host. It may be impossible to prove or disprove the existence of an immune surveillance mechanism (30), but it is possible for us to identify those agents or procedures that appear to increase the probability of neoplastic disease or complications from neoplasms. In terms of cancer chemotherapy, the practical result of these theories is that we should strive for programs of treatment that are minimally immunosuppressive wherever possible (40–42). Even if one believes that the immune system plays no important role in the etiology of cancer, it clearly is an important host defense mechanism for many of the complications that occur during treatment. Specifically, infections commonly lead to the death of patients with advanced cancer, and impaired immunity may contribute to such a death (12, 43). Therefore, while awaiting further studies to define the basic mechanisms involved, we should consider carefully the effect of treatment on the immune system of our patients.

Immune Function in Patients with Cancer

Detailed reviews of immunologic function in patients with cancer are available (3, 4, 11, 40–42, 44), and the techniques of immunologic assessment utilized therein

have been reviewed (45). Immunologic studies in patients with cancer commonly utilize tests of delayed cutaneous hypersensitivity, either with recall antigens or with dinitrochlorobenzene (DNCB) to determine cellular immune function (46–49). Humoral immunity is clinically assessed by the level of immunoglobulins (44); however, for research purposes this must be supplemented by additional techniques (45). Considerable controversy surrounds the use of newer techniques of immune evaluation in patients, such as tests of antitumor cellular cytotoxicity (49–51) and T- and B-cell quantitation (52).

Innumerable studies confirm that profound disturbances in immune function may accompany human cancer (11). Patients with early and indolent forms of malignancy are less severely affected than those with rapidly progressive disseminated tumors. Highly sophisticated techniques are required to demonstrate any defects in immune function occurring in very early stages of neoplasia. Leukemias and lymphomas are associated with profound immune defects, as with the well-known anergy which accompanies Hodgkin's disease (11, 44). Cell-mediated immunity is the initial arm of the immune system to be altered in most cases, and disturbances of T-lymphocyte function have been demonstrated by both in vivo and in vitro methods. In late stages of disease, humoral immunity also becomes depressed.

In groups of patients with solid tumors, anergy to DNCB or recall antigens generally signifies a poor prognosis (41, 44, 53). Bolton and colleagues (54) tested the response to DNCB as an indicator of a primary response and the Mantoux reaction as an index of recall responses in patients with colonic cancer, breast cancer, and gastric cancer. Cellular immunity was lost earliest and to the greatest extent in patients with colonic cancer; gastric cancer occupied an intermediate position, and severely depressed immunity was seen in breast cancer only with very advanced disease. A paradoxical result was seen in breast cancer where DNCB responsiveness was excellent in patients with intermediate stages of disease, but was depressed in patients both with early disease and with very advanced disease. This study serves to underline the need to very carefully assess groups of patients by specific type of neoplasm (55–64), with appropriate control groups by stage as well as by age (65, 66), nutritional status (67, 68), and other factors that may influence immunologic function. Unfortunately, this kind of detailed information is not available for most tumors, and statements about the value of DNCB skin testing for populations of patients may not be useful in assessing the prognosis of an individual patient (69).

DRUG-INDUCED IMMUNOSUPPRESSION

Major improvements in cancer chemotherapy have followed a better understanding of the mechanisms of drug action, pharmacology, and cellular biology (12). We now know that one must consider anticancer drug action as a function of the cell cycle (with a distinction between phase specific and phase nonspecific drugs), as well as the fact that tumor cell populations appear to grow by Gomperzian kinetics. It is also known that chemotherapy kills cancer cells by a fractional cell kill mechanism, usually best described as a logarithmic function (log cell kill hypothesis).

We have learned that choosing the proper dose and schedule of drugs is critical, and major improvements in treatment have resulted from combinations of drugs. Combination chemotherapy has been a particularly important factor in improving the treatment of patients with cancer, and several principles underlying combination chemotherapy have emerged. The successful programs of combination chemotherapy utilize only drugs that are active against the cancer in question, have different mechanisms of action, and varying spectra of toxicities so that full doses can be employed. In addition, most successful combination chemotherapy regimens employ intensive pulses of combination drug treatment, followed by a period of rest. This rest period allows for reconstitution of hematopoietic and other cellular functions.

The aforementioned principles have contributed to improvements in cancer chemotherapy over recent years; however, how may we improve these results further and what are the clear-cut deficits of such therapy? The toxicity of these various programs of chemotherapy are fairly well defined as they relate to bone marrow function and the function of other major organ systems. Reasonably extensive studies have defined the immunosuppressive effects of the antineoplastic drugs used as single agents (70). However, most of these studies have been done in animals with the schedule of drug administration chosen to optimize immunosuppression. Much less is known about the immunosuppressive effects in man of cancer chemotherapy used as clinical treatment of cancer (70, 71).

In this review, I do not discuss in detail animal studies of immunosuppression with the clinically useful anticancer drugs. Rather, I summarize the sites of action of the commonly used immunosuppressive agents on the immune response in Table 1, as defined in animal studies. In the sections that follow I briefly describe the results of single-agent chemotherapy and combination chemotherapy on the established immune response in man. It is likely that the major deleterious impact of chemotherapy in man is upon already established immunity, since in all probability the critical event of antitumor immunity occurred before the cancer was diagnosed.

Table 1 Stages of the immune response inhibited by drugs

Antigen recognition and/or processing	Amplification	Antibody production	Immune effect
Alkylating agents (cyclophosphamide)	Alkylating agents (cyclophosphamide)	Alkylating agents (cyclophosphamide)	Corticosteroids
X irradiation	Actinomycin D		Antilymphocyte serum
Actinomycin D	5-Fluorouracil		
Corticosteroids	6-Mercaptopurine		
Antilymphocyte serum	Cytosine arabinoside		
	L-Asparaginase		
	Vinca alkaloids		

Single-Agent Chemotherapy

A recent review details attempts to suppress humoral immunity selectively, while sparing cellular immunity in experimental animals (72). This review and other major ones on immunosuppression (70, 71) clearly illustrate that the commonly used antineoplastic agents rarely suppress previously established immune function.

6-MERCAPTOPURINE 6-Mercaptopurine (6-MP) is one of the most extensively studied immunosuppressive agents (40, 70, 73). Its use in man depresses the primary antibody response; it can retard allograft rejection and prevent the development of new delayed hypersensitivity reactions. It may also induce tolerance with proper scheduling of antigen administration. However, conventional doses of 6-MP used in cancer patients appear to have no important effect on established delayed hypersensitivity (73).

5-FLUOROURACIL Mitchell & DeConti (74) studied 12 cancer patients undergoing 5-fluorouracil therapy. Eight of 10 patients failed to demonstrate a primary antibody response to Vi-antigen, and a secondary response was completely inhibited in 4 of 9 patients. Five of 6 patients tested failed to achieve a delayed cutaneous hypersensitivity reaction to DNCB. Three of 6 showed reversion to positive of one or more skin tests after therapy. This study suggests that 5-fluorouracil given in clinical doses to man is a potent immunosuppressant, having some effect on established immunity as well as on primary immunity. An additional study of interest is that of Suhrland, Benson & Labelle (75), in which subtherapeutic doses of 5-fluorouracil in mice (1 mg/kg/day) led to an enhanced growth of a transplantable mammary adenocarcinoma, whereas a standard therapeutic dose (15 mg/kg/day) led to marked inhibition of this same tumor. Further studies indicated that the stimulating dose for tumor growth was able to suppress the secondary antibody response to bovine gamma globulin. These findings underline the importance of choosing the proper dose, whether the concern is immunosuppression or antitumor effect.

METHOTREXATE Methotrexate can suppress humoral antibody formation in man, primarily when given after antigenic stimulation (70, 76). It does not appear to block either the expression of established delayed hypersensitivity or the ability to acquire new delayed hypersensitivity, although it can reduce the intensity of these reactions. It may also inhibit the local inflammatory response in man.

CYTOSINE ARABINOSIDE Cytosine arabinoside has been intensively studied by Heppner & Calabresi (72) as a potential selective immunosuppressant, based on early studies of its selective ability to inhibit humoral immunity in tumor-bearing mice. Further studies in mice confirmed marked dependency on the schedule of administration of drug and antigen, as well as drug dosage. Mitchell and colleagues (76) have studied schedules of cytosine arabinoside similar to those that are optimal for the treatment of malignancy in patients with cancer. Such schedules partially

suppress the primary and secondary antibody response, but established delayed hypersensitivity reactions were unaffected.

CYCLOPHOSPHAMIDE This drug has been widely studied in animals and man (70, 71, 77-80). Administered as maintenance therapy to patients with lymphomas in an oral dose of 100 mg/day, no interference with the development of normal humoral and cell-mediated immune responses to keyhole limpet hemocyanin was found (71). In vitro lymphocyte blastogenesis after stimulation with phytohemagglutinin was also unaffected. Given in larger doses intravenously (7 mg/kg/day for 7 days), it is capable of blocking the antibody response to Vi antigen. There was, however, no significant reduction in established delayed hypersensitivity. Clearly depending on the timing of administration and dose employed, cyclophosphamide can be a potent immunosuppressant drug. However, I am unaware of any studies demonstrating significant depression of established delayed hypersensitivity reactions.

VINCA ALKALOIDS Vincristine and prednisone, when combined to treat acute leukemia, inhibit the primary immune response to a variety of antigens (70, 71). Other studies in man are inadequate to make a firm statement about the immunosuppressant qualities of this class of drugs, although most studies suggest that the vinca alkaloids are only weakly immunosuppressant. There are major species differences in the immunosuppressive properties of the vinca alkaloids, and potent immunosuppression has been observed only in the rat (81).

ADRIAMYCIN AND DAUNOMYCIN I am unaware of any detailed immunologic studies in man with these two drugs. A study comparing the immunosuppressive activity of these drugs on humoral antibody production and tumor allograft rejection has been done in mice (82). It was found that adriamycin induced a greater reduction in the number of antibody-producing cells after primary stimulation with sheep erythrocytes, whereas daunomycin was more suppressive of the secondary response to the same antigen. With a tumor allograft model, daunomycin was significantly more immunosuppressive than was adriamycin administered at equitoxic doses. It was suggested that the greater immunosuppressive effect of daunomycin may account for the superiority of adriamycin in most clinical settings. This interesting hypothesis requires additional study in man, including the effect of drug treatment on established immune function.

IMMUNE SUPPRESSION BY MICROORGANISMS Schwab (83) has reviewed suppression of the immune response by microorganisms. Of greatest interest has been the suppression of the immune system seen with certain bacterial enzymes, most importantly *l*-asparaginase (84). This appears to inhibit thymus-dependent (T-cell) lymphocytes primarily, although under certain circumstances B cells are also inhibited (85). One fascinating aspect of the toxicity of *l*-asparaginase is the development of allergic reactions to the enzyme. This has been extensively studied in man (86). Prior to treatment, patients are not allergic to this medication and they have no antibody or skin reactivity to the enzyme. After one course of treatment, positive

skin test reactivity is observed. Circulating antibodies have also been detected, and patients have, in some cases, developed anaphylactic shock upon repeated exposure.

There are other bacterial products which are immunosuppressive (83), but the important ones (bacillus Calmette-Guérin and *Corynebacterium parvum*) are discussed in the context of immunotherapy in a later section, since these same agents are primarily being employed as immunostimulants.

Combination Chemotherapy

There is a paucity of information on the impact of combination chemotherapy on the immune system. The major studies have taken place in acute leukemia, where a number of investigators have analyzed the impact of various programs of intensive combination chemotherapy on long-term survival and immunologic function (40, 87–91). Leventhal, Cohen & Triem (91) have reviewed the literature on this subject, and concluded that the majority of patients with acute leukemia showed depressed B-cell function during combination chemotherapy. There was also a correlation shown between a poor prognosis and depressed T-cell function during the induction phase of chemotherapy. They postulated that this poor survival was probably due at least in part to an increased incidence of fatal infections. Depressed T-cell function undoubtedly was not a major function of chemotherapy, since it predated the initiation of treatment in most patients.

Of additional interest is the impact of long-term chemotherapy on immunologic function after the conclusion of treatment. Children with acute lymphoblastic leukemia in continuous remission for two and one half to three years treated at St. Jude's Hospital in Tennessee were studied after discontinuation of chemotherapy (87, 88). Children less than five years of age demonstrated a rise in lymphocyte number and increased immunoglobulin and antibody production. This was not seen in the older group of patients. After drugs were discontinued, one fourth of the patients demonstrated a rise in antibody to the Hong Kong influenza virus without evidence of reexposure to the same antigen. Further studies confirmed that lymphocyte function promptly recovered even after three years of antineoplastic therapy, and there were variations from patient to patient in the speed of this form of immunologic rebound. It was suggested that any studies of immunotherapy in this population would have to be carefully controlled, because of the variable rate of immune recovery with immunostimulation.

Several groups have studied the effect of combination chemotherapy on the immune system in patients with solid tumors. The earliest studies were by Hersh and colleagues (40, 70, 92–94), originally performed at the National Cancer Institute and subsequently continued at M. D. Anderson Hospital. One widely quoted study is particularly relevant (12, 42, 94). Patients with solid tumors received five-day courses of intensive combination chemotherapy. The immunological factors included macrophage entry into experimental inflammatory sites (a skin window), antibody response to primary antigenic stimulation, and lymphocyte blastogenic response to phytohemagglutinin. There was a marked decrease in all of these parameters during treatment; however, within two or three days there was complete or nearly complete recovery in immunological response. Indeed, some patients developed an "immunological overshoot" during the recovery period. Thus, when such

five-day courses of combination chemotherapy were given every two to four weeks, the patient's immunological function was normal most of the time.

Harris and colleagues (95–97) have extended these results by demonstrating a high correlation of an overshoot response in lymphocyte function in patients with solid tumors who enjoy a substantial reduction in tumor size with combination chemotherapy. Nonresponding patients failed to demonstrate the overshoot, whereas responding patients almost universally demonstrated the phenomenon. This was true for 6 of 13 responding patients who were immunologically hyporeactive before treatment.

Studies are in progress to define further the immunologic effects of combination chemotherapy (98), with attention to the details of patient selection by diagnosis and stage, as well as pretreatment immunologic function. However, while awaiting the results of such studies, it would appear prudent to utilize combination chemotherapy in intermittent regimens wherever possible to take advantage of what appears to be a reduced amount of immunosuppression by such regimens (99).

IMMUNOTHERAPY AND CHEMOIMMUNOTHERAPY

Encouraged primarily by the theory of immunologic surveillance as an explanation for the development of cancer in animals and man, there has been considerable interest in stimulating the immune system as a potential approach to treating or preventing the development of cancer. The subject of immune stimulation has generated a large number of scientific studies and many reviews (4–8, 44, 100).

Immunotherapy can be divided into three areas: passive immunotherapy, adoptive immunotherapy, and active immunotherapy. Passive immunotherapy involves administration to the patient of antibodies produced in other individuals or animals. By definition it does not actively involve the host's resources in the immunotherapeutic process. Adoptive immunotherapy involves the introduction of immunocompetent cells into the cancer patient. These cells may be from related or unrelated individuals, and they may be either immune or nonimmune. Immune cells may be sensitized in vivo or in vitro, either to the patient's tumor, to other tumors, or even to oncogenic viruses. Although both passive and adoptive immunotherapy have been utilized with some success in experimental animals, they have never been proven to be of value in treating human cancer and are not discussed further at this juncture. The remaining form of immunotherapy, active immunotherapy, involves the host playing an active role in the induction or modulation of the immune response. Active immunotherapy can be either specific or nonspecific. A number of agents, including bacillus Calmette Guérin (BCG) (101), methanol-extracted residue (MER) of BCG (102), *Corynebacterium parvum* (103), levamisole (104), and synthetic polynucleosides (105), have been shown to have a nonspecific stimulatory effect. However, as described briefly above, some of these materials may also have immunosuppressive qualities, depending on the dose and route of administration (83).

At the present time, preliminary data suggest that active immunotherapy of a nonspecific type may be useful in the treatment of selected human tumors, primarily

adult acute myelogenous leukemia (106–108), metastatic malignant melanoma (7, 109, 110), various skin cancers (111), and possibly Hodgkin's disease (112). However, other human tumors initially thought to be responsive to immune manipulation have failed to respond to such therapy in subsequent trials. This is particularly true of childhood acute lymphocytic leukemia, where initial success (113) failed to be seen in subsequent studies (108, 114). In addition, reports of successful immunotherapy with BCG in malignant melanoma have all utilized retrospective controls, and some of the apparent benefits of BCG in some subsets of patients were not seen in subsequent studies utilizing other strains or doses of BCG (115). These variable results and the inherent risks of BCG in man (116) underline the highly experimental nature of immunotherapy for human malignant diseases. Indeed, given the complexities of the immune system these results should not be a surprise. Lacking a reproducible and consistent record of therapeutic success with immunotherapy, I do not believe that it can be recommended beyond the experimental clinic at the present time.

Programs of chemoimmunotherapy are in a similar state of flux. This form of combined therapy has usually involved single agent or combination agent chemotherapy plus either BCG, *C. parvum,* or levamisole (117). The current status of such studies are reviewed individually by agent.

Bacillus Calmette Guérin

Bacillus Calmette Guérin has been used extensively in malignant melanoma as an immunologic adjunct to chemotherapy with imidazole carboxamide (DIC) (115, 118) or various programs of combination chemotherapy (119, 120). An early study combining DIC with BCG appears to have increased the survival of patients with malignant melanoma involving regional lymph nodes, but it had no effect on survival in patients with lesions involving the trunk (118). In a subsequent study, the Southwest Oncology Group has compared the survival and response of patients with malignant melanoma receiving a program of combination chemotherapy or combination chemotherapy plus BCG. Preliminary analysis of this more recent study has failed to show the dramatic difference which was suggested by the earlier study (120). For malignant melanoma, it remains an open question whether or not the addition of BCG to chemotherapy provides a practical and substantial improvement over the results seen with drug therapy alone. BCG has been combined with 5-fluorouracil in the treatment of patients with potentially cured colon cancer (121), and it has also been used as an adjunct to chemotherapy in advanced breast cancer (122). In both cases, preliminary results suggest that the duration of disease control may be somewhat improved by BCG. These studies require confirmation as well as clarification of some methodological problems (123).

Corynebacterium parvum

C. parvum has been utilized in Europe as an adjunct to chemotherapy (103), primarily in the pioneering studies of Israel and colleagues (124, 125). Israel has shown an increased survival and duration of antitumor response to chemotherapy in patients with lung cancer and breast cancer with the use of subcutaneous *C.*

parvum. Similar studies are currently under way in the United States, using a different preparation of *C. parvum* and different routes of administration. Hopefully, such studies will show a similar improvement in treatment.

Experience at UCLA with *C. parvum,* as well as other available data in the United States, has not been as optimistic (126). In a limited study of patients with breast cancer receiving combination chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, the response rate and duration of response in a small group was similar for those receiving *C. parvum* as for those receiving chemotherapy alone. Bone marrow tolerance to chemotherapy appeared to be reduced by the addition of *C. parvum,* and serious side effects with this agent given intravenously were common. Chills, fever, and changes in blood pressure were not unusual. Therefore, I believe that this drug must be carefully studied in additional patients before its clinical use as an adjunct to chemotherapy can be considered established.

Levamisole

Levamisole is a potent deworming agent which has been shown to stimulate the immune system in immunologically incompetent animals and man (104, 127). It does not appear to stimulate the already intact immune system, and there have been variable results in patients with cancer. Some studies have failed to show a significant immunostimulatory effect with this agent. However, Rojas (128) has shown in a controlled trial a significantly prolonged survival and disease-free interval after radiation therapy for patients with advanced regional breast cancer who received levamisole, in comparison with a control group that did not receive the agent. Similarly, European investigators have found an improved duration of disease-free survival in patients with lung cancer who have received levamisole in a controlled clinical trial (129). Both of these latter studies suggest that levamisole may be a useful agent in improving the survival and outlook for patients with advanced cancer. Further studies are needed to confirm and extend these early observations.

CONCLUSIONS AND PROSPECTS FOR THE FUTURE

Immunologic theories of cancer are clearly in evolution. The immune response has been shown to be extremely complex in patients with cancer, with many interrelated suppressor and stimulator cells or factors. Because of this complexity, it is naive to think that some simple form of immune stimulation will be universally successful in controlling all forms of cancer at all stages of disease in conjunction with all forms of systemic therapy. Indeed, it is likely that immunologic impairment in the majority of cancer patients is a consequence rather than a contributing cause of the illness. Moreover, the suggestion of some workers that one of the reasons for the success of cancer chemotherapy may be due to selective immunosuppression deserves further clarification and study (130–132). An increased effort to define more precisely immunologic function in patients with cancer and the immunologic impact of various forms of local and systemic therapy is needed. In the meantime, cautious and carefully controlled experimental trials of immunotherapy and chemotherapy in patients with cancer appear warranted.

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