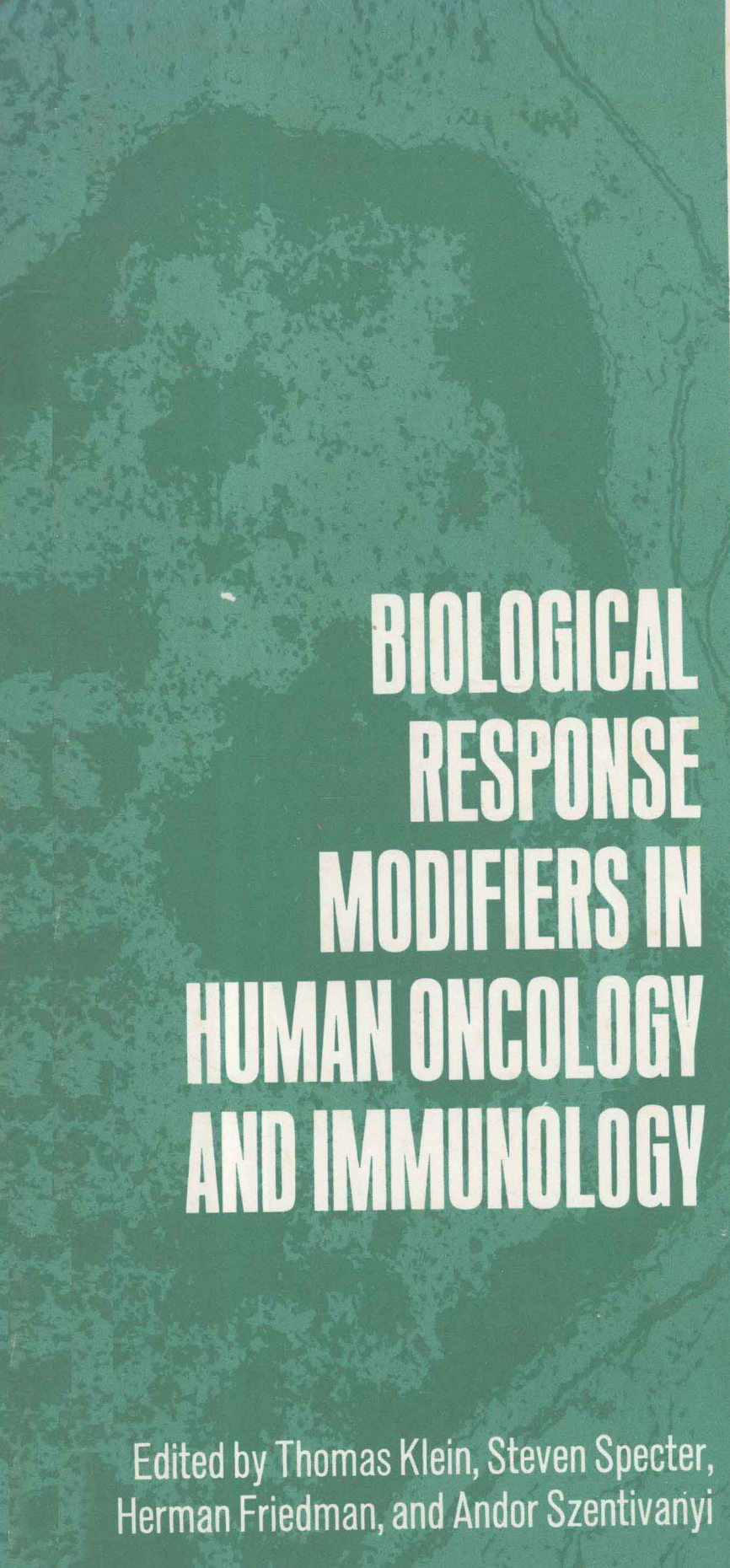

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

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BIOLOGICAL RESPONSE MODIFIERS IN HUMAN ONCOLOGY AND IMMUNOLOGY

Edited by Thomas Klein, Steven Specter, Herman Friedman, and Andor Szentivanyi

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PREFACE

The topic of biological response modifiers has attracted the attention of many biomedical investigators, including immunologists, oncologists, pharmacologists, microbiologists, and biochemists, as well as clinical practitioners of medicine. This has occurred mainly because of the realization that the complex system of cellular and humoral interactions culminating in a productive immune response is under exquisite regulatory control for normal immune responses and that loss of control may markedly influence the capability of a host to respond in a productive manner to the numerous immunologic "insults" encountered in the environment. Furthermore, biological response modification is considered by many to be a natural offshoot of the relatively new application of "immunotherapy" to cancer.

It is widely recognized that "immunotherapy" was practiced at the end of the last century and the beginning of this century when it was recognized that microbial infections were caused by distinct species of bacteria and that passive administration of serum containing antibody to these microbes or their products could, in many cases, favorably influence the outcome of an infectious process. Furthermore, in the area of infectious disease it became quite apparent that "vaccines" prepared from killed microorganisms, or products thereof, could render an individual specifically resistant to that microorganism and, in many cases, increase in a nonspecific manner resistance to other organisms. This became quite evident with the advent of the use of attenuated mycobacteria for vaccination against tuberculosis. The use of the attenuated bovine strain of Bacille Calmette-Guerin (BCG)' ushered in an era of potential vaccination not only against a specific microbe but the induction of "nonspecific" immunity to other organisms. Nevertheless, it is quite evident that this idea of immunotherapy or immunomodulation in terms of infectious diseases was not pursued with much vigor because of

the discovery of antibiotics. Thus, specific drugs were found to be not only effective in killing or inhibiting the growth of bacteria in vitro, but also in vivo. The "rediscovery" that BCG might be of some value in patients with certain malignancies, especially those of the lymphoid system, ushered in a new era of possible treatment of malignant disease by nonspecific immunotherapy.

There has been much criticism concerning immunotherapeutic approaches in cancer. There are both proponents and detractors for the idea that malignancies may be controlled by immunologic methods better than by more conventional methods such as surgery, radiation, and chemotherapy. There are also proponents of the idea that immunotherapy should be used as an adjunct treatment for cancer. Regardless of the view of investigators in this field, it is apparent that there are many approaches now being taken attempting to specifically and nonspecifically stimulate the immune response of patients with tumors with a wide variety of immunomodulating agents. Furthermore, it is quite evident that in many other disease states, including those induced by infectious agents, genetic disorders, etc., there may be marked diminution of immune competence either at the level of individual immunological pathways or at the level of immune cells. Similarly, there are many pathologic situations in which enhanced immune responses, or inappropriate responses, contribute to the disease state. Thus, there has been much interest in developing immunomodulating agents and biological response modifiers, not only for cancer but for other aspects of immunology.

Among those individuals concerned with immunomodulating agents are the immunopharmacologists who constitute a new group of investigators attempting to bridge the area between the two parental disciplines of immunology and pharmacology. In July 1982 the Second International Congress on Immunopharmacology was held in Washington, D. C. The organizers of the Congress proposed a specific satellite symposium be held in Tampa, FL, immediately following the Congress. The topic of the symposium was Biological Response Modifiers in Human Oncology and Immunology. This volume is based on the proceedings of that satellite symposium which brought together over 120 investigators from numerous countries to discuss in detail pros and cons of biological response modification in cancer and in the general field of human immunology. The volume consists of manuscripts derived from both symposium talks and contributed research papers involving both clinical and basic studies utilizing animal models.

The first chapter represents the keynote address presented by Dr. Y. Yamamura, President of Osaka University. Dr. Yamamura

summarizes various forms of cancer immunotherapy, including studies employing microbial adjuvants, synthetic adjuvants, monoclonal antibodies, and cytokines. The introduction is followed by a major section of the volume dealing with biological response modifiers derived from leukocytes. This section begins with a consideration of the interferons. A great deal of new information is available concerning these substances and this is reviewed by Drs. Stewart and Stebbing. The next group of chapters deals with monoclonal antibodies, substances of great importance which were not even considered possible less than a decade ago. The utilization of monoclonal antibodies in cancer therapy is reviewed by Dr. Oldham and others. Thymosin and thymic extracts, which have been studied for nearly two decades as possible immunomodulating agents, are reviewed in a number of papers concerning cancer immunology. Dr. Talal's chapter on interleukin completes this section of the volume and discusses these interesting intermediary soluble molecules which have been described and examined in recent years as important mediators of a wide variety of immune responses, especially those considered to be mediated by T cells and macrophages.

The third section of the volume deals with biological response modifiers derived from microorganisms. A variety of microbial products and their potential usefulness is described. Dr. Kotani reviews in detail muramyl dipeptides and synthetic analogs which, in the last half dozen years or so, have been shown to have marked immunomodulatory effects. Subsequent chapters in this section deal with the influence of various other microbial products on tumor progression and immune status in a variety of clinical and animal studies.

Synthetic biological response modifiers are discussed in the fourth section of the volume. Included in this section are sulfur-containing compounds such as Imuthiol and other chemically defined drugs such as Isoprinosine and NPT 15392. A vast amount of information is reported concerning the effect of these substances on human and animal tumors as well as the effects on immune function. The subsequent section of the volume describes the acquired immunodeficiency syndrome (AIDS) including descriptions of the disease, the immune abnormalities involved and the potential for treatment with biological response modifiers. The volume is then completed with summaries of workshops on animal models for studying biological response modifiers and clinical models.

It appears likely that the broad range of topics discussed in this volume will focus attention on the extremely rapid evolution of

the subject of biological response modifiers in human immunology. It appears somewhat unique that the bioscientists from many disciplines, including biochemistry, pharmacology, immunology, microbiology, etc., have focused their interest and attention on the exciting possibility of restoring immunoresponsiveness and/or reversing immunodeficiency in patients with diseases as diverse as cancer, autoimmunity and infections. It is hoped that publication of this series of papers will stimulate additional investigative work in the area of disease process alteration by biological response modifiers.

Thomas Klein
Steven Specter
Andor Szentivanyi
Herman Friedman

CONTENTS

IMMUNOSTIMULATION IN CANCER PATIENTS

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INTRODUCTION

The studies on the cancer immunology and its application to the cancer immunotherapy in humans are attractive subjects for the immunologists and oncologists. However, in order to discuss the immunostimulation and its application to cancer patients, the following should be considered.

(1) Does the immunity against tumor cells really exist? Is it possible to detect the tumor-specific or tumor-associated antigen which is clearly different from normal cells?

(2) Is the immune response in cancer patients able to be cytotoxic to cancer cells? Does it show the suppressive effect on tumor growth and regress tumors?

(3) If it is possible, what kinds of effector cells should be stimulated.

(4) What is the most effective modality for the stimulation of effector cells?

Immune cells such as killer T lymphocytes, macrophages, and natural killer cells are known to be cytotoxic for tumor cells. Other T cell populations which augment or suppress killer T cells are also reported to associate with tumor immunology. In the case of cancer immunotherapy, it is very important to potentiate the amplifier T cells and eliminate the suppressor T cells. It may be very difficult to say how many cells and what kinds of

immune competent cells are required for the development of the maximum cytotoxicity to tumor cells to induce the regression of tumors. It is highly dependent on the antigenic characteristics or number of cancer cells. The discrepancies obtained in in vitro experiments and in cancer patients has made it difficult to find out the effective treatment with immunological modalities.

In this keynote address, we would like to summarize the results on cancer immunotherapy which were obtained based on recent progress in basic immunology.

OVERVIEW ON CANCER IMMUNOTHERAPY WITH IMMUNOPOTENTIATOR

Under the term "cancer immunotherapy," many kinds of immunopotentiators are now being used in the treatment of various kinds of human cancers, however, there is no clear evidence that these immunopotentiators develop antitumor activity via immune response against cancer cells, and few clinical trials were confirmed to be effective statistically under the well-controlled randomized design.

Table 1 summarizes the various trials for cancer immunotherapy. Active cancer immunotherapy involves the induction of specific tumor immunity by immunization with tumor cells, modified tumor cells or their components. Adoptive cancer immunotherapy includes cancer treatment prevention of cancer by the stimulation of antitumor activity of cancer patients using passive transfer of antibodies to cancer cells, immune competent cells cytotoxic for tumor cells or cytokines such as lymphokines, lymphotoxins, interleukins and interferons. Nonspecific immunotherapy which stimulates the immune status of cancer patients using immunoadjuvants is the most popular modality for the treatment of cancer patients.

STIMULATION OF ANTITUMOR IMMUNITY WITH IMMUNOADJUVANTS

Initially, immunotherapy using immunoadjuvants such as living BCG, Corynebacterium parvum, and methanol-extracted residue of tubercle bacilli (MER) were widely employed for the treatment of human leukemia and malignant melanoma. More recently various kinds of living or killed bacterial cells, their fractions, polysaccharides prepared from various kinds of mushrooms, low molecular weight chemicals such as bestatin, levamisole, vitamin A derivatives, have been used in experimental tumor systems and clinical trials. However, some of these adjuvants were not evaluated as real immunopotentiators, and clinical effectiveness was not proved by well-controlled randomized trials. The Second International Conference on "Present Status in Human Cancer Immunotherapy" which was held in April, 1980 at the National Cancer Institute (United

Table 1. Cancer Immunotherapy

Active immunotherapy	
(1)	Tumor cells
(2)	Modified tumor cells
(3)	Tumor antigens
(4)	Tumor vaccine + immunoadjuvants
Adoptive immunotherapy	
(1)	Antibody (monoclonal)
(2)	Lymphocytes (In vitro cultured with TCGF)
(3)	T cell factors
(4)	Transfer factors and immune RNA
Nonspecific immunotherapy	
(1)	Microbial preparations
(2)	Polysaccharides
(3)	Synthetic compounds
(4)	Thymic factors
(5)	Fat-soluble vitamins

States) played a very important role for the evaluation of cancer immunotherapeutics in human cancer treatment (32).

Previously we reported the adjuvant activity of BCG cell wall skeletons (BCG-CWS) especially the augmentation of cytotoxic killer T cells and macrophages and the prolongation of survival of tumor-bearing animals in experimental models and cancer patients (2, 35). We have also shown that the cell-wall skeleton of Nocardia rubra has a similar chemical structure to BCG-CWS and more potent adjuvant activity, but less toxicity than BCG-CWS (1, 25, 38). Sato and his coworkers at Chiba University have examined the efficacy of N-CWS on gastric cancer in a well-designed randomized trial (31). The patients in the control group received surgical operation and chemotherapy with mitomycin. Immunotherapy group patients were treated by intradermal injection of N-CWS in addition to surgical removal and chemotherapy. A total 118 patients in control group and 137 patients in N-CWS treated group were registered, and the survival periods of both groups were examined statistically. The analysis of background factors indicated that no significant difference existed between control and N-CWS treated groups in terms of sex, age, histological types, and macroscopic and pathological findings at the surgical operation. The prolongation of survival periods of all patients was not observed, however, the survival