CLINICAL IMMUNOBIOLOGY

EDITED BY

Fritz H. Bach

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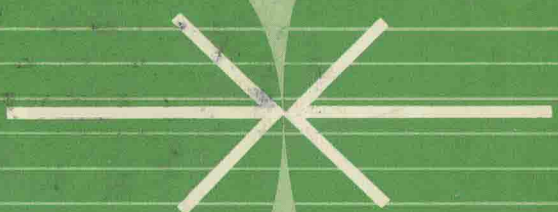

Volume 2

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Clinical Immunobiology

Edited by

VOLUME 2

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Preface

We present the second volume of the serial publication *Clinical Immunobiology*, which has been designed to help the physician and student keep abreast of advances in the burgeoning field of clinical immunobiology. In the initial volume we made an effort to give some background of the fundamental lore of this rapidly developing discipline. We now launch our considerations of the advances in clinical immunobiology by presenting through the writings of several leaders in the field progress being made to apply bone marrow transplantation to the treatment of such devastating diseases as aplastic anemia, aregenerative pancytopenia, leukemia, uniformly fatal severe combined immunodeficiency diseases, and Wiskott-Aldrich syndrome. The successes we report here represent, we are certain, only the toddling first steps in a new era of medical therapy. We will look to cellular engineering in the form of bone marrow and thymus transplantation, and ultimately to macromolecular pharmacology, to correct inborn errors of metabolism, the effects of exposure to excessive amounts of radiation or cytotoxic chemicals, and hematopoietic failure based on malfunction of the complex process of normal hematological development and maintenance.

In these articles it is clearly brought forward that studies of marrow transplantation in man have provided new and exciting leads to the understanding of fundamental biological principles. For example, these studies have generated vital efforts toward the wider application of our new understanding of the histocompatibility determinants in man. This will surely need to be expanded and developed in future issues because studies in this direction not only make possible better matching for marrow transplants heretofore thought to be impossible, but yield evidence of fundamental relationships between the histocompatibility

determinants and the capacity to maintain our individuality in a hostile world through the ability to recognize and eliminate from the body that which is not self. Further, fundamental new information about leukemia seems to be contained in the evidence that, after successful marrow transplantation for this disease, the transplanted marrow may catch the leukemia.

In the chapters by Lawrence, and Spitler, Levin, and Fudenberg, the rapidly expanding use of transfer factor to treat human disease is presented against its appropriate background of fundamental studies. With this approach, some of the most recalcitrant and devastating of man's diseases are now being treated with a methodology that apparently engages the immunological system—or refurbishes a flagging or depressed cellular immunity. The results in some instances have been so extraordinary and the diseases apparently manipulated favorably so awful that the objections to the theoretical validity of the transfer factor approach often stated by critics (for example, the editors) must be satisfied while progress in this fantastic form of macromolecular pharmacology is recorded. Because of its theoretical importance in the contexts of these contributions, a brief scientific report by Griscelli is presented—even though at the outset the editors promised no detailed scientific research papers in a series designed to present scientific advances to the practioner and student in a digested form. In the work of Griscelli and his colleagues (that is, incidentally, supported by simultaneous discoveries by Ballow and others in Minneapolis), the possibility of reconciling the influence of transfer factor and the immunologic dogma may emerge; it looks as though transfer factor may not be acting as specifically as was originally thought. It is certainly much less difficult to harmonize a nonspecific influence of this relatively small molecule with the demands of molecular biology, than it is to postulate highly specific influence requiring the transfer of information. Perhaps inclusion of this bit of relatively raw research data is not such a bad idea, and from time to time the editors may use this approach as future controversies need to be resolved or an important advance documented before the dust has settled.

Because immunobiology is making a vigorous effort to analyze cancer and even to address the issue of prevention and treatment of cancer, as was indicated in George Klein's chapter in Volume 1, a major section of Volume 2—five chapters—is devoted to these struggles. Strong, very cogent criticisms of the theory of immunosurveillance against cancer as stated originally by Ehrlich, reiterated by Thomas in relation to transplantation immunity in 1958, and extensively promulgated by Burnet, Good, and others, presents a needed balance as the Hellströms, Schmidtke and Simmons, and Oettgen, and Bortin present different,

and apparently useful, ways not only for looking at, but for manipulating imunity to cancer. Prehn's concept that a little immunity may be essential to stimulate some malignant cells represents a fresh new view for which considerable support has been accumulated by the author and his associates. There seems little doubt that the general concept of immunosurveillance may have to be set aside or modified to fit those challenges.

In the chapter by the Hellströms, the importance of factors capable of suppressing the cellular immunity that regularly develops in experimental and clinical malignancies is described and defined. Antigen–antibody complexes appear to be among inhibiting factors which suggest a number of approaches to the abrogation of such an influence. Oettgen's chapter balances the Hellström view with evidence that states clearly the complexity of approaching cancer from the immunologic view. He emphasizes the fact that antibodies of appropriate class and nature may have usefulness as we approach cancer therapy and management with immunological tools. Indeed, evidence has accumulated that some of the cell-mediated immunities involved in resistance to cancer cells may utilize antibodies. Details of this advance will be set forward in a future volume. It is clear already that antibodies are not all bad in cancer, nor is cell-mediated immunity necessarily all good.

As was set down in the first volume by Starzl and Putnam, and Klein, it is clear that widely disseminated epithelial malignancy inadvertently transplanted along with successful organ transplants can be eliminated from the body by immunological attack if only the host can look at the tumor as though the antigens added are "strong" rather than "weak" antigens. The final two chapters in this series concern themselves with the possibilities of this approach. Simmons shows that in some experimental tumor systems manipulation of the surface of the cancer cell by enzymatic means can provide this advantage and will permit, in these experimental circumstances, prevention and even treatment of established cancer. Bortin presents ingenious means by which allogeneic recognition and immune assault might be used in approaching residual cancer or leukemia.

We anticipate that clinicians will find as much that is useful and exciting in the second compilation of this series as we have found in bringing together this cluster of advances in clinical immunobiology. It is becoming clear to us in responses to, and reflections on, Volumes 1 and 2, what some of the requirements of future volumes may be. Rapidly developing methodologies in this field require forthwith a volume defining the best and most useful immunobiologic methodologies presented in a manner that will be helpful to the physician and to his laboratory associates. This will come soon. The magnificent potential

of cellular engineering, coupled as it is to advancing knowledge of immunogenetics, requires that the current state of the latter part be put forward succinctly and clearly so that it can be understood and used by doctors. Rapidly developing knowledge of immunobiological perturbations during infection, and especially the clinical immunobiology of viral, bacterial, and fungal diseases and their relationships to autoimmunity, needs exposition. Descriptions of new knowledge of the primary immunodeficiencies, and especially of the diseases associated with genetically based perturbations of the biologic amplification systems, like complement and phagocytosis, must be attended to. Even the correction of some of these can be the basis for exciting reading. We feel certain that the series on advances in clinical immunobiology is fairly launched and we look forward to future volumes with enthusiasm.

Fritz H. Bach
Robert A. Good

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Selective Immunotherapy with Transfer Factor

H. Sherwood Lawrence

Transfer Factor

Lynn E. Spitler, Alan S. Levin, and H. Hugh Fudenberg

Bone Marrow Transplantation[1]

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[2] Recipient of Research Career Award 5 K6 AI 02425 from the U.S. Public Health Service.

I. Introduction

Modern marrow transplantation began about 1950 with the irradiation protection experiments of Jacobson and of Lorenz and their colleagues. These workers found that mice given otherwise lethal doses of irradiation could be protected from subsequent death due to marrow failure by the administration of spleen or marrow cells. At first it was thought that this protective effect might be due to a humoral factor, but about 1955 several laboratories, using different markers, showed that the protective effect against lethal irradiation was due to the recolonization of the recipient marrow by donor-type cells. These laboratory studies stimulated interest in the clinical application of marrow transplantation for protection in the event of accidental lethal irradiation, or for patients with hematopoietic malignancy who might benefit from high-dose irradiation or chemotherapy given to eradicate their disease. The first article on clinical marrow transplantation appeared in 1957 (Thomas *et al.*, 1957). Despite the promise of these early studies, the next decade was one of frustration and disappointment for would-be marrow transplanters (Thomas and Epstein, 1965; Mathé *et al.*, 1965a). Most of the procedures were carried out in terminally ill patients who did not live long enough for a graft to be evaluated. The few successful allogeneic grafts were followed by an immunological reaction of the engrafted marrow against the host, resulting in a lethal outcome. Recent advances in the knowledge of histocompatibility typing, in the management of graft-versus-host (GVH) disease, and in supportive measures for patients with no marrow function, have renewed interest in the subject of marrow transplantation.

Most of the immunological principles involved in marrow grafting have been defined in inbred mice, and this literature has been reviewed by van Bekkum and de Vries (1967) and by Trentin (1972). Studies