

Principles of Organ Transplantation

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To my wife, Phyllis, and our sons, Christopher and Brandon,
I express my gratitude for their patience, understanding, and support.

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Foreword

During the past several years the field of clinical transplantation has advanced at an extraordinary pace primarily due to new anti-rejection agents as well as continuing improvement in the perfection of surgical techniques. For these reasons, it is quite timely that Dr. M. Wayne Flye, Professor of Surgery and Chief of the Transplantation Service at Barnes Hospital-Washington University, is introducing this masterwork, *Principles of Organ Transplantation*. It represents a monumental achievement characterized by excellence and thorough coverage of the entire field. The editor is uniquely qualified since he is not only an outstanding clinical surgeon but, in addition, holds a doctorate in immunology and has contributed much to the basic understanding of transplantation biology. Moreover, he has assembled a formidable group of co-authors, including such respected contributors as Belzer, Bollinger, Lower, Penn, Reitz, Russell, Shumway, Simmons, Starzl, Sutherland, Veith, and Wells.

The text begins with an engaging description of the "History of Transplantation," written by the editor himself; this chapter is followed by another of his personal contributions on "Transplantation Immunobiology." The opening statement of this chapter is admirably worded and serves as an unusually meaningful introduction to this text that combines the essentials of basic immunology with clinical application. The editor states: "The rejection response, which is critical to the success or failure of an organ transplant, was not designed by nature to thwart transplantation efforts. On the contrary, rejection happens to be one part of a more encompassing recognition and defense mechanism possessed by the host to protect against a hostile environment."

The memory of the immune system to react to antigens is reviewed together with those basic features associated with the remarkable T cell, delayed hypersensitivity, cell mediated cytotoxicity, and antibody-dependent cell mediated cytotoxicity. The roles of B cells, immunoglobulins, and isotypes are then individually described, as are those of macrophages and helper T cells, interferon, and lymphokines. Included is a review of interleukin 1 and 2. The roles of complement, Class I and II loci, and T cell sensitization are presented, and each of these features is assessed in relationship to its role in the success or failure of tissue or organ transplants. The reader of this text will rapidly gain admiration for the clear and engaging style with which the editor describes these basic features of transplantation biology. The entire field of graft rejection is dealt with quite effectively, including the enigma of the fetal graft. The important areas of induction of tolerance and immune response regulation are the concluding subjects in this important chapter.

Another key chapter prepared by the editor concerns "Immunosuppressive Therapy," which begins with a concise description of the early work by the Nobel laureate Medawar on graft rejection. The various agents including azathioprine, cyclophosphamide, steroids, and the recent and very important era of cyclosporine are thoughtfully reviewed. Despite the many positive features of the latter agent, its shortcomings and the complications it may cause

are thoroughly presented. The role of anti-lymphocyte serum in current management as well as present and future applications of monoclonal antibodies forms an important part of this chapter. Both total lymphoid irradiation and donor specific immunosuppression are thoroughly considered, and the chapter concludes with the current immunosuppressive protocol recommended by the editor and his colleagues at Barnes Hospital-Washington University in a concise and straightforward manner. The editor himself also provides the chapters on "Immuno-hematology," "Infectious Complications in Renal Transplant Patients," "Long-term Follow-up of the Renal Transplant Patient," and "Neurologic Transplants." His choice of other contributors, with their 28 additional chapters, makes this new and much needed work a pace-setter in the field. This reviewer is thoroughly convinced that this monograph will be used worldwide and will rapidly become the standard with which all other similar works will be compared. It is an essential text for all those engaged in transplantation.

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Preface

Surgeons for centuries have yearned to be able to replace damaged or diseased tissues or organs with grafts from another individual or from lower animals. The discipline of medicine has evolved from one of passive support to one of active therapeutic intervention. In no area is this more true than in organ replacement surgery—transplantation. From the early faltering efforts at the turn of the century, increasing appreciation of the immunological basis of transplantation has allowed biologists and surgeons to make clinical transplantation a practical and successful reality since World War II.

Transplantation has not, however, developed in a vacuum. It has developed hand in hand with immunology. Each area has served to stimulate advances in the other and in a variety of other disciplines, including oncology, genetics, biochemistry, molecular and cellular biology, hematology, sociology, jurisprudence, and cryobiology.

Investigative studies in immunobiology have provided conceptual advances which, after appropriate trials, have led to clinical application. These have included histocompatibility testing, antilymphocyte globulin, total lymphoid irradiation, the transfusion effect in renal transplantation, the concept of passenger cells, polyclonal antilymphocyte globulin and subsequently monoclonal antibodies such as OKT3. Chemical immunosuppression has been essential for graft acceptance and primarily consisted of steroids and azathioprine until the introduction of cyclosporine in 1978. Cyclosporine, more than any other factor, has been responsible for the improved success rate and consequent increased frequency of extra-renal grafts.

Although the general tone in transplantation is that of optimism, there is still much room for improvement. Donor organ availability continues to limit the wider application of this form of treatment. Improved organ preservation would allow more precise recipient selection and improve the organ dysfunction that often follows prolonged preservation times. Despite improved immunosuppression, rejection continues to threaten graft survival, and, as a consequence of anti-rejection therapy, patient survival. Although the threat of rejection is greatest early after transplantation, the graft always remains "foreign" and with only rare exceptions requires continued immunosuppression. Much of the current acute and chronic morbidity and mortality of clinical transplantation results from toxic immunosuppressive drugs. The hope for the future is that a relatively safe means of abrogating the immune response in an antigenically specific manner will soon be realized. While not yet possible in man, it is encouraging that this is attainable in certain experimental models.

Each tissue or organ is to some extent unique in its requirement for allotransplantation, and this has influenced surgical and immunological considerations. Blood is the transplantable tissue that enjoyed early success, but since the 1950's the kidney has been the prototype solid organ transplant. Its paired anatomy allowed living related donation, which was so important in demonstrating the feasibility of transplantation. The grafting of cornea, heart, liver,

and bone marrow is also now well established clinically, while transplants of pancreas, lung (including heart and lung), bone, joint, and tympanic membrane are just now emerging as clinical treatment alternatives. Allografting of a digit, a limb, endocrine organs, the intestine, and skin and appendages, as well as neural tissue, is in its infancy, with much to be learned. In addition, the highly sensitized individual represents a special problem in graft acceptance and shares some of the immunological barriers most vividly demonstrated by the humoral response to a xenograft. Improved insight into this aspect of the immune response will not only allow the previously "untransplantable" patient to receive an appropriate allograft but could also conceivably improve the donor organ shortage by the use of xenografts.

Since it is not possible to prepare a definitive text on transplantation, the goal is to furnish the reader with an up-to-date interim report of progress in this dynamic and rapidly changing discipline. We believe that this text will serve as a useful source of information for the practicing physician who wants to gain depth in the areas of immunology and transplantation or who seeks an answer to an immediate clinical problem, since a clinician in any area of medicine may now encounter the transplanted patient. It will also be useful for undergraduate medical students, residents, and fellows who read it primarily to acquire a basic understanding and overview of transplantation. Most importantly, we hope the contents of this book will serve as a stimulus for creative thinking about the unsolved problems of transplantation immunobiology.

I am grateful to the contributors for the efforts they have extended in the preparation of their chapters and for their cooperation in response to our editorial comments. I appreciate the expert editorial help provided by the W. B. Saunders Company and its staff, especially Dean Manke, Edward Wickland, and Susan Short. I thank my mentors, Drs. D. Bernard Amos, David C. Sabiston, Jr., H. F. Seigler, Delford Stickel, David H. Sachs, Steven A. Rosenberg, and Jay C. Fish, who set me on my professional course in the exciting fields of immunology and transplantation. The surgical staff and my investigative colleagues at the Yale University and Washington University Schools of Medicine, as well as the all-important recipient of our efforts, the patient, have served as a continuous stimulus in these areas and during the preparation of this text. I owe special words of gratitude to Mrs. Nancy Williams, who has worked tirelessly to provide secretarial assistance, and to my family, which has always been a source of support and encouragement.

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