# KIDNEY TRANSPLANT REJECTION

## Diagnosis and Treatment

Edited by
G. Melville Williams
James F. Burdick
Kim Solez



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MARCEL DEKKER, INC. New York and Basel

**Library of Congress Cataloging-in-Publication Data**

Kidney transplant rejection.

(Kidney disease ; v. 7)
Bibliography: p.
Includes index.
1. Kidneys--Transplantation--Complications and sequelae. 2. Graft rejection--Prevention. 3. Immunosuppressive agents. I. Williams, G. Melville. II. Burdick, James, [date]. III. Solez, Kim, [date]. IV. Series. [DNLM: 1. Graft Rejection. 2. Kidney—transplantation. W1 KI586R v.7 / WJ 368 K455]
RD575.K5 1986 617'.461 86-8810
ISBN 0-8247-7496-5



MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

*The Johns Hopkins University*
*School of Medicine*
*Baltimore, Maryland*

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# ABOUT THE SERIES

This book is the seventh in a series of texts on nephrology intended to cover all aspects of that discipline. Nephrology has grown at a great rate over the past decade, and the available knowledge has outstripped the texts available. The discipline has, however, attained such maturity that a description of any one of its parts becomes more than ephemeral—or worse, outdated before it even appears. We aim to fill some of the many gaps that exist, not only for the specialist in nephrology, but also for the general physician interested in nephrology. In this description, we include the study and management of hypertension, since these two are interwoven at so many points. We welcome comments on the series as it evolves, or suggestions for topics that might be considered for future volumes.

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## REFERENCE INSERT

**Kidney Transplant Rejection**
**Diagnosis and Treatment**

*G. Melville Williams*
*James F. Burdick*
*Kim Solez*

Please note that Color Plates 1 through 7, containing figures from Chapters 10, 12, and 18, are located between pages 268 and 269.

# PREFACE

In the early years of clinical renal transplantation, most surgeons and pathologists thought they could recognize allograft rejection. It was accepted that deterioration of renal function meant rejection and was associated with an intense mononuclear cell interstitial infiltration. Twenty years later, clinical pathological correlations are less clear. Renal failure episodes may be caused by cyclosporine toxicity, cytomegalovirus infection, poor glucose control, and technical complications as well as by rejection. Further, we now realize that significant interstitial lymphocyte infiltrates are present in the majority of grafts and may be intense in some kidneys with normal function and sparse in some destined for complete rejection. Some animal studies have confirmed this view. We have undertaken two clinical studies in the past in which kidney transplants were biopsied at set intervals irrespective of function. Each study has engendered a healthy skepticism regarding the ability of the transplant biopsy to predict rejection, reversibility, and prognosis. Therefore, it seems quite pertinent at this time to take a broad look at the various forms of rejection as we know them clinically and bring together modern studies by distinguished pathologists in the hope of improving our understanding and therapy.

By way of introduction, we would like to present the view that antibody, T lymphocytes mediating "cytotoxicity" or "help" or "delayed type hypersensitivity," and all of the cells with Fc receptors are involved in rejection. At one end of this spectrum, antibody seems clearly to be the predominant effector mechanism in hyperacute rejection. Ironically, 5 to 10 years ago, the worst thing prognostically for the patient was to have a biopsy done at the time of worsening renal function that showed "no evidence of active rejection." The report meant that there were few interstitial lymphoid cells and we had learned that steroid or ALG therapy rarely succeeded in reversing rejection under these histological circumstances. This led to a greater appreciation for the role of antibody in chronic vascular damage. Chronic rejection is probably always a complex mixture of humoral antibody working through both complement-mediated and cell-mediated cytotoxicity, and cellular immunity working through both delayed type hypersensitivity and specific cytotoxic T lymphocytes. At the other end of the spectrum, the acute rejection crises occurring 6 to 20 days following the transplantation are predominantly the result of lymphocyte-mediated cytotoxicity and delayed type hypersensitivity occurring within the kidney.

Perhaps the most controversial of these ideas is the one relating acute rejection to delayed type hypersensitivity. However, this view is supported by considerable evidence. We know from a variety of transfer experiments in experimental animals that the T-helper cell

is at least a more consistent mediator of acute rejection than the T-cytotoxic cell. It is now also well established that the cytotoxic factors produced by specific cytotoxic T cells are found in very low concentration, making it likely that cells only in the immediate proximity of the cytotoxic T cell are killed. Thus, it would seem extremely difficult to produce enough cytotoxic T cells to destroy an entire 250-g kidney or its endothelium, and much more attractive to blame the T-helper cells, which are capable of amplifying their presence through the release of lymphokines such as interleukin 2. Finally, it would not be surprising to find a potpourri of cells present in biopsies from patients with acute rejection because of the recruitment phenomena present in delayed type hypersensitivity. Whether T-helper cells are directed toward induction of exquisitely specific cytotoxicity or toward more general delayed type hypersensitivity, the effectiveness of cyclosporine may be explained by its interference with helper cell interleukin 2 production.

For decades it has been the hope of physicians involved in transplantation that a new immunosuppressive agent would be found which would greatly reduce the likelihood of rejection-induced graft loss. In the 1980s this hope has been realized in the form of highly specific monoclonal antibodies and cyclosporine. The advent of cyclosporine has proved to be a giant advance in the field of transplantation. Cyclosporine, however, is a giant with an Achilles' heel, because its nephrotoxicity can sometimes completely negate its beneficial immunosuppressive effect.

From the clinical standpoint, it is important to avoid rejection, but when it occurs a reproducible means of reversing it is a necessity. Clinical trials using the monoclonal antibody OKT-3 have demonstrated unequivocally the central role of the T cell in most acute rejection episodes, since essentially all of these can be reversed with a short course of OKT-3. Given the puzzling patient with recurrent renal failure episodes on cyclosporine therapy, a course of OKT-3 coupled with drastic reductions in other agents "clears the air" and renal function commonly improves greatly. Finally, an even more certain means of producing long-term resignation of the host to its new ingredient will be necessary. Cyclosporine, by virtue of its apparent sparing of suppressor cells, may have provided a serendipitous first step toward this goal. However, the issue of mechanisms of immunoregulation, and possible ways to manipulate them, turns out to be complex.

Should not there be other ways to sort out rejection, nephrotoxicity, and CMV infection? Should not there be a measurable immunological component of rejection that precedes renal functional impairment? Should it not be possible to engineer immunosuppression with far greater precision? We think so, and it is the purpose of this book to see how close we are through the collection of the most recent information available about the biology of the allograft response, the diagnosis of rejection, and new ways to control it. Much is known, and we hope the reader will find in this book the answer to many questions and further will be stimulated to formulate his or her own hypotheses, test them, and increase our knowledge about this rapidly expanding subject.

We are very grateful to the many prominent individuals from around the world who have contributed to this book. We also are most appreciative of the financial support provided by Becton Dickinson, Boehinger-Ingelheim, Ortho Pharmaceutical Corporation, the Upjohn Company, and Sandoz, Inc., to defray costs of the color plates. Finally, we would like to thank our secretaries, Gail Fodel, Pamela Creevey, Donna Wolford, and Nancy Lambert, for keeping us organized during the preparation of this book and for typing and retyping numerous manuscript drafts.

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