

# KIDNEY TRANSPLANT REJECTION

Diagnosis and Treatment

Edited by

G. Melville Williams

James F. Eurdick

Kim Solez

一九九二年十月 第八期



# KIDNEY TRANSPLANT REJECTION

## Diagnosis and Treatment

Edited by

**G. Melville Williams**

**James F. Burdick**

**Kim Solez**

*The Johns Hopkins University*

*School of Medicine*

*Baltimore, Maryland*



**MARCEL DEKKER, INC.**

**New York and Basel**

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

**Kidney transplant rejection.**

(Kidney disease ; v. 7)<sup>9</sup>

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 K1586R v.7 / WJ 368 K455] RD575.K5 1986 617'.461 86-8810 ISBN 0-8247-7496-5

**COPYRIGHT © 1986 by MARCEL DEKKER, INC. ALL RIGHTS RESERVED**

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

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



2

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

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 K1586R v.7 / WJ 368 K455] RD575.K5 1986 617'.461 86-8810 ISBN 0-8247-7496-5

**COPYRIGHT © 1986 by MARCEL DEKKER, INC. ALL RIGHTS RESERVED**

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

**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**

## 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.

J. Stewart Cameron  
*London, England*

Richard J. Glassock  
*Torrance, California*

Andrew Whelton  
*Baltimore, Maryland*

## 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, Boehringer-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.

G. Melville Williams  
James F. Burdick  
Kim Solez

## CONTRIBUTORS

**J. Thomas August, M.D.** Professor and Director, Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**William E. Beschorner, M.D.** Assistant Professor, Departments of Pathology and Oncology, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**James F. Burdick, M.D.** Associate Professor of Surgery and Director of the Transplant Service, Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**Paul M. Colombani, M.D.** Assistant Professor, Department of Surgery and Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**Robert Colvin, M.D.** Director, Immunopathology Unit, Massachusetts General Hospital, and Associate Professor of Pathology, Department of Pathology, Harvard Medical School, Boston, Massachusetts

**A. Benedict Cosimi, M.D.** Chief, Clinical Transplant Surgery, Department of Surgery, Massachusetts General Hospital, and Associate Professor of Surgery, Department of Surgery, Harvard Medical School, Boston, Massachusetts

**Francis L. Delmonico, M.D.** Department of Surgery, Massachusetts General Hospital, and Assistant Professor of Surgery, Department of Surgery, Harvard Medical School, Boston, Massachusetts

**Ahmed H. Esa, Ph.D.** Postdoctoral Fellow, Department of Oncology, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**Stuart M. Flechner, M.D.** Associate Professor, Department of Surgery, Divisions of Urology and Organ Transplantation, University of Texas Medical School at Houston, Houston, Texas

**Olaf Ganghoff, M.D.** Postdoctoral Fellow in Transplant Surgery, Department of Surgery, East Carolina University School of Medicine, Greenville, North Carolina

**Uli Gross, M.D.** Postdoctoral Fellow in Transplant Surgery, Department of Surgery, East Carolina University School of Medicine, Greenville, North Carolina



**Brian W. Haag, M.D.\*** Fellow in Organ Transplantation, Department of Surgery, University of Chicago, Chicago, Illinois

**Douglas W. Hanto, M.D.†** Fellow in Transplantation, Department of Surgery, University of Minnesota Health Sciences Center, Minneapolis, Minnesota

**Pekka J. Häyry, M.D., Ph.D.** Professor of Transplantation, Surgery and Immunology, Transplantation Laboratory, University of Helsinki, Helsinki, Finland

**Allan D. Hess, Ph.D.** Assistant Professor of Oncology, Immunology and Infectious Diseases, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**James E. K. Hildreth, D.Phil. (Oxon)** Postdoctoral Fellow, Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**Barry D. Kahan, Ph.D., M.D.** Professor of Surgery and Director, Division of Immunology and Organ Transplantation, Department of Surgery, University of Texas Medical School at Houston, Houston, Texas

**Paul A. Keown, M.D., Ch.B., M.R.C.P.F.R.C.P. (C)** Chief, Division of Nephrology, Department of Medicine, University Hospital, University of Western Ontario, London, Ontario, Canada

**Ronald H. Kerman, Ph.D.** Associate Professor of Surgery, Department of Surgery and Head, Immune Evaluation Laboratory, Division of Organ Transplantation, University of Texas Medical School at Houston, Houston, Texas

**Robin P. Lowry, B.Sc., M.D., F.R.C.P.(C)** Assistant Professor, Transplantation Division, Department of Medicine, Royal Victoria Hospital Research Institute, McGill University, Montreal, Quebec, Canada

**Daniel J. McGraw, M.D.** Intern, Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**Michael J. Mihatsch, M.D.** Associate Professor, Department of Pathology, University of Basel, Basel, Switzerland

**Patrick A. Murphy, M.D.** Associate Professor of Medicine, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**T. Steen Olsen, M.D.** Professor of Pathology, University Institute of Pathology, Municipal Hospital, Aarhus, Denmark

**Robert H. Rubin, M.D.** Chief of Infectious Disease for Transplantation, Massachusetts General Hospital, and Associate Professor, Department of Medicine, Harvard Medical School, Boston, Massachusetts

**Bernhard Ryffel, M.D.** Toxicologist, Department of Preclinical Research, Sandoz Ltd., Basel, Switzerland

**Helen Siegl, M.D.** Professor of Preclinical Research, Sandoz Ltd., Basel, Switzerland

---

**Present Affiliations:**

\*Director of Organ Transplantation, Department of Medical Research, Methodist Hospital Graduate Medical Center, Indianapolis, Indiana

†Assistant Professor of Surgery, Washington University School of Medicine, St. Louis, Missouri

**Richard L. Simmons, M.D.** Professor of Surgery and Microbiology, Department of Surgery, University of Minnesota Health Sciences Center, Minneapolis, Minnesota

**William J. Smith, Ph.D.** Assistant Professor, Department of Surgery, Division of Transplantation and Vascular Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**Kim Solez, M.D.** Associate Professor of Pathology and Medicine, Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**Calvin R. Stiller, M.D., F.R.C.P. (C)** Chief, Multi-organ Transplant Service, University Hospital, University of Western Ontario, London, Ontario, Canada

**Frank P. Stuart, M.D.** Professor, Department of Surgery, University of Chicago, Chicago, Illinois

**Gilbert Thiel, M.D.** Professor, Division of Nephrology, Department of Internal Medicine, University of Basel, Basel, Switzerland

**Francis T. Thomas, M.D., F.A.C.S.** Professor and Chief, Division of Transplantation, Department of Surgery, East Carolina University School of Medicine, Greenville, North Carolina

**Judith M. Thomas, Ph.D.** Professor, Department of Surgery, East Carolina University School of Medicine, Greenville, North Carolina

**Charles T. Van Buren, M.D.** Associate Professor, Department of Surgery, Division of Immunology and Organ Transplantation, University of Texas Medical School at Houston, Houston, Texas

**Eeva von Willebrand, M.D.** Consultant in Clinical Immunology, Transplantation Laboratory, University of Helsinki, Helsinki, Finland

**A. Cameron Wallace, M.D.** Professor of Pathology and Director of Surgical Pathology, Department of Pathology, University Hospital, University of Western Ontario, London, Ontario, Canada

**Carol A. Wideman, R.N.** Transplant Coordinator, Department of Surgery, Division of Organ Transplantation, University of Texas Medical School at Houston, Houston, Texas

**G. Melville Williams, M.D.** Professor of Surgery, Division of Transplantation and Vascular Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland

**Henry J. Winn, Ph.D.** Immunologist, General Surgical Services, Massachusetts General Hospital, Department of Surgery, Harvard Medical School, Boston, Massachusetts

**KIDNEY  
TRANSPLANT REJECTION**



# CONTENTS

<i>About the Series</i>	iii
<i>Preface</i>	v
<i>Contributors</i>	vii

## BIOLOGY OF THE ALLOGRAFT RESPONSE

<b>1</b>	<b>Proteins and the Molecular Basis of Cell-Mediated Immunity</b>	<b>3</b>
	<i>J. Thomas August and James E. K. Hildreth</i>	
	Major Histocompatibility Complex Antigens	3
	Glycoproteins on T Cells	5
	Soluble Factors	8
	Accessory Cell Membrane Proteins: Lymphocyte Function-Associated Antigen	8
	References	10
<b>2</b>	<b>Antibody-Mediated Rejection</b>	<b>17</b>
	<i>Henry J. Winn</i>	
	Animal Studies	18
	Enhancement	22
	Humoral Antibody in Clinical Transplantation	22
	Major Blood Group Antibodies	23
	Anti-HLA Antibodies	23
	Chronic Rejection	25
	Summary and Concluding Comment	25
	References	26
<b>3</b>	<b>Mechanisms of Cell-Mediated Rejection</b>	<b>29</b>
	<i>Francis T. Thomas, Judith M. Thomas, Olaf Ganghoff, and Uli Gross</i>	
	General Considerations for Models of Allograft Rejection	29
	Recent Approaches to Define the Cellular Effector Mechanisms of Rejection	30
	Types of Rejection	31

	The Central Role of T Cells in Rejection	34
	Diversification of the T-Cell System into Distinct Subsets	34
	The Controversy Over Which T-Cell Subset Is the Effector of Rejection	36
	Studies from Adoptive Transfer Models in Rodents	37
	T-Cell Subsets in Human Kidney Allografts	38
	Other Associations Between CTL Activity and Allograft Rejection	39
	Macrophages in Rejection	42
	Immunocompetent Cell Migration Patterns During Rejection	43
	Summary	44
	References	45
<b>4</b>	<b>The Interleukins</b>	<b>55</b>
	<i>Patrick A. Murphy</i>	
	Interleukin-1	56
	Interleukin-2	59
	Interleukin-3	64
	$\gamma$ Interferon	64
	B-Cell Growth Factor and Other Lymphokines Directing the Development of Immunoglobulin: Secreting Cells	67
	Summary	70
	References	70
<b>5</b>	<b>Immunologic Enhancement and Its Relationship to Clinical Transplantation</b>	<b>75</b>
	<i>Robin P. Lowry</i>	
	Immunologic Enhancement: Historical Perspective	75
	Understanding Enhancement: Lessons from Early Immunology	78
	Enhancement and Modulation of the Alloimmune Response in Experimental Transplantation	81
	Mechanism of Enhancement	82
	Pathogenesis of Allograft Rejection	86
	Relationship of Immunologic Enhancement to Clinical Transplantation	89
	Conclusions	99
	References	100
<b>6</b>	<b>Role of Anti-Idiotypic Responses in Regulating Allograft Rejection</b>	<b>113</b>
	<i>Frank P. Stuart and Brian W. Haag</i>	
	Terminology	113
	The Idiotypic Network Theory	114
	Genetic Basis of the Idiotypic Repertoire on B and T Cells	116
	Immunoglobulin Idiotypes on T Cells	116
	Sharing of Idiotypes by B and T Cells	117
	Role of the Idiotypic Networks	117
	Tolerance and Chimerism	118
	Idiotypic Networks and Pregnancy	120
	Anti-Idiotypic Responses After Blood Transfusion and Kidney Transplantation	121
	Therapeutic Implications of Anti-Idiotypic Responses	123
	References	124

<b>7</b>	<b>Suppressor Cell Regulation and Allograft Potentiation</b>	<b>127</b>
	<i>James F. Burdick</i>	
	Biology of Suppressor Cells	127
	Suppressor Cells and Responses to Experimental Tissue Grafts	138
	Suppressor Cells in Human Immune Responses	146
	Suppressor Cells: Status and Prospects	148
	References	149
 <b>DIAGNOSIS OF REJECTION</b>		
<b>8</b>	<b>Pathology of Renal Allograft Rejection</b>	<b>173</b>
	<i>T. Steen Olsen</i>	
	Classification and Nomenclature of Renal Allograft Rejection	173
	Hyperacute Rejection	174
	Acute Rejection	177
	Chronic Rejection	185
	The Problem of Glomerulonephritis in the Allograft	193
	Conclusion	194
	References	195
<b>9</b>	<b>Hyperacute Rejection and Perfusion Injury</b>	<b>199</b>
	<i>Kim Solez and G. Melville Williams</i>	
	Hyperacute Rejection	199
	Perfusion Injury	200
	Pathologic Features	200
	Other Conditions Simulating Perfusion Injury	202
	References	205
<b>10</b>	<b>Pathology of "Acute Tubular Necrosis" and Acute Rejection: Observations on Early Systematic Renal Transplant Biopsies</b>	<b>207</b>
	<i>Kim Solez, Daniel J. McGraw, William E. Beschorner, and James F. Burdick</i>	
	Background: The Renal Biopsy as the "Gold Standard" in the Diagnosis of Rejection	207
	Systematic Early Transplant Biopsies in Clinical Transplantation	209
	Leu 7 <sup>+</sup> Lymphocytes in Clinical Acute Rejection	214
	Experimental Renal Transplantation in Rats	218
	References	219
<b>11</b>	<b>Localization of the Cellular Components of Acute Rejection</b>	<b>225</b>
	<i>William E. Beschorner</i>	
	Renal Allograft Rejection Compared with Acute Rejection of Other Types of Grafts	226
	Cellular Targets of Acute Rejection	228
	Methods for Characterization of Intra- and Intergraft Inflammatory Cells	231
	Interstitial Infiltrates	233
	Intravascular Infiltrates	236
	Intraepithelial Infiltrates	237
	Summary	239
	References	241



<b>12 Aspiration Cytology in Monitoring Human Allografts</b>	<b>247</b>
<i>Pekka J. Hayry and Eeva von Willebrand</i>	
Technical Aspects	247
Interpretation of Cytology Specimens	248
Concluding Remarks	259
References	260
<b>13 Monitoring the Components of the Immune System</b>	<b>263</b>
<i>William J. Smith</i>	
Methodologies Employed in Immunologic Monitoring	264
Clinical Relevance of Monitoring Data	267
Activation Markers and Future Directions	272
References	273
<b>14 Cytomegalovirus Infection in Renal Transplantation:</b>	
<b>Clinical Importance and Control</b>	<b>283</b>
<i>Robert H. Rubin and Robert B. Colvin</i>	
Virologic Characteristics of CMV	283
Epidemiology of CMV Infection in the Renal Transplant Patient	284
Factors Influencing the Course of CMV Infection in the Renal Transplant Patient	286
Clinical Effects of CMV Infection in the Renal Transplant Patient	287
CMV Glomerulopathy	293
Role of CMV in Posttransplant Malignancy	297
Prevention and Treatment of CMV Infection in the Renal Transplant Patient	298
Summary	299
References	300

## NEW IMMUNOSUPPRESSIVE AGENTS

<b>15 The Biology of Immunosuppression Mediated by Antilymphocyte Antibodies</b>	<b>307</b>
<i>James F. Burdick</i>	
Polyclonal Antilymphocyte Sera	308
Comparisons Between Monoclonal and Polyclonal Sera	309
Possible Mechanisms of Action of Monoclonal Antibodies	310
Factors Influencing Monoclonal Antibody Effectiveness	316
Considerations in the Generation of Monoclonal Reagents	324
References	325
<b>16 Antilymphocyte Antibody Immunosuppressive Therapy</b>	<b>335</b>
<i>A. Benedict Cosimi and Francis L. Delmonico</i>	
Polyclonal Antilymphocyte Preparations	336
Production and Administration of Polyclonal Antilymphocyte Antibodies	336
Use of ATG as a Prophylactic Adjunctive Agent	337
Use of ATG as Treatment for Acute Rejection	338
Complications of ATG Therapy	340