REPLACEMENT OF RENAL FUNCTION BY DIALYSIS

A textbook of dialysis

Third edition

Updated and enlarged

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Edited by

JOHN F. MAHER

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To Marge

It is difficult to say what is impossible,
for the dream of yesterday is the hope of
to-day and the reality of to-morrow.

ROBERT H. GODDARD

FOREWORD TO THE THIRD EDITION

BELDING H. SCRIBNER

The foreword to this edition is more difficult for me to write than that for the first edition because we are just entering a new era in the use of hemodialysis to treat end-stage kidney disease. This new era results from a substantial increase in our knowledge of the pathophysiology of renal failure and its therapy (see below). Consequently, I feel I must become bolder in my speculations.

Last spring (1987), the second patient to enter the Seattle hemodialysis program which began in 1960, died suddenly of a myocardial infarction on a golf course in Palm Springs, California. He was in his 28th year of renal replacement therapy, having received a transplant from his mother in 1968. Patient #5 of the original Seattle group remains on dialysis and is beginning his 27th year. Dr. Robin Eady, an academic dermatologist in London, began dialysis in Seattle in February of 1963. After 25 years on dialysis, he recently had his first renal transplant at Oxford. He had waited for one and one-half years for a negative cross match. Since he reacted to 100% of the test panel, this successful transplant exemplifies the great advances being made in transplant immunology.

These three patients are among the several hundred worldwide who have survived more than 20 years on renal replacement therapy. Based on the unexpectedly long survival of these original patients and considering the fact that by today's standards their dialysis therapy during the first 5 years was terrible, one can entertain the following important prediction: A patient with end-stage renal failure who is in the 20 to 50 year age range and is otherwise well who starts renal replacement therapy in the 1980's *should have a nearly normal life expectancy*. There are, however, two caveats that must be fulfilled: 1) circulatory access must be maintained and 2) hypertension must be controlled beginning with the onset of chronic renal failure.

The subject of control of hypertension raises immediately my concern over the long-term effects of so called 'high flux' dialysis. That term, from the patients' perspective, translates into less time on dialysis which accounts for the current enormous popularity worldwide and its enthusiastic promotion by the manufacturers of the numerous devices needed to provide the required technology. On the plus side, I must admit that I am amazed that urea can be removed at these high transfer rates without causing CNS complications. After all, the neurosurgeons used to use urea to shrink the brain. Nevertheless, very high urea clearances and dialysis times as short as 120 min seem to be well tolerated with less post-dialysis morbidity. The latter benefit could be due to the fact that the membranes used for high flux dialysis cause less immunologic insult as discussed below.

The down side of high flux dialysis lies in two areas. The first is a concern over the increase in morbidity and mortality that seems inevitable as a result of placing the required 'high tech' equipment in inexperienced hands. Any time you push a system toward its technological and physiological limits, the chance of malfunction increases dramatically. I fear that such malfunction may increase as the use of high clearance dialysis becomes widespread. Of even greater concern is the adverse effect that shortening dialysis time has on extracellular fluid removal and hence adequate control of blood pressure. In the February 1983 issue of *Nephron*, Bernard Charra and his colleagues presented a classic paper that is yet to be fully appreciated. They showed that by using long, slow 'low flux' dialysis, blood pressure control was excellent, toxic anti-hypertensive drugs could be eliminated, and the risk of accelerated atherosclerosis was reduced to near zero. High flux dialysis represents the opposite end of the spectrum. One simply cannot remove enough fluid to achieve good control of blood pressure in so short a time, especially in patients who have poor compliance with a low salt diet. The net result is either poor control of blood pressure or high doses of anti-hypertensive medication or both, which in my view, in the long-term represents a dangerous trend.

The above prediction of a nearly normal life expectancy for patients on renal replacement therapy, even if it is overly optimistic, has important implications for the future.

Unfortunately, the economic implications head the list. Longer survival means that the total number of patients on renal replacement therapy (dialysis plus renal homografts) will continue to increase for several more decades. At the same time, the percent of the gross national product devoted to health care continues to increase, at least in the United States, despite serious efforts to reverse the trend. A conflict between these two trends appears inevitable and will not be easy to resolve. One possibility is a return to 'do it yourself' home hemodialysis but with easy to use, fully automated equipment. Home peritoneal dialysis with on-line preparation of the dialysis fluid at the bedside, may become another good alternative.

The implications of long survival for a patient's chances of obtaining a kidney transplant are more difficult to predict. On the one hand, longer survival translates into more demand for grafts. On the other hand, as Dr. Eady's case demonstrates, improvement in transplant matching and im-

munotherapy undoubtedly will increase the number of successful grafts as well as their longevity, decreasing the need for second transplants. Therefore, the situation probably will remain indefinitely as it is today, namely, a chronic shortage of renal homografts. Hence, various forms of dialysis will continue to carry the major burden.

A NEW ERA FOR DIALYSIS THERAPY

About 20 years after the discovery of insulin, the various degenerative complications of diabetes became manifest. It, therefore, is an interesting historical parallel that beginning in 1980 as we passed the 20-year mark for the use of dialysis to treat end-stage renal disease, several problems began to emerge that were new and unexpected. Two have been particularly worrisome. The first, chronic aluminum intoxication, is covered in depth in this edition, and shows promise of being prevented in the future. The second, dialysis amyloid syndrome, first was described by Laurent and colleagues in 1981. This complication also is dealt with in detail herein. However, we are just beginning to understand the possible relationship between this disease and the hemodialysis process itself. Indeed, a whole new area of investigation, the immunologic impact of the hemodialysis process, is just now being investigated and much of the early work is covered in this edition.

I am not an immunologist, so I will try to summarize the current situation as I understand it in clinical terms because I believe the implications for the future are very great indeed.

Each time a patient undergoes hemodialysis, the immunologic systems are stimulated by at least three factors: 1) blood-membrane interaction, 2) acetate infusion and 3) pyrogens in dialysis fluid. There may be additional factors as yet unidentified. The consequences of this stimulation include the familiar sequestration of leukocytes in the lung, increased production of β_2 microglobulin and a newly discovered severe catabolic reaction in skeletal muscle. This catabolic reaction was described by Jonas Bergström in a landmark presentation at the International Congress of Nephrology in London last summer (1987). Bergström and his colleagues demonstrated that sham dialysis in normal individuals caused destruction of skeletal muscle. The effect occurred at the end of the 2 h sham dialysis and persisted for at least 2 additional hours; it could account for the post-dialysis fatigue syndrome. This catabolic effect was prevented when dialysis membranes that do not stimulate the immune system were substituted for cellulose membranes.

Closely related to Bergström's observation are the unpublished data from Seattle of Robertson and Ahmad. They have demonstrated a remarkable muscle weakness in even the healthiest dialysis patients. Using the maximum exercise test, they showed that muscle weakness was the limiting factor to exercise, unlike normal individuals for whom cardiac output is limiting. Furthermore, they found that curing the anemia with erythropoietin did not fully correct exercise ability, providing further confirmation of the marked degree muscle weakness of the hemodialysis patient.

Since the factors in a dialysis that are known to stimulate the immune response are all amenable to correction, they will be altered in the future provided costs per dialysis can be kept down. Thus, using compatible membranes that do not stimulate the immune system will help reduce β_2 microglobulin production and also, unlike cellulose membranes, will remove some β_2 microglobulin with each dialysis. These new membranes also will reduce the catabolic effect of each dialysis on skeletal muscle. Switching to bicarbonate dialysate and making it pyrogen-free also may further reduce the immune response to a dialysis.

The question of whether or not reducing the immune response to dialysis will help in the long run to prevent the amyloid problem, improve muscle strength and perhaps benefit the patient in other as yet unidentified ways will undoubtedly be answered in the pages of the 4th edition of this book. However, other developments of this new dialysis era already are underway and are sure to improve the quality of life of the dialysis patient by correcting hormonal deficiencies of chronic renal failure. The first of these, the introduction of 1,25-$(OH)_2$ vitamin D_3, which has so greatly improved management of renal osteodystrophy is covered in detail in this edition. The second more recent development, the introduction of the renal hormone, erythropoietin, will have a major impact on patients' well being, as described in the chapter by Eschbach. As this volume goes to press, the magnitude of that impact is not yet fully appreciated because so little time has elapsed since human recombinant erythropoietin became available. Suffice it to say that the combined impact of all these developments of this new dialysis era could be so beneficial to the quality of life of dialysis patients that the decision to go for a transplant, especially a second transplant, could become very difficult indeed.

FOREWORD TO THE FIRST EDITION

BELDING H. SCRIBNER

The year was 1942 and William Kolff was hard at work perfecting the device that would not only revolutionize the treatment of renal failure, but more importantly point the way to the development of the entire field of extracorporeal devices in general and cardiac bypass devices in particular.

The enormity of the impact that Kolff's contribution was to have on medicine was revealed retrospectively to me when I recalled that in that same year, 1942, I was a second year medical student at Stanford University, taking among other things, P.J. Hanzlik's required course in pharmacology. I have two memories of that course. One was the requirement that we students learn to recognize 64 old time drugs by appearance, smell and taste. For better or worse, almost all of the 64 have disappeared from the scene. The other memory is the more pertinent one. I can still visualize the scene in the small classroom in the attic of the old red brick Stanford Lane building at Webster and Sacramento Streets. Professor Hanzlik had a pigeon for a 'patient' and had planned a dramatic demonstration. I can still hear him command one of my fellow students to 'Seize the patient!', which the student did in fear and uncertainty as the poor bird struggled against its fate. Hanzlik then proceeded with great flair and ceremony to inject some drug intended for intravenous use into the poor pigeon, where upon the bird promptly expired and Hanzlik drove home the point that intravenous therapy of any kind was dangerous and should be avoided at all costs. This 'conservative' attitude was quite consistent with that prevailing throughout the practice of medicine in that era. If intravenous therapy was dangerous, then a device for extracorporeal circulation must be an invention of the devil! Indeed, for the decade after the first clinical dialysis in Europe and Canada, acceptance was painfully slow and often resisted by all the usual techniques of those in power. During the early 60's, we encountered exactly the same kind of resistance to the concept of chronic dialysis. But as has happened over and over again in all of science, the heresy of one decade becomes the practice of the next – a phenomenon that the young heretics among the third generation readers of this volume should not forget.

And so, today Drukker, Parsons and Maher have successfully undertaken the very difficult task of bringing together in one volume all the diverse elements of dialysis therapy. The size of the volume reflects not only the magnitude of the interdisciplinary effort that brought about the technical and clinical advances, but also the many clinical and other ramifications of dialysis therapy.

In 1977, this therapy will cost the United States taxpayer nearly one billion dollars as the number of dialysis patients in the United States soars above 30,000, while the projection of the ultimate number increases from 40,000 to 60,000 and the cost projection to two billion per year by 1985. Concurrently, in the United States, the percentage of patients on home dialysis has dropped from a high of 41% in 1973 to just under 15%. This trend away from home dialysis cost the United States taxpayer an additional 150 million dollars in 1976. In an effort to control costs, the United Kingdom has increased the percentage of patients on home care to nearly 70%. In addition, the United Kingdom and perhaps other Western countries are beginning to exert subtle but effective cost control on dialyses by limiting the numbers of dialysis patients (1). In contrast, in the United States in 1977, there is no cost control on dialysis. What this contrast means to me is that dialysis is having an impact on Western medicine far beyond its significant impact on the patients, family, physicians and staff who are directly involved.

The nature and enormity of this impact began to become apparent to me in 1962 when magazine writer Shana Alexander came to Seattle to do a story on the artificial kidney. I shall always remember how incredulous I was that she did not want to see or hear about the patients whose lives had been saved – no interest there. She wanted to find out all about the 'life and death committee'. As a result, her article on the Seattle Life and Death Committee appeared in *Life Magazine* that fall (2) and set off discussion and controversy that have persisted to the present (3); indeed, the current British versus American approach to chronic dialysis is but a dramatic extension to international medicine of the basic 'who shall live' issue that was raised by the Seattle Life and Death Committee. I believe that what has happened is that dialysis has greatly accelerated the process of bringing to the forefront a basic issue in Western medicine that up to now has been kept hidden. That issue is *priorities*. Can the United States really afford to spend two billion dollars per year on dialysis? If not, who will decide to curtail expenses, and how will the decision be implemented? Significant curtailment already is being implemented in the United Kingdom by limiting the dialysis population (1). The question is how are they able to 'get away with it', and if the real truth were known, could they get away with it?

To put this issue in a different context, I believe the rapid development of dialysis marks the beginning of the end for unrestrained expansion of expensive medical technology – just as surely as the energy crisis tells us that unlimited expansion of a petroleum based Western civilization is about

to come to an end. I believe that the energy crisis poses the greatest threat to democracy that has ever been posed in peacetime because the basic inability of the democratic process to cope with decisions about priorities in times of crises. Does dialysis and other very expensive technology pose a similar threat to medical free enterprise as still practiced mainly in the United States? Unless we put our house in order, I believe it does.

Let us take a brief look at another example of costly medical technology that already has overtaken dialysis in terms of total cost. Coronary by-pass surgery is currently costing Americans nearly two billion dollars per year. Preston, in a just published critique of the operation (4), points out that not only is its efficacy unproven, but he makes a strong case for the point that the economic incentives of the free enterprise system rather than medical efficacy explain why in 1975 the operation was performed on 28 patients/100,000 population in the United States in contrast to 2.1 patients/100,000 population in Western Europe.

Dialysis doctors can take comfort in the fact that at least the question of efficacy is not an issue with our expensive technology. But important and unresolved issues nag at our conscience with respect to the cost-benefit ratio of dialysis. These issues are far too complex to be resolved during the life-time of the first generation of readers of this volume and pose the ultimate challenge to the younger generations. The clinical and technological aspects of dialysis must not remain static at the state of the art level described in this volume while the demand for costly services increases. Rather, we must build on the knowledge reviewed in this book to improve the cost-benefit ratio of our services. Meanwhile, we function as our technological advances create new social problems. And so my advice to all three generations is to try and understand and cope with a new responsibility that dialysis, because of its high cost, has introduced into the basic doctor-patient relationship. How can each of us fulfill our basic responsibility to our patients while at the same time doing everything possible to reduce the overall cost to society of this very expensive treatment?

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PREFACE

In this rapidly evolving field it is appropriate to update frequently our state of the art knowledge of uremia therapy. Hence, this third edition of *Replacement of Renal Function by Dialysis* appears before many of its predecessors have been destroyed by normal wear and tear over 11 and 6 years of use, respectively.

The first two editions of this book were designed to be integrated comprehensive reviews of the pertinent aspects of dialysis and related fields with sufficient clarity for the novice to learn, yet adequate depth for the expert to rely on them as encyclopedic desk references on renal replacement therapy. Based on the favorable readers' comments and reviewers' opinions these editions achieved their goal. The success of those editions is a tribute to the expertise of the authors and to the skill and dedication of my coeditors Dr. William Drukker and Dr. Frank M. Parsons, with whom it was an honor, an education and a pleasure to associate (Figure 1). When Dr. Drukker and Dr. Parsons announced their retirements, I was somewhat reluctant to undertake the task of editing this text again, especially without their capable association. Nevertheless, I felt that it was important to proceed with another edition as new information developed. When I did not identify European colleagues who had the expertise who could expend the time and with whom I could work so smoothly, I began alone.

Although I was tempted to ask all the same authors as had written so well previously to contribute again, I realized that the new edition must be revitalized. Accordingly a fraction of the authors changed, some new topics have been added and others have been deleted. The multinational character of authorship has been maintained. Existing chapters have been rewritten thoroughly, and new authors have provided as requested a full discussion and bibliography in keeping with the previous editions.

As previously, the first half of the book emphasizes the techniques and procedures for blood purification, while clinical considerations of various types follow in the latter pages. This edition begins with a description of uremia toxicity and includes the classical chapters on the history of dialysis, now updated. New chapters dealing with technical aspects of renal replacement therapy are those on continuous arteriovenous hemofiltration, short treatment, single-needle hemodialysis and continuous ambulatory peritoneal dialysis. Other new chapters relate to the complement sys-

Figure 1. Dr. Drukker (standing), Dr. Parsons (sitting right), and Dr. Maher (center) during an editorial meeting in Amsterdam in 1981.

tem, acid-base homeostasis and pulmonary, gastrointestinal and oral aspects of renal failure and dialysis. The changing dialysis patient population can be appreciated by the chapters devoted to long-term survivors of dialysis treatment, diabetes mellitus, and acquired immunodeficiency syndrome. Importantly, a chapter has been added about the prevention of end-stage renal failure. Nephrologists should all strive to prevent uremia, the treatment of which provides their income.

The editor acknowledges with gratitude the excellent contributions of over 100 distinguished colleagues without whom the book would not be a reality. Included among the authors are a group of peers who have enlightened me considerably about these topics over the past few decades, as well as some younger colleagues who provide fresh insights.

The characteristic chromatogram showing peak 7C from the studies of Dr. Jonas Bergström and Dr. Peter Fürst has been kept as the symbolic cover illustration. It represents the success of our therapy and advances in our knowledge of uremia as well as the limitations of our insights and the need for further research.

The production and publication by Kluwer Academic Publishers (Martinus Nijhoff) has also been integral to the success of the book and is appreciated. Mr. B.F. Commandeur has been primarily responsible for this effort which has assisted the editor appreciably.

My colleagues, particularly Dr. P. Hirszel and Dr. E. Marks, graciously abided the distractions that editing created.

I am especially grateful to Mrs. Barbara Fitzgerald who provided outstanding secretarial assistance throughout the preparation of this edition.

Finally, adding an editing task to an already full agenda takes personal time from those who are most giving and understanding, from family. Thus, the patience, tolerance, encouragement and devotion of my wife, Marge, is most appreciated, for without it this publication would not have occurred.

JOHN F. MAHER

CONTRIBUTING AUTHORS

Michael Adler, M.D.
Associate Professor
Department of Gastroenterology
Université Libre de Bruxelles
Chef de Clinique
Department of Gastroenterology
C.U.B. Hôpital Erasme
Brussels, Belgium
Chapter 39

Allen C. Alfrey, M.D.
Professor of Medicine
University of Colorado
Chief of Renal Section
Veterans Administration Medical Center
Denver, CO USA
Chapter 49

Anthony J.F. d'Apice, M.D., FRACP, FRCPA
Assistant Director
Department of Nephrology
Royal Melbourne Hospital
Victoria, Australia
Chapter 27

Conrad A. Baldamus, M.D.
Professor, Internal Medicine and Nephrology
Medizinische Universitätsklinik I
University Hospital
Cologne, FRG
Chapter 14

Claudio Bazzi, M.D.
Assistant, Division of Nephrology
San Carlo Hospital
Milan, Italy
Chapter 30

Christopher R. Blagg, M.D., FRCP
Professor of Medicine
University of Washington, Seattle
Director Northwest Kidney Center
Seattle, WA USA
Chapter 33

Juan Bosch, M.D.
Professor of Medicine
Director of Renal Diseases
George Washington University Medical Center
Washington, DC USA
Chapter 15

Michel J.C. Broyer, M.D.
Professor of Pediatrics
Necker's School of Medicine
Université Paris V
Director, Pediatric Nephrology
Hôpital des Enfants Malades-Necker
Paris, France
Chapter 32

Felix P. Brunner, M.D.
Professor of Medicine
University of Basel
Department of Internal Medicine
Kantonsspital
Basel, Switzerland
Chapter 31

Hans O.A. Brynger, M.D., Ph. D.
Associate Professor of Surgery
University of Göteborg
Director Transplant Unit
Sahlgren's Hospital
Göteborg, Sweden
Chapter 31

Vardaman M. Buckalew, Jr., M.D.
Professor of Medicine and Physiology
Chief of Nephrology
Department of Medicine
Bowman Gray School of Medicine
of Wake Forest University
Winston-Salem, NC USA
Chapter 55

John M. Burkart, M.D.
Assistant Professor of Medicine
Bowman Gray School of Medicine
of Wake Forest University
Medical Director, Piedmont Dialysis Center
Winston-Salem, NC USA
Chapter 55

Cyril Chantler, M.A., M.D., FRCP
Professor Paediatric Nephrology
Evelina Children's Department
United Medical and Dental Schools of
Guy's and St. Thomas's Hospitals
Guy's Hospital
London, England
Chapter 32

Stefano Chiaramonte, M.D.
Associate of Clinical Nephrology
Department of Nephrology
St. Bortolo Hospital
Vicenza, Italy
Chapter 37

Jack W. Coburn, M.D.
Professor of Medicine
University of California, Los Angeles
Nephrology Section
Veterans Administration Wadsworth Medical Center
Los Angeles, CA USA
Chapter 44

Jean Crosnier, M.D.
Professeur
Université René Descartes
Faculte de Médecine Necker Enfants-Malades
Clinique Néphrologique
Hôpital Necker
Paris, Cedex, France
Chapter 42

Nancy Boucot Cummings, M.D.
Associate Director for Research
and Assessment, NIDDK
National Institutes of Health
Bethesda, MD USA
Chapter 57

Giuseppe D'Amico, M.D.
Professor of Medicine
University of Milan
Head, Division of Nephrology
San Carlo Hospital
Milan, Italy
Chapter 30

Norman Deane, M.D.
Chairman, Section on Nephrology
Doctors Hospital
Director Manhattan Kidney Center
New York, NY USA
Chapter 18

Wilfried A. De Backer, M.D.
Pulmonary Medicine Division
University Hospital Antwerp
Antwerp, Belgium
Chapter 38

Marc E. De Broe, M.D., Ph. D.
Professor of Medicine
University of Antwerp
Director Nephrology Division
University Hospital Antwerp
Antwerp, Belgium
Chapter 38

Françoise Degos M.D.
Service d'Hépatologie
Hôpital Beaujon
Clichy, France
Chapter 42

Barbara G. Delano, M.D.
Associate Professor of Clinical Medicine
Director-Home Dialysis Program
State University of New York
Health Science Center at Brooklyn
Brooklyn, NY USA
Chapter 29

Raymond A. Donckerwolcke, M.D.
Pediatric Nephrologist
Department of Pediatrics
University of Utrecht
Director, Dialysis and Transplant Program
Wilhelmina Children's Hospital
Utrecht, The Netherlands
Chapter 32

William Drukker, M.D.
Formerly Reader in Dialysis
Department of Medicine Queen Wilhelmina
University Hospital, Amsterdam
Emeritus Director Department of Nephrology and Dialysis
St. Lucas Hospital, Amsterdam
Present Address: De Lairessestraat 75
1071 NV Amsterdam, The Netherlands
Chapters 3, 19, 22

Sheila R. Dykes
Administrator
EDTA Registry
St. Thomas Hospital
London, England
Chapter 31

Joseph W. Eschbach, M.D.
Clinical Professor of Medicine
Division of Nephrology
Department of Medicine
University of Washington
Seattle, WA USA
Chapter 40

Aldo Fabris, M.D.
Associate of Clinical Nephrology
Department of Nephrology
St. Bortolo Hospital
Vicenza, Italy
Chapter 37

Winfried Fassbinder, M.D.
Professor of Nephrology
University Hospital
Frankfurt am Main
Head, Department of Nephrology
Städtische Klinikum
Fulda, FRG
Chapter 31

Mariano Feriani, M.D.
Associate of Clinical Nephrology
Department of Nephrology
St. Bortolo Hospital
Vicenza, Italy
Chapter 37

Eli A. Friedman, M.D.
Professor of Medicine
Chief, Renal Diseases Division
State University of New York
Health Science Center at Brooklyn
Brooklyn, NY USA
Chapter 54

Peter W. Gardner, B.S.
Chief Research Technician
Dialysis Unit, Nephrology Section
Medical Service, Wadsworth Division
West Los Angeles Veterans Administration Medical Center
Los Angeles, CA USA
Chapter 16

Ram Gokal, M.D., FRCP
Consultant Nephrologist
Honorary Lecturer
University of Manchester
Manchester Royal Infirmary
Manchester, England
Chapter 25

Frank A. Gotch, M.D.
Associate Clinical Professor of Medicine
University of California, San Francisco
Medical Director
Dialysis Treatment and Research Center
Davies Medical Center
San Francisco, CA USA
Chapter 4

Hans J. Gurland, M.D.
Professor, Director Nephrology Division
Medical Department I. Klinikum Grosshadern
University of Munich
München, FRG
Chapter 21

Robert W. Hamilton, M.D.
Associate Professor of Medicine
Bowman Gray School of Medicine
of Wake Forest University
Medical Director, Dialysis Unit
North Carolina Baptist Hospital
Winston-Salem, NC USA
Chapter 55

Lee W. Henderson, M.D.
Professor of Medicine
University of California, San Diego
Veterans Administration Medical Center
San Diego, CA USA
Chapter 13

Robert J. Heyka, M.D.
Medical Director – CCF West Side Dialysis Center
Department of Hypertension/Nephrology
The Cleveland Clinic Foundation
Cleveland, OH USA
Chapter 34

Nicholas A. Hoenich, Ph.D.
Lecturer in Clinical Science
Department of Medicine
Medical School
Newcastle upon Tyne, England
Chapters 5, 17

Peter Ivanovich, M.D.
Professor of Medicine
Section of Nephrology
Northwestern University Medical School
Director of Hemodialysis
Department of Medicine, Section of Nephrology
Veterans Administration Lakeside Medical Center
Chicago, IL USA
Chapter 6

Stefan Jacobson, M.D., Ph.D.
Assistant Professor, Institute of Medicine
Karolinska Institute
Associate Physician
Division of Nephrology, Department of Medicine
Karolinska Hospital
Stockholm, Sweden
Chapter 26

Frans G.I. Jennekens, M.D.
Senior Neurologist
Head of the Laboratory for Neuromuscular Diseases
Department of Neurology
University Hospital Utrecht
Utrecht, The Netherlands
Chapter 46

Aagje Jennekens-Schinkel, M.D.
Neuropsychologist, Department of Neuropsychology
University Hospital Leiden
Leiden, The Netherlands
Chapter 46

Paul Jungers, M.D.
Département de Néphrologie
Hôpital Necker
Paris, France
Chapter 42

William F. Keane, M.D.
Professor of Medicine
University of Minnesota School of Medicine
Division of Nephrology
Hennepin County Medical Center
Minneapolis, MN USA
Chapter 41

Prakash R. Keshaviah, Ph.D.
Senior Research Associate
University of Minnesota, Department of Medicine
Director of Dialysis Regional Kidney Disease Program
Hennepin County Medical Center
Minneapolis, MN USA
Chapters 7, 12

Carl M. Kjellstrand, M.D., FACP
Professor of Medicine and Surgery
University of Minnesota
Chief, Division of Nephrology
Department of Medicine
Karolinska Hospital
Stockholm, Sweden
Chapter 26

Franciszek Kokot, M.D.
Professor of Medicine
Department of Nephrology
Silesian School of Medicine
Katowice, Poland
Chapter 45

Giuseppe La Greca, M.D.
Professor of Medicine
Director of Department of Nephrology
St. Bortolo Hospital
Vicenza, Italy
Chapter 37

Robert MacGregor Lindsay, M.D., FRCP(E), FRCP(C), FACP
Professor, Department of Medicine
The University of Western Ontario
Director of the Renal Unit
Department of Medicine
Victoria Hospital Corporation
London, Ontario, Canada
Chapter 11

Lars-Eric Lins, M.D., Ph.D.
Associate Professor, Institute of Medicine
Karolinska Institute
Senior Physician
Division of Nephrology, Department of Medicine
Karolinska Hospital
Stockholm, Sweden
Chapter 26

Robert R. Lins, M.D.
Director Nephrology Division
General Hospital Stuivenberg
Antwerp, Belgium
Chapter 38

Francisco Llach, M.D.
Professor of Medicine
University of Oklahoma Health Sciences Center
Veterans Administration Hospital
Nephrology Section
Oklahoma City, OK USA
Chapter 44

A. Peter Lundin, M.D.
Associate Professor of Medicine
State University of New York
Health Science Center at Brooklyn
Brooklyn, NY USA
Chapter 56

Michael M. Maddy, M.D.
Fellow in Nephrology
Department of Medicine
Hennepin County Medical Center
Minneapolis, MN USA
Chapter 41

John F. Maher, M.D., FACP
Professor of Medicine
Director, Nephrology Division
F. Edward Hébert School of Medicine
Uniformed Services University of the Health Sciences
Bethesda, MD USA
Chapters 1, 35, 51

Timothy H. Mathew, M.D., B.S., FRACP
Director Renal Unit
Queen Elizabeth Hospital
Adelaide, S.A., Australia
Chapter 28

Joseph H. Miller, M.D.
Associate Research Renologist
Department of Medicine
University of California at Los Angeles
Chief, Dialysis Instrumentation
Dialysis Unit, Nephrology Section
Medical Service, Wadsworth Division
West Los Angeles Veterans Administration Medical Center
Los Angeles, CA USA
Chapter 16

Charles M. Mion, M.D.
Professor of Medicine, Head Division of Nephrology
University Hospital Montpellier
Service de Néphrologie, Hôpital Saint-Charles
Montpellier, France
Chapter 24

William E. Mitch, M.D.
Professor of Medicine
Director, Renal Division
Department of Medicine
Emory University School of Medicine
Atlanta, GA USA
Chapter 53

S. Fazal Mohammad, Ph.D
Associate Professor of Pathology
University of Utah
Director, Hematology Laboratories
Institute for Biomedical Engineering
Division of Artificial Organs
Salt Lake City, UT USA
Chapter 10

John F. Moorhead, FRCP
Director
Department of Nephrology and Transplantation
The Royal Free Hospital
London, England
Chapter 36

Salim K. Mujais, M.D.
Assistant Professor of Medicine
Section of Nephrology
Northwestern University Medical School
Staff Physician
Department of Medicine, Section of Nephrology
Veterans Administration Lakeside Medical Center
Chicago, IL USA
Chapter 6

Karl D. Nolph, M.D.
Professor of Medicine
Director, Division of Nephrology
University of Missouri Health Sciences Center
Harry S. Truman Memorial Veterans Administration Hospital
Columbia, MO USA
Chapter 23

Emil Paganini, M.D., FACP
Head, Section of Dialysis and Extracorporeal Therapy
Department of Hypertension/Nephrology
The Cleveland Clinic Foundation
Cleveland, OH USA
Chapter 34

Bettine C.P. Polak, M.D.
Lecturer in Opthalmology
Erasmus University
Eye Hospital
Rotterdam, The Netherlands
Chapter 47

Manfred Pollok, M.D.
Senior Resident
Department of Nephrology
Medizinische Klinik I.
University Hospital
Cologne, FRG
Chapter 14

David S. Precious, M.D.
Chairman, Department of Oral Diagnosis and Oral Surgery
Dalhousie University
Halifax, Nova Scotia, Canada
Chapter 48

T.K. Sreepada Rao, M.D., FACP
Associate Professor of Medicine
Director of Hemodialysis
State University of New York
Brooklyn, NY USA
Chapter 43

Severin G. Ringoir, M.D.
Professor of Medicine
University of Ghent
Director, Division of Nephrology
University Hospital
Ghent, Belgium
Chapters 2, 17

Gianfranco Rizzoni M.D.
Head, Division of Nephrology and Dialysis
Department of Pediatric Research and Teaching
Ospedale Bambino Jesu
Rome, Italy
Chapter 32

Claudio Ronco, M.D.
Associate of Clinical Nephrology
Department of Nephrology
St. Bortolo Hospital
Vicenza, Italy
Chapters 15, 37

Walter Samtleben, M.D.
Privat Dozent, Nephrology Division
Medical Department I. Klinikum Grosshadern
University of Munich
München FRG
Chapter 21

John A. Sargent, Ph.D.
Quantitative Medical Systems, Inc.
Emeryville, CA USA
Chapter 4

Ad C. Schoots, Ph.D.
Senior Researcher Analytical Biochemistry
Laboratory for Instrumental Analysis
Faculty of Chemical Engineering
Eindhoven University of Technology
Eindhoven, The Netherlands
Chapter 2

Belding H. Scribner, M.D.
Professor of Medicine
Division of Nephrology
University of Washington
Seattle, WA USA
Forewords to the First and Third Edition

Neville H. Selwood, M.D.
Deputy Director
UK Transplant Service
Southmead Hospital
Bristol, England
Chapter 31

Stanley Shaldon, M.A., M.D. (Cantab), MRCP
Professor of Nephrology
Université de Nimes
Centre Hospitalier Regional, Service de Néphrologie
Nimes, France
Chapter 12

James H. Shinaberger, M.D.
Adjunct Professor of Medicine
University of California, Los Angeles
Chief, Dialysis Program
Dialysis Unit, Nephrology Section
Medical Service, Wadsworth Division
West Los Angeles Veterans Administration Medical Center
Los Angeles, CA USA
Chapter 16

Anne M. Smith, B.Sc., M.B.Ch.B.; MRCP(UK), FRCP(C)
Clinical Assistant Professor of Medicine
The University of Western Ontario
Laboratory Hematology, and Oncology
Victoria Hospital Corporation
London Regional Cancer Centre
London, Ontario, Canada
Chapter 11

Theodore I. Steinman, M.D.
Associate Clinical Professor of Medicine
Harvard Medical School
Director Dialysis Unit
Beth Israel Hospital
Boston, MA USA
Chapter 53

William Kinnear Stewart, M.D., Ph.D., FRCP(Lond), FRCP(Edin)
Reader in Medicine
University of Dundee
Hon. Consultant Physician
General Medicine (special interest Nephrology)
Royal Infirmary
Dundee, Scotland
Chapter 8

Paul Sweny, M.D., FRCP
Senior Lecturer
Department of Nephrology and Transplantation
Royal Free Hospital Medical School
London, England
Chapter 36

Nicholas E. Tawa Jr., M.D.
Clinical Fellow in Surgery
Harvard Medical School
Resident in Surgery
Brigham and Women's Hospital
Boston, MA USA
Chapter 7

Nicholas L. Tilney, M.D.
Professor of Surgery
Director, Surgical Research Laboratories
Harvard Medical School
Director, Transplant Service
Brigham and Women's Hospital
Boston, MA USA
Chapter 9

Charles R.V. Tomson, M.B., B.S., MRCP
Medical Research Council Training Fellow
Department of Medicine
University of Newcastle upon Tyne
Royal Victoria Infirmary
Newcastle upon Tyne, England
Chapter 50

Charles Toussaint, M.D.
Professor
Department of Clinical Medicine, Nephrology
Université Libre de Bruxelles
Head, Nephrology Department
C.U.B. Hôpital Erasme
Brussels, Belgium
Chapter 39

John E. Utting, M.A. M.B., B. Chir., FFARCS
Professor of Anaesthesia
The University of Liverpool
The University Department of Anaesthesia
Royal Liverpool Hospital
Liverpool, England
Chapter 52

Albert W.J. van Doorn, Ph.D.
Scientific Consultant
Arnhem, The Netherlands
Chapter 19

Raymond Vanholder, M.D., Ph.D.
Instructor, Renal Division
University of Ghent
Associate, Renal Division
University Hospital
Ghent, Belgium
Chapters 2, 17

Zachariah Varghese, Ph.D.
Associate Director
Renal Research Unit
Royal Free Hospital
London, England
Chapter 36

Rowan G. Walker, M.D., B.S., FRACP
Director, Dialysis and Transplantation
Royal Childrens Hospital
Victoria, Australia
Chapter 27

Michael K. Ward, M.B., B.S., FRCP
Consultant Physician/Senior Lecturer in Medicine
University of Newcastle upon Tyne
Royal Victoria Infirmary
Newcastle upon Tyne, England
Chapter 50

David C. Wheeler, M.B., Ch.B., MRCP
MRC Training Fellow
Renal Research Unit
Department of Nephrology and Transplantation
The Royal Free Hospital
London, England
Chapter 36

Andrzej Wieçek, M.D.
Department of Nephrology
Silesian School of Medicine
Katowice, Poland
Chapter 45