STRATEGY IN RENAL FAILURE

EDITED BY

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Foreword

Shortly after Dr. Friedman asked me to write this Foreword, an old friend and former patient whom I had not seen for several years, James Albers, dropped by to say hello. Jim had come to me in 1959 with chronic renal failure. At that time he was a graduate student in physics at the University of Washington. Jim bore an ominous and uncanny resemblance to another graduate student in physics whose death from slowly progressive uremia is so delicately and tenderly described in the final chapter of the book *Glomerular Nephritis* by my mentor, Dr. Thomas Addis (1). Lest the reader forget what end-stage kidney disease really meant twenty years ago, I recommend rereading that moving chapter.

Even though Jim's serum creatinine crept upward during the summer and fall of 1959, I delayed discussing my feelings of foreboding with him. As it turned out, I never had to bring up the subject because in March of 1960, Mr. Clyde Shields had an all-teflon arteriovenous shunt placed in his left forearm and thereby became our first chronic dialysis patient.

Jim did well on his own polycystic kidneys during that hectic first year of chronic dialysis, but by the spring of 1961 he was failing badly. At that time our dialysis research program was running out of funds and had been forbidden to take any new patients by the medical director of the University Hospital. Three events saved Jim's life: One of our four patients died of a myocardial infarction; the John A. Hartford Foundation made a grant to establish an experimental community dialysis center in downtown Seattle; Jim was well known to us and fortunately the only patient in our clinic near end-stage at that time. Because of these three factors, I was able to make Jim the first Seattle patient prospectively selected for dialysis treatment. This selection process later was taken over by the Seattle "life and death" committee (2), a system which generated extensive discussion (3).

But for Jim the drama did not end there. The first shunts were all teflon which made them very stiff. Hence, when the patient moved his limb, the tip tended to dig into the intima. Consequently, the average set of cannulas lasted only two to three months. My engineering colleague, Mr. Wayne Quinton, and I knew that we needed a "shock absorber" in the system in the form of a silicone rubber segment. The Dow-Corning people told Quinton that it was impossible to extrude silicone tubing that had a sufficiently smooth inner surface to prevent clotting in a shunt circuit. But Mr. Quinton believed it could be done and worked feverishly during

the winter and spring of 1961 to produce silicone tubing that would not clot when tested in Mr. Shield's shunt circuit. As each new sample of silicone tubing lasted a little longer, I decided to take the risk of holding Jim Albers off dialysis until we had a satisfactory silicone segment available. Quinton succeeded (4), and in August 1961 Jim Albers received the first teflon-silicone A-V shunt. I shall always remember Jim at that stage. He was so weak he could barely get around, but his brain still was functioning so well that he continued a full course load at the University during the summer of 1961.

That experience with his first cannulation made a profound impression on Dr. Albers, because to this day, sixteen years later, he has had cannulas only in his left forearm. According to Jim, his other three extremities are "in reserve." Indeed, as I recall it, he kept that original set of cannulas for nearly four years, mainly by greatly restricting all movement in his left arm.

In April of 1962, Jim went to the annual meeting of the American Society for Artificial Internal Organs in Atlantic City, New Jersey, and gave an excellent paper on the problem of how often one needed to change the dialysis bath for optimum efficiency (5). No one at the meeting realized that Jim was himself a dialysis patient until I showed a picture of him during a presentation at the American Society of Clinical Investigation in Atlantic City the following month.

And so, as Jim and I sat talking the other day, I realized once again what a truly remarkable man he is: the longest survivor on dialysis, Associate Dean at Western Washington State College, a family man with a wife and two children, and a world traveler. He and his wife went to Europe last summer using the suitcase artificial kidney created by the remarkable author and editor of this volume.

What do dialysis patients of the stature of Dr. James Albers tell us about the current and future ethical dilemmas that have been created by worldwide dialysis and transplant therapy? For me, dialysis patients like Dr. Albers represent one end of a wide spectrum of patients whose life on the machine ranges from beautiful to horrible. Indeed, there exists a small number of patients at the other end of that spectrum for whom dialysis truly seems to be a fate worse than death. I believe that we simply must develop strong moral and ethical guidelines that will enable us, without guilt or misgivings, to withhold and/or terminate dialysis therapy in those patients whose "life" is in reality pure agony prolonged through continued dialysis treatment. A partial solution to this terrible problem is continued research so that the results of transplantation and the quality of life on the machine become much better than they are today. However, this basic tragic problem is here to stay because technology in medicine is here to stay. Even if we eliminate the need for the artificial kidney by perfecting transplantation, the place of dialysis soon will be taken by another type of life-sustaining technology, such as the artificial gut system, to treat end-stage bowel disease (6, 7). Thus, I believe that however painful and unpleasant the prospect, we must press on with our colleagues in theology, philosophy, and law to find a more mature life and death ethic that will ease the intolerable burden on patient, family, and physician.

Is there a possibility that research will improve transplantation to such a degree that dialysis no longer is necessary? I think not. I believe it is much more likely that the means will be found to control and even eliminate the immune trauma to the patient's own kidneys that brings the patient to the end-stage of the

disease. The recent results of Lockwood et al. (8, 9) represent a possible step in that direction. As to dialysis and transplantation, the most urgent problem is to develop means of predicting which patients will do poorly following cadaveric transplantation, so that these unfortunate dialysis patients can be spared the trauma of transplantation followed by graft rejection. And for these and all other patients who are not transplant candidates, we must continue our research efforts to improve the quality of life on dialysis. How should we proceed? Most important is improved circulatory access. Also, we should strive to replace the endocrine function of the kidney by developing a substance such as injectable erythropoietin. On the other hand, I believe that the efforts to produce a "wearable" artificial kidney possibly are misplaced. In the early development of our artificial gut system, we developed a wearable infusion system (6). This approach very quickly was abandoned when it became apparent that patients who could not eat remained entirely well if they infused nutrients only at night while they slept. These patients had absolutely no interest in being burdened during their waking hours by a wearable nutrient infusion device. Similarly, I believe dialysis patients do not want to be burdened with a wearable artificial kidney, unless, of course, it could be made as easy to wear as a wristwatch. However, there is every reason to believe that one hour of dialysis once a day could be made sufficient to maximize its benefits, and our research efforts should be directed accordingly. We must strive to make dialysis so efficient, so simple, and so easy that it can be carried out during a brief one-hour session each day that requires no more effort than shaving or taking a shower. Among other things, one hour of daily dialysis will give the patient "dialysis reserves" so that from time to time he could skip dialysis for three to four days without ill effect.

To be successful, the daily dialysis technique will have to be completely automatic, with quick connect-disconnect blood circuit and no more difficult to operate than a dishwasher. If and when such a technique is developed, life on the machine will become far superior to what it is today. This technique should be of special benefit to future patients, because it should be so safe, so trouble free and so simple that it virtually will eliminate the need for in-center dialysis for all but the sickest patients. That in turn will save the taxpayers of this country hundreds of millions of dollars each year. Indeed, a reduction in the percentage of patients on in-center dialysis from 80% to 40% would have saved $150 million this current fiscal year (10). Of more importance, such a reduction would have improved the quality of life of the 40% of the dialysis population who went home by making them more independent and less anxious about their treatment. Three visits to a dialysis center each week reinforces the "sick image" of a dialysis patient and encourages deep dependent feelings, which have a negative effect. Jonson has summarized the problem very well indeed (11): "All chronic illness fosters dependence and interferes with the essence of human life—purposefulness. Chronic illness causes the patient to deflect from his set and spontaneous purposes and imposes upon him the foreign purposes of fighting debility and rearranging his life. The best treatment of any chronic illness is the one which minimizes dependence and fosters a restoration of normal, purposeful behavior."

The suitcase artificial kidney created by Dr. Friedman and his colleagues (12), represents another important example of the application of Jonson's principle to the treatment of the dialysis-dependent patient. I would hope that those who read

this book will also devise methods to improve the application of Jonson's principle to the treatment of end-stage kidney disease and will keep this principle in mind when planning therapy for their individual patients.

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Preface

Prior to the development of maintenance hemodialysis, it mattered little how the physician chose to manage irreversible uremia. Before 1960, the uremic patient was subjected to a protein and salt-restricted diet and relied on sedatives to mute progressively severe twitches which often culminated in generalized convulsions as the patient became agonal.

Less than a generation after Scribner demonstrated that uremia could be successfully reversed by repetitive hemodialysis, the nephrologist is able to select which of three quite different therapeutic regimens (hemodialysis, peritoneal dialysis, or renal transplantation) is best suited to his patient. Other derivative questions must be answered as the treatment protocol is tailored to individual patient need. Should dialysis be performed at home or in an outpatient facility? Is a transplant from a cadaveric donor as acceptable as from a sibling, parent or child? Does the coexistence of systemic diseases such as diabetes or systemic sclerosis preclude dialysis or transplantation?

This book is aimed at easing the management of patients with progressive dimunition of renal function, and goes beyond the levels of renal physiology, pathology, and epidemiology, and natural history of specific renal diseases. The text begins with the examination of the azotemic child or adult and indicates which aspects of the therapy of renal insufficiency may forestall the inevitable need for dialysis or transplantation. Detailed discussions are included of the emotional toll of a machine-dependent life or hosting an engrafted kidney; of the impact of a uremia program on a teaching hospital; and of the Federal Government's efforts to cope with the cost of treating 60 to 90 per million per year newly diagnosed uremic patients. The final chapter reviews several novel approaches to treating uremia which may supplement or even replace dialysis and transplantation as "conventional" therapies within a decade.

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Acknowledgments

There is probably no single stimulus or individual responsible for inciting the ego-gratifying decision to write a book. In my case, I am warmly aware of my efforts to emulate scholars who served as role models of teaching faculty in medical college.

Perrin H. Long, Chief of Medicine at Downstate Medical Center when I was a student, urged me into academic medicine at a point where I had little understanding of what the words meant. George W. Thorne and John P. Merrill at the Peter Bent Brigham Hospital had faith in my potential to keep up with the pace at that wondrous Institution, where excellence is taken for granted. John Merrill's truly incredible ability to blend a knowledge of immunology with basic physiology and clinical nephrology prompted me during my fellowship to try to function in his league of competence. Ludwig W. Eichna, my Chief, upon return to Downstate Medical Center, inspired me to work even harder because his standards were set so high that they continuously eluded my grasp. From Eichna I learned what I know about scientific writing, and I am forever grateful. My current Chief, Alfred Jay Bollet, has been kind enough to allow my division to grow. His trust serves as ample stimulus to maintain and exceed standards.

Throughout the process of writing this book, when I was often sequestered away at home, paying little attention to the management of family and marriage, my wife Barry showed tolerance, acceptance, and a quiet good humor, which allowed me to produce without guilt. I especially am thankful to the cheerful editorial assistance provided by Ms. Caroline Leto, and to the very worldly perspective imparted by Mrs. Fran Roth as she offered cool-headed support. Ms. Kathy Nelson and Mr. John M. de Carville of John Wiley & Sons were kind and helpful to me, and showed great restraint when each of the chapters arrived later than promised.

ELI A. FRIEDMAN

Contents

Chapter 1

Introduction

When I began subspecialty training in renal disease in 1958, the concept of nephrology as a separate discipline was being resisted by those cardiologists who claimed the kidney as their special interest. Although monozygotic-twin kidney isografts had been accomplished ten times, and the lives of more than a dozen patients had been prolonged for a few weeks to several months by intestinal dialysis, uremia due to irreversible renal disease was an inexorably fatal condition. The nephrology fellow of a generation ago was mainly concerned with tubular transport, body composition, and acid-base balance, while a few participated in the emerging field of transplantation immunology. All of his uremic patients, however, died despite control of hypertension, protein-restrictive diets, and potent antiemetic drugs. He learned skill in timing of magnesium sulfate injections that would mute the twitching and seizures of agonal uremia.

In 1959, a world-famous economist who was dying of polycystic kidney disease requested that my mentor, John P. Merrill, prolong his life so that he could finish a major textbook. Each hemodialysis then meant preparatory boiling of cellophane membrane, assembly of a huge, temperamental, rotating-drum "artificial kidney," dissolving the appropriate chemicals, which were tasted to confirm identity, and a vascular surgeon in attendance for insertion of glass intraarterial and intravenous cannulae. At the conclusion of a hemodialysis, the cannulae were removed with loss of the distal artery, and the wound was sutured closed. The economist improved substantially with each dialysis and wrote at a brisk pace. There was a race between completion of his book and exhaustion of arterial cannulae sites for hemodialysis. After all four extremities had been used twice, it became evident that the writing would have to end soon. Immediately after the last chapter was sent to the publisher, the patient was discharged. He died at home a few days later. A creative mind and a useful citizen were lost to a reversible intoxication.

One year later, Belding H. Scribner reported the feasibility of repetitive hemodialysis by means of a permanent Teflon extrarenal arteriovenous shunt (1). This single event altered the prognosis of end-stage renal failure from a totally lethal disease to one in which better than 90% survive for at least a year of therapy (2). The incredible impact of modern uremia therapy was far reaching and not entirely predictable at the time. In the United States, there resulted the birth of the American Society of Nephrology, a nationwide network of dialysis and transplant centers at a cost in excess of $600 million of tax money in 1976. To take full

advantage of this therapeutic evolution, physician and patient need to weigh the choices open to each uremic patient. In this text, pediatrician, internist, surgeon, psychiatrist, sociologist, administrator, immunologist, and radiologist provide the basic information required for suiting treatment to the individual patient.

BEGINNING CONTRIBUTIONS

Like other historical changes, scientific advances may have a blurry beginning and an undefinable end. Listed in Figure 1 is an admittedly arbitrary and biased selection of "key events" that improved the survival of treated uremic patients. It is arguable, for instance, at which point and due to what contribution(s) the full scope of treatment by dialysis or transplantation was first appreciated. Sharkman (3) takes "The Story of Kidney Transplantation" back to Hunter's 1771 experiment in heterotransplantation of a human tooth into a cockscomb (4). Similarly, the origin of contemporary dialysis might have been traced back to Thomas Graham in Glasgow; in 1854, he exposed urine to an albumin-coated parchment membrane, removing a white powder, later identified as urea, and coined the word dialysis (5).

I chose in Figure 1 to list first Kolff's World War II fabrication of a workable "artificial kidney" in Kampen, the Netherlands, because of his extraordinary

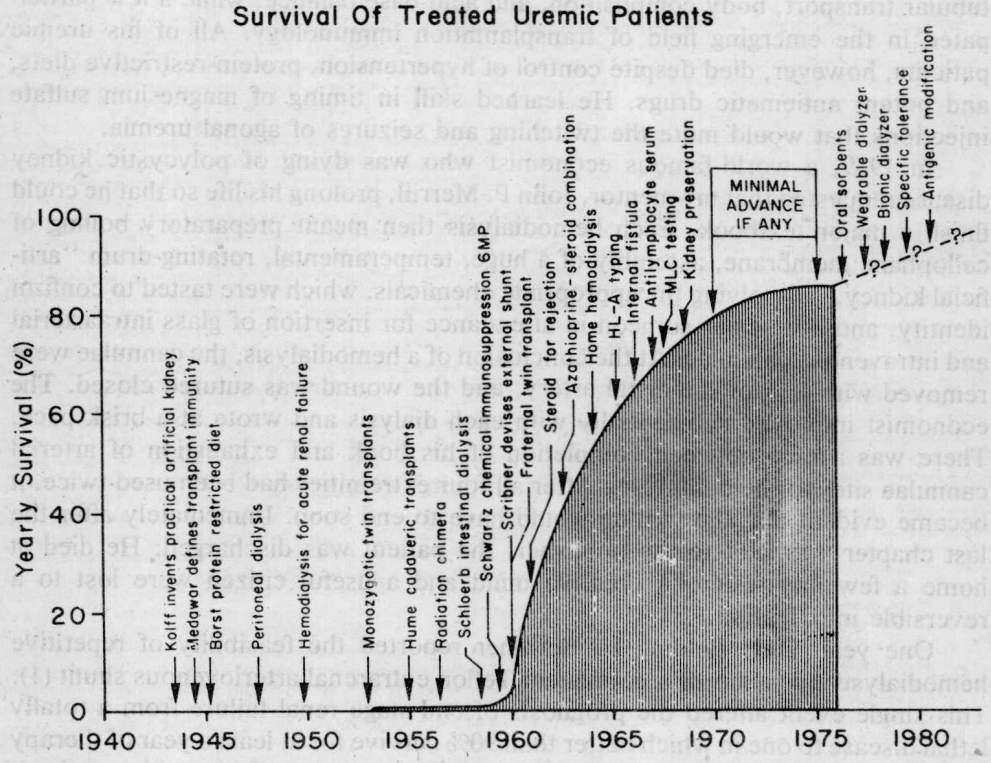

Figure 1. Kolff, with his invention of a practical hemodialysis system, and Medawar, who defined the immunological basis of allograft rejection, opened the modern era of effective therapy for renal failure. Note: (1) the lag between scientific discovery and impact on patient survival, and (2) the apparent lull in new advances in the 1970's.

ability to overcome shortgages of materials while working under the Nazi occupation of his homeland. When Kolff was denied metal, he built with wood (6). In a similar vein, Medawar's brilliantly simple and original elucidation of skin homograft rejection in the rabbit, performed in wartime Britain, fathered a chain of experiments that led to the discovery of allograft tolerance. Medawar had to compete with a protein-starved, blockaded population for the few rabbits needed for grafting. Side by side, dialytic and surgical approaches to the uremic patient matured for a decade until Merrill's group in 1953 demonstrated the total and permanent reversibility of uremia by renal isografting.

Given a machine that would sustain a functionally anephric patient, an operation that was potentially curative, and a recurrent cause of graft failure (allograft rejection), the next thrust forward hinged on advances in applied immunology. Immunosuppressive measures, including radiation, lymphocyte depletion, steroid and antimetabolic drugs such as 6-mercaptopurine and nitrogen mustard, were beginning to improve longevity when Scribner's initial paper on chronic dialysis was presented to the American Society for Artificial Internal Organs. At first, only Scribner had the vision to appreciate what his four patients' survival meant. Soon, he advised, we would have to plan for the management of every uremic patient in the United States who might be salvageable were the uremic syndrome corrected. Scribner was right! Gradually, it became apparent to organized medicine, legislators, and the lay public that the patient in end-stage renal failure would not be allowed to die untreated. As this is written, more than 30,000 Americans are undergoing maintenance hemodialysis. These patients demand an increasing proportion of the nephrologist's time and thought. New syndromes as well as unusual aspects of previously rare disorders continue to be described in dialysis patients.

The number of patients living with someone else's kidney is increasing almost as fast. Following Starzl's combination of azathioprine plus prednisone for recipient immunosuppression, the morbidity and mortality of both cadaveric and intrafamilial renal transplantation improved to the point at which it rivals, and in selected groups (diabetics, for example) exceeds, the best results of dialytic therapy. By the early 1970s, the argument over whether dialysis or transplantation was the superior therapy had been mooted by the growing sophistication of medical and surgical nephrologists who understood the wisdom of individualizing treatment to suit each patient's circumstances.

Reflection on the cause of patient survival depicted in Figure 1 allows for drawing several inferences: (a) There was a lag of more than 15 years between Kolff's widely publicized invention and the first benefits of hemodialysis for the chronically uremic patient. (*b*) It has been nearly a decade since any "apparent" substantial improvement in patient survival has been effected. (*c*) Recognition of a discovery's full importance may require a second advance years later. (*d*) Therefore, one or more as yet unrecognized contributions of the past few years may indeed prove highly significant to the uremic patient.

PATIENT CONSUMERISM

Dialysis centers initially utilized elaborate selection criteria to admit patients. Age, occupation, and "worth to society" were some of the factors weighed in the