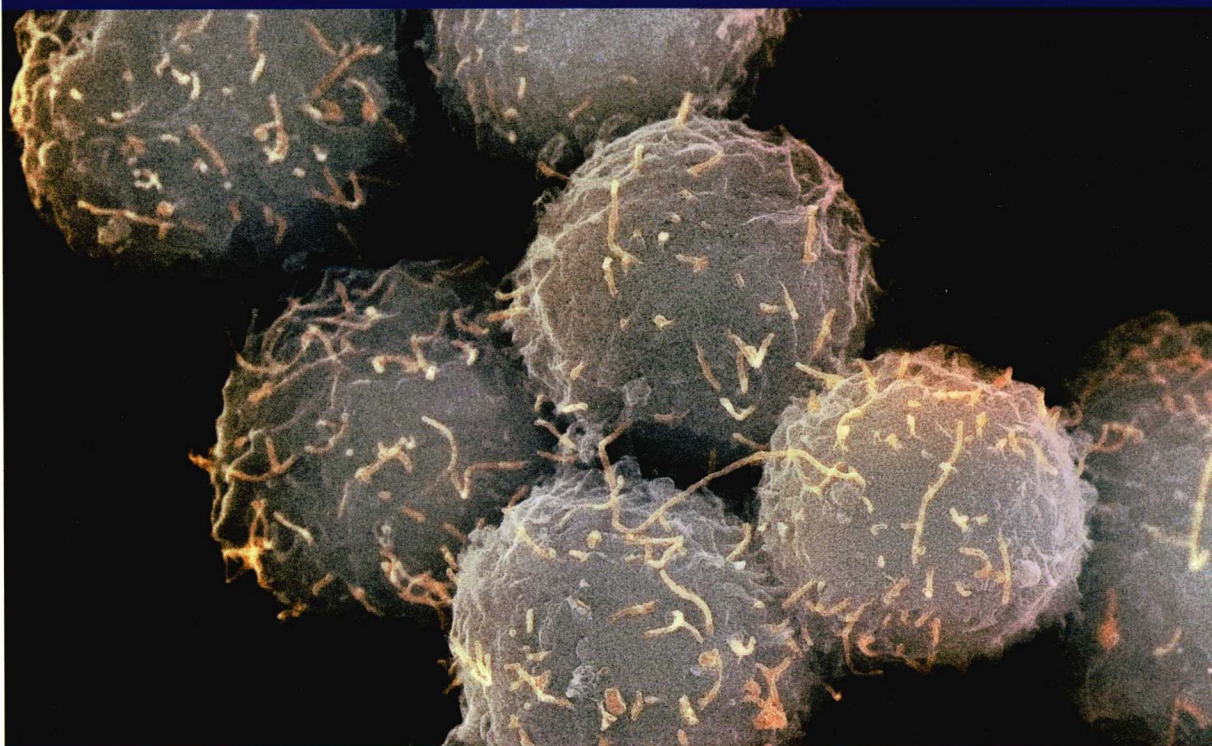


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TWO

THOMAS' HEMATOPOIETIC CELL TRANSPLANTATION



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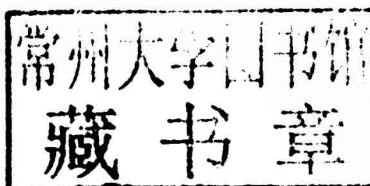
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Preface to the First Edition

The widespread application of bone marrow transplantation (BMT) to the treatment of a steadily increasing number of life-threatening hematological, oncological, hereditary, and immunological disorders is the culmination of more than four decades of research by many investigators. Early attempts in the 1950s to transplant living cells from one individual to another were carried out in the face of considerable skepticism. It was generally accepted as axiomatic that the immunological barrier to "foreign tissue" could never be overcome.

The horrors of Nagasaki and Hiroshima spurred interest in studies of the lethal effects of irradiation. It was discovered that mice given total body irradiation in doses lethal to the marrow could be protected from death by shielding the spleen or by an infusion of marrow, and that the marrow of such animals contained living cells of donor origin. These observations suggested that patients with leukemia might be given a lethal exposure of total body irradiation, which would destroy the malignant cells along with remaining normal marrow. The exposure would also destroy the immune system, making it possible to protect against lethality by a transplant of normal marrow cells.

The theory was correct, but results were disappointing. Because the procedure was both unproved and dangerous, only those patients who had no other options were considered. Except for a few patients with an identical twin donor, there were no survivors beyond a few months. Understanding of the human leukocyte antigen (HLA) system was not yet available, and little was known about the complication we now call graft-versus-host disease (GVHD). Thus, after a brief period of enthusiasm, most investigators abandoned this seemingly hopeless pursuit. Fortunately, work in animal models continued. Studies in inbred rodents defined the genetics of the major histocompatibility system and the fundamental rules of transplantation biology. Immunosuppressive drugs were developed to limit the severity of the immune reactions between donor and host. Demonstration of successful marrow transplants in the canine model using littermates matched for the major histocompatibility complex set the stage for successful transplantation of marrow between human siblings. Thus, it is clear that a long series of experimental studies in animals ultimately made human marrow transplantation possible.

By the late 1960s, much was known about the HLA system, more effective antibiotics were available, and platelet transfusions were becoming routine. Thus began the modern era of human BMT. The past 25 years have witnessed an almost exponential growth in the number of transplants being performed and the number of diseases being considered for BMT. Initially, most grafts employed marrow from an HLA-identical sibling. Autologous marrow, long known to be effective in animal systems, is now being used with increasing frequency following intensive cancer chemotherapy. Hematopoietic progenitor cells from the peripheral blood are now being used for BMT, either alone or to supplement marrow. As a result of increasing national and international cooperation, large panels of volunteer marrow donors of known HLA type are becoming available to patients whose own marrow cannot be used or who do not have a family donor.

Currently, thousands of transplants are being performed each year world-wide. With the demonstration that marrow could be transplanted and that the cure rate would be substantial, the logical step was taken to treat patients early during the course of their respective disease (i.e. in leukemia when the burden of malignant cells was relatively low and when the patient was in excellent clinical condition). With improved patient selection, development of improved tissue typing methods, availability of potent antimicrobial agents, advances in supportive care, and improved prevention of GVHD, the results of BMT have continued to improve.

Marrow transplantation is now being applied to a long list of diseases with a wide range of results depending on the disease, the type of transplant, and the stage of the disease. For some of the diseases, BMT has already proven to be the most effective therapy (e.g., some leukemias and severe aplastic anemia), whereas for others it is the only available curative treatment (e.g., thalassemia). In very rare genetic disorders, one successful BMT may establish the success of the treatment. For other more common disorders, controlled trials are necessary to define the proper role of allogeneic or autologous BMT, or therapy not involving BMT.

Only through rigorous study and long-term follow-up can novel approaches be confirmed as effective (or ineffective). For those working in the field of marrow transplantation, a source of intellectual satisfaction has been the interdisciplinary nature of the studies. A view of the wide-ranging disciplines involved can be gleaned by reading the chapter titles for this book. A successful BMT program is always a team effort. There must be cooperation between blood banks, referring physicians, radiation oncologists, immunologists, and physicians from many subspecialties. A dedicated support staff of technicians, data managers, and, above all, nurses, is crucial. The nursing team in particular is responsible for the day-to-day care of patients. Nurses not only provide the bedside management of complex protocol studies, but also bear the burden of emotional support through the difficult hospital period. They are the most readily available source of information for the patients and families day and night. Without a strong nursing team, the entire BMT program is jeopardized.

Most important are the patients who come to the transplant center with the courage to accept days, weeks, and sometimes months of discomfort in the hope of surviving a fatal disease. We must ensure that we acknowledge and respect the dignity and individuality of each patient, that we provide adequate information for informed decision making and then include patients and families in the decision process. The greatest reward for clinical investigators is to see patients reintegrated into their personal, social, and professional lives, free of their disease and its complications.

Stephen J. Forman
Karl G. Blume
E. Donnall Thomas
Summer, 1993

Preface to the Fifth Edition

Twenty-one years ago after the first edition and six years following the fourth edition of this textbook, the editors and publisher, Wiley-Blackwell, are proud to present the fifth edition of *Thomas' Hematopoietic Cell Transplantation*. The inspiration for the development of this fifth edition came from the rapid expansion of knowledge underlying transplantation biology, increased understanding of the complications of treatment, and new information related to the pathogenesis and treatment of diseases for which transplantation is utilized. The book also covers the expansion of stem-cell donor options and the genetic manipulation of cells of the hematopoietic and immune system.

In comparing this edition with the previous one, readers will find that there are new chapters focused on contributions to the field provided from basic science experiments in stem-cell biology, immunology, and tolerance. Along with these new chapters, previous contributions have been revised to reflect the deepening of our understanding of the benefits and challenges of transplantation and the impact of new therapies in the treatment of diseases for which transplant is a potentially curative therapy. In order to expand the information in each chapter, we have limited references to include only those that are most relevant.

New to the fifth edition is a companion digital edition replacing the CD ROM. The digital edition contains the entire text of the book in a searchable form and includes all the figures in a convenient downloadable format. The availability of the digital edition reflects changes in the way readers, including basic science and clinical investigators, clinicians, and nurses, access new information for both their research work and clinical care of patients.

We, the editors, also greatly appreciate the assistance of the staff at Wiley-Blackwell, who have been extremely helpful in the process of creating this new edition, now in two volumes, with a very different and modern cover presentation. The editors feel very proud to have assembled such a talented group of authors representing our colleagues who are experts in the clinical and basic science of transplantation. In addition, this edition would not have been possible without the dedicated work of our assistants, Sara E. Clark-Fuentes, Tanya Chiatovich, and, most importantly, Kimberlie Laramie. Finally, this edition honors the memory of Dr. Karl G. Blume and Dr. E. Donnall Thomas, who passed away in 2012. Their laboratory and clinical contributions helped begin and expand the field of transplantation as a curative therapy for patients suffering from leukemia and, over time, many other disorders. Both Dr. Thomas and Dr. Blume were the first two editors of the book and this edition is dedicated to them, and also to our patients and their families whose trusting partnership makes it possible to make progress and extend hope. We also honor the memory of Dr. Thomas' wife, Dottie, who we warmly consider to be the "mother" of hematopoietic cell transplantation, for her own contributions in helping Dr. Thomas and the field and for her support and editing of the first four editions of the book. They were our colleagues, mentors, and friends, and their impact will be felt in the field for many years to come.

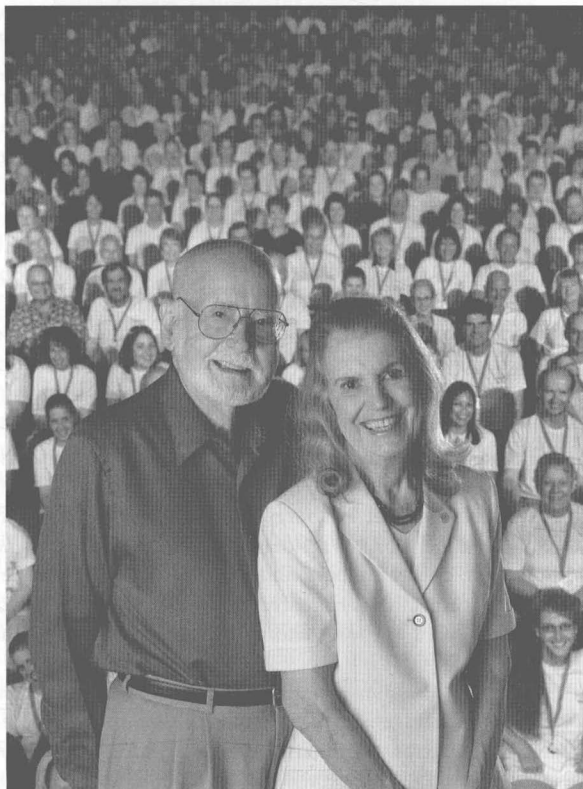
Stephen J. Forman, MD

Robert S. Negrin, MD

Joseph H. Antin, MD

Frederick R. Appelbaum, MD

Tribute



Our textbook honors Dr. E. Donnell Thomas, the single individual most responsible for creating the subject of this book, and Karl G. Blume, the Founder of the Transplant Programs both at City of Hope and Stanford University. Don and Karl were the first editors of this textbook and both passed away in the years following the publication of the fourth edition. We include this tribute as a remembrance of each of them, given the work that they did in their rich, professional lives to develop stem cell transplantation as a curative therapy for so many patients around the world.

E. DONNALL THOMAS, M.D.

March 15, 1920–October 20, 2012

Don was born on March 15, 1920, and was the son of a solo general practitioner in a small Texas village. As a child he often recalled accompanying his father to his small office and to patients' homes and between he and his father, they spanned the period from horse and buggy house calls to our modern high-tech medicine. Don received his B.A. and M.D. from the University of Texas where he met his wife, Dottie (September 18, 1922–January 9, 2015). Besides raising three children and eight grandchildren together, Dottie was



Don's partner in every aspect of his professional life, from working in the laboratory to editing manuscripts and administering grants. Anyone who has been fortunate enough to work with Don knows that if he was the father of marrow transplantation, then Dottie was, without question, the mother, and we honor her memory as our friend and colleague in this tribute, too.

Don graduated from Harvard Medical School in 1947 and completed his internship and residency at Peter Bent Brigham Hospital in Boston. It was while in medical school that Don first became interested in normal and malignant hematopoiesis. During those years, Sidney Farber was initiating his first studies of the use of antifolates to treat children with acute leukemia, and Don witnessed the very first patient to achieve a remission with this approach. He was exposed to the pioneering work of Allan Erslev and his search for erythropoietin, and most importantly, he learned from Leon Jacobson and his studies showing that shielding the spleen protected mice from the otherwise lethal effects of total body irradiation. As data emerged that a similar irradiation protection effect could be achieved by transferring bone marrow from a nonirradiated to an irradiated mouse, Don became convinced of the clinical potential of marrow transplantation.

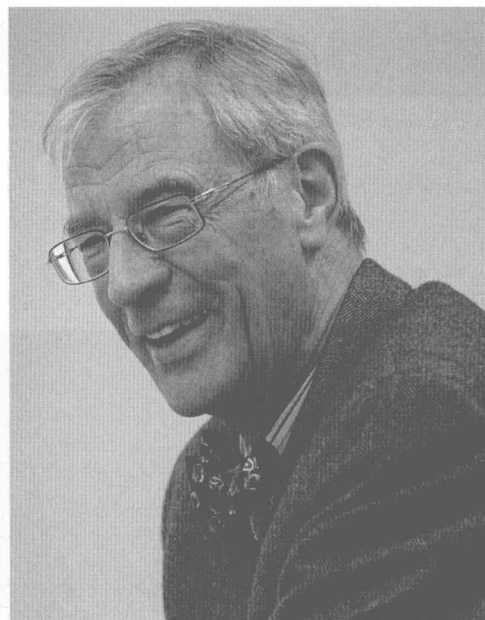
In 1955, Don moved to Cooperstown, New York, and the Mary Imogene Bassett Hospital, a Columbia University affiliate, where he began working on marrow transplantation both in the canine model and in humans with Dr. Joseph Ferrebee. In 1957, he published the first report on human patients, showing that complete remissions of leukemia could be achieved using total body irradiation followed by infusion of marrow from an identical twin. At that

time, there was little understanding of the principles of human histocompatibility and so attempts to expand these studies to patients without identical twins were uniformly unsuccessful. These failures were the stimulus for a long series of experiments conducted by Don in the canine model, showing that it was possible to expose dogs to supralethal doses of irradiation and rescue them by reinfusing their own marrow, that the marrow could be cryopreserved, and that large doses of peripheral blood could substitute for marrow. However attempts at allogeneic transplantation in this outbred species continued to fail because of graft-versus-host disease or graft rejection.

In 1963, Don moved to Seattle and the University of Washington to become the first head of the Division of Oncology. There he developed techniques for rudimentary histocompatibility typing in the dog and, by the mid-1960s, showed that by selecting matched donors and using methotrexate posttransplant, it was possible to successfully transplant marrow between matched littermates in almost every case. At the same time, based on the work of Dausset, Payne, Amos, and others, understanding of human histocompatibility dramatically increased and so, in the late 1960s, Don made the decision to return to the subject of allogeneic transplantation in humans. He began to assemble a team of physicians, nurses, and support personnel (many of whom are still part of the current Seattle Transplant Program) and obtained a program project grant from the National Cancer Institute. In November 1968, Dr. Robert Good and his colleagues carried out the first marrow transplant from a matched sibling for an infant with immunodeficiency, and in March 1969, Don performed the first matched sibling donor transplant for a patient with leukemia.

The Seattle Transplant Program was originally housed at the Seattle Public Health Hospital, but in 1972, when the hospital was faced with closure by the federal government, the Program moved to Providence Hospital. In 1975, Don and his team moved to the newly created Fred Hutchinson Cancer Research Center, a move that provided Don with increased space, resources, and scientific collaborations. That same year, he and his colleagues published their classic *New England Journal of Medicine* paper summarizing the field of allogeneic transplantation and particularly the early Seattle experience. These results demonstrated not only the feasibility of the procedure but also that there was a plateau on the survival curves following transplantation, suggesting that some of these patients were cured with this novel technique. Don continued to lead the Clinical Research Division of the Center and its transplant program until his partial retirement in 1989. He continued writing manuscripts, delivering lectures, and participating in research discussions at the Center.

Appropriately, Don received almost every possible award for his work, including the American Society of Hematology's Henry M. Stratton Award, the General Motor's Kettering Prize, the American Society of Oncology's Karnofsky Award, the Presidential Medal of Science, and, of course, the 1990 Nobel Prize in Medicine which he shared with Joseph Murray. With each award, Don always emphasized how much of his work was a team effort. He invariably mentioned the contributions of Rainer Storb, Dean Buckner, Reg Clift, Paul Neiman, Alex Fefer, and Bob Epstein, who helped form the original Seattle Transplant Team, and of Ted Graham, who moved with Don from Cooperstown to help in the animal research. Don never failed to credit the nursing and support staff who played such a critical role in these efforts and, like Karl, always acknowledged the patients and their families who were true partners in his work.



KARL G. BLUME, M.D.

April 10, 1937–January 9, 2013

Karl G. Blume was born in Germany on April 10, 1937; he received his medical education under the mentorship of Professor Georg W. Löhr at the University of Freiburg and graduated in 1963. After graduation he undertook his residency at Marburg and then held two fellowships: one at Freiburg and the other at City of Hope in 1970 and 1971, respectively. His early work was in red cell biochemistry, and he pursued his postdoctoral fellowship under Dr. Ernest Beutler.

In 1975, after discussions with Dr. E. Donnall Thomas in Seattle and with his encouragement, Dr. Beutler decided to develop an allogeneic bone marrow transplantation (BMT) program at City of Hope and recruited Karl to return to City of Hope to establish the program. The program at City of Hope was, in many ways, derived from work and discussions that Karl had with colleagues at the Fred Hutchinson Cancer Research Center and resulted in lifelong friends from those early days of the development of transplantation to treat diseases of bone marrow and immune system origin. The first transplantation at City of Hope was performed on May 18, 1976.

Karl's clinical and research work focused on the problems that confront patients undergoing transplantation, namely, prevention of relapse, understanding the process of immune reconstitution, the treatment and prevention of graft-versus-host disease and cytomegalovirus infection management, and, among his early insights, issues related to patients' quality of life after transplantation and their long-term health. In 1981, Karl was the principal investigator for City of Hope's National Cancer Institute's first approved program project grant in transplantation, which contained projects that focused on those problems, and he organized a talented group of young laboratory and clinical scientists to work together in understanding and solving these challenges. He published the first results from City of Hope on the transplants for acute leukemia in the *New England Journal of Medicine* in 1981, showing the impact of remission status on outcome.

Based on his success at City of Hope, in 1987 Karl was recruited by Stanley Schrier and Ron Levy to begin a new transplant program