E. Donnall Thomas (1920–2012)

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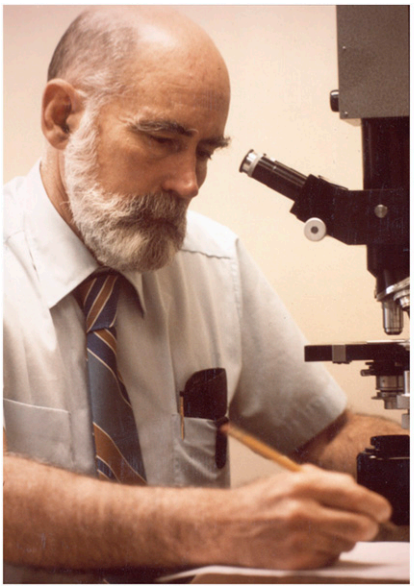
E. Donnall Thomas, M.D., Emeritus Director of the Clinical Research Division of the Fred Hutchinson Cancer Research Center and Emeritus Professor of Medicine at the University of Washington in Seattle, was once called a humble humanitarian. That was when he already had received the Nobel Prize for Medicine and Physiology in 1990—but this is only one side of the man who had been a dedicated researcher all his life. He is considered the driving force behind the successful development of transplantation of blood-forming cells, making this treatment modality clinically feasible and widely applicable. The number of patients with life-threatening diseases who have undergone transplantation of hematopoietic grafts containing blood stem cells and progenitor cells has now exceeded 1 million.

Hundreds of thousands of lives have been saved or extended by a series of advances in transplantation of blood-forming cells, but it was not always apparent that this therapy could work: without Don, in fact, blood and marrow transplantation would have been the subject of a footnote registering the failure of an impractical idea.

The story of the origins of this medical field is largely the story of Don's elucidation of what seemed to him to be a simple idea: if leukemia was a disease largely seen in the bone marrow, and if radiation clears the marrow of cells, could not one irradiate the leukemic host and regenerate the host's marrow with blood-forming cells from a healthy donor? Don pursued that simple idea for several years, each step working between experimental systems, mainly in dogs, and human clinical tests. To paraphrase Norman McLean, in Don's bone marrow transplant family, there was no clear line between basic research and clinical trials medicine.

In an initial 1957 study in which patients with terminal leukemias were irradiated, then infused with donor marrow, Thomas and Ferrebee showed that graft failure was the result. However, in 1959, Don showed that marrow from a healthy identical twin restored the blood-forming system of the leukemic twin and ameliorated the leukemic disease. This implied that some type of genetic matching between donor and host might be required for successful allogeneic marrow to engraft. At that time the nature of major genetic determinants of solid organ graft rejection



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was being elucidated, and the MHC complex of linked subloci discovered—H2 in mice, HLA in humans. Don and colleagues turned to their experimental animal, the dog, and discovered and prepared typing reagents for the dog leukocyte antigen (DLA) loci. In a critical test that has changed blood-forming cell transplantation, they demonstrated that DLA-matched grafts succeeded, whereas mismatched grafts failed. Going back to patients, in 1969 Don and his team were prepared to anticipate and respond to all aspects of patient selection and peritransplant clinical care and then transplanted HLA-matched bone marrow into a patient with the late, acute leukemic phase of chronic myelogenous leukemia. The marrow inoculum engrafted with appearance of donor-derived blood cells by two weeks, but the patient developed an immune reaction of donor cells against host tissues, called graft vs. host disease (GvHD), and after immunosuppressive treatment to ameliorate the immune reaction, the patient died of an opportunistic viral infection. This experience taught the team what problems next needed to be solved, and this has become the medical art of transplantation, balancing GVHD and immunosuppression. Don reasoned that if transplanted marrow could regenerate the blood-forming system of a patient with leukemia, how about grafting patients with acquired bone marrow failure conditions, such as severe aplastic anemia, and genetic diseases of the blood-forming system, such as thalassemia, and even sickle cell anemia? The expansion of hematopoietic cell transplantation to these diseases rightly could be called the beginning of the era of regenerative medicine.

By 1972 Don and his group had used healthy sibling HLA-matched marrow for a growing number of patients, most of whom initially engrafted, but with the complications of GvHD, infections, and relapse of the underlying disease presenting as serious and often fatal obstacles. However, in a very short time Don and colleagues had turned a mostly failing—and highly criticized—potential therapy, hematopoietic cell transplantation, into a therapeutic advance for both defective and malignant hematologic diseases. More than that, the team was also performing rational clinical trials based on biomedical research advances and taking lessons from those clinical observations back to the laboratory to improve the outcome of clinical studies.

In 1976 it became clear that some leukemia patients who without exception had failed the best available conventional therapies could be saved and in fact be cured; Don took the step to transplant patients who were in first remission (i.e., at a time when the burden with malignant cells was relatively low, leukemic clones were not yet resistant to therapy, and patients were in better overall condition compared with those with multiply recurrent malignancies). This bold approach worked, and the number of cured patients increased dramatically, from 10–15% in patients with advanced leukemia to 60–70% transplanted in first remission.

During several of the following decades the spectrum of successfully transplanted diseases widened and included most variants of acute and chronic leukemia, lymphoma, multiple myeloma, and myelodysplasia, as well as nonmalignant conditions such as thalassemia, sickle cell disease, and several inherited metabolic disorders. New sources of hematopoietic grafts were explored by transplanting cell collections from unrelated volunteer donors, and the conventional marrow graft has now

Author contributions: K.G.B. and I.L.W. wrote the paper.

The authors declare no conflict of interest.

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been mostly replaced by the collection of blood cells enriched for stem and progenitor cells by mobilizing regimens. Every novel step along the way was tested by comparing the promising, newly developed technique, method, or drug prospectively with the previous standard. Don and his team in Seattle were exemplary in this important scientific approach.

Over the course of 60 years Don led the field of hematopoietic cell transplantation to its present level. There were often setbacks and doubters—Don marched on. He could do all this demanding work by being determined, thoughtful, careful, and witty.

In his work he was assisted by his wife and collaborator Dottie Thomas, who was with him every day, initially in his research laboratory and later in the office. They would relax by fishing and hunting together and by enjoying good company. Don died on October 20th, 2012 at the age of 92. He is survived by his wife, their children E. Donnall Jr, Jeffrey, and Elaine Thomas, eight grandchildren, and a great-grandchild.