INTERVIEW WITH E. DONNALL THOMAS, M.D.
by Carol M. Ostrom

In January, 1999, Seattle Times reporter Carol M. Ostrom talked with Dr. E. Donnall Thomas about his decades-long quest to solve the mysteries of bone marrow transplantation. He was the first to show that bone marrow could safely be infused into a human patient and that marrow transplants could be used to treat acute leukemia patients. In 1990, he was awarded the Nobel Prize in physiology or medicine for that work.

Trained in chemical engineering, Thomas later turned to medical research. In 1989, he stepped down after 15 years as director of oncology for the Fred Hutchinson Cancer Research Center in Seattle. Thomas, 78, continues writing and editing with the assistance of his long-term research associate and wife, Dottie Thomas.

- Dr. Thomas, tell me about growing up in a little town in Texas.

My father was a general practitioner, the only doctor in Prairie Hill, a town of about 800 people. He was born in 1870, and with his family migrated from Tennessee to Texas in a covered wagon in 1874. He went to medical school in Louisville, with virtually no training before that. His mother taught him to read and write, and he was a natural student. So he managed to get into medical school -- no college. He started practicing in Texas in 1890. He had three children by his first wife. She died of tuberculosis in 1917, and he married my mother. I was born in 1920. I tell you that story because he was so much older than I am. I grew up in that environment, the only child in the second marriage. I can't remember when I started going on housecalls with him, and helping him in his office. My task was to light a bunsen burner so that he could do his little laboratory things. For a little kid, lighting a burner was very memorable. But as time went on, I did more and more things helping him, because he didn't have a nurse or an assistant. Of course, there was no hospital there. All the medical care was in the home. From the very earliest time I can remember, I had planned to be a doctor. I guess because he was, and because I admired him so much. I never gave any thought to anything else. Except that things intervened. This was the Depression; there was no money. My father was killed in an automobile accident when I was a student at the University of Texas, and I did not see how I could have money to go to medical school. So I switched to chemical engineering. In fact, my bachelor's degree and my master's degree are in chemistry and chemical engineering.

- Were there other influences in those early years?

My older half-brother, 22 years older than me, was a professor of mathematics. My mother had been a teacher of English. So the whole family was a stimulating environment. My brother and I used to sit on the front porch in the warm Texas evenings and do one thing or another in math. When I finally went to the University, it took me two years to get to the point in mathematics where I already was from his tutoring. I made A's in calculus at the university, no sweat, because I already knew it.

- So instead of plinking tin cans with a .22, you were out there doing math problems?
I was doing both. Both my father and my brother liked to go hunting and fishing. My father and I
didn't do much together, except for an hour here and there, because he was always on call. My
brother, who is really sort of a second father, because he is so much older, also took me fishing and
things like that. Of course, growing up in that rural Texas, there wasn't much else to do except go
fishing; I had a horse, and did the kind of thing you do in Texas.

- It seems that something helped create a strong work ethic in you; you probably know that
some people call you a workaholic.

My father was. I mentioned he was always on call. It's interesting thinking now about the cost of
medical care. At that time, there weren't all these special drugs and tests. In fact, I can remember
when he first used sulfonamide for pneumonia in the 1930s and how excited he was because the
patient with lobar pneumonia got well so quickly. And I also remember that he took care of
everybody no matter whether they could pay or not. He complained bitterly, but he never turned
anyone away. I remember him saying, "We give medical care; I just wish someone would pay us
for it." When I was growing up, we'd plan to go fishing or something, and some woman would go
into labor, or someone would get a leg broken -- he couldn't do major surgery, he couldn't in that
environment -- but trauma or obstetrics, and he'd cancel our trip. In the middle of the night, he'd get
called. As I remember it, every night. I'm sure it wasn't every night, but that's the way I remember
it. But later on, having grown up in this environment, and being in love with medicine, I decided
that with my chemistry background I'd much prefer to be in the scientific end of medicine. I didn't
want to be the only doctor in a small town. And the sequel to that now: My son came along, and
was equally fascinated with medicine, and he saw me worrying about the next grant, arguing with
the dean, and he decided he didn't want this. He wanted to go take care of people. He's the only
internist, until recently, in a relatively small town in Montana. Of course, they have a hospital there
and he has doctors he works with who cover for him, so he has a lot more freedom than my father
did.

- Since you mentioned your son, I'll bring up your wife. You met Dottie when she hit you with
a snowball. How did you get from there to here, being not only husband and wife, but
partners in research?

I was a senior at the University of Texas when she was a freshman. I was waiting tables at the girl's
dormitory, which is how I got my food. It snowed in Texas, which is very unusual -- January 20,
1940. And I came out of the dormitory after we'd finished serving breakfast, and there was about
six inches of snow. This girl whacked me in the face with a snowball. She still claims she was
throwing it at another fellow and hit me by mistake. One thing led to another, and we seemed to hit
it off. She's a workaholic, too, and was then. In those days, the girls lived in the dormitories and
they had to be checked out in the evening and checked in by 11 p.m. The dormitory supervisor
called Dottie in toward the end of her freshman year, and said, "You know, you can't have a date
every night, because your grades are going to suffer. I'm your surrogate mother, and you can't do
that." What the matron didn't know was that we were having a date every night, but we were
spending it in the library. At the end of the semester, Dottie brought her report card, which was all
As. That settled that. Dottie has never made anything but As, high school or college or anywhere.
Dottie was a journalism major in college, and had planned her career in journalism. We were
married in December of 1942, and I had mentioned, I always wanted to be a doctor. After finishing my master's degree in chemistry, I got a job at the medical school in Galveston as an instructor in pharmacology. I didn't know anything about pharmacology, but I spent three weeks reading a pharmacology book, and I knew enough to be a lab assistant. I went to Galveston and did my first semester as a medical student there. I had a half-time job so I could go to medical school. And in January of 1943, when the war was really getting going, it was announced that the Army and Navy were taking over the medical schools to accelerate the training of doctors for wartime purposes. Since I already had a reserve commission in the Army, I decided that as long as the Army was going to be paying my way to medical school, I might as well apply to some of the famous medical schools. And so I applied to Harvard and Johns Hopkins and Columbia, I think it was. On February 20, 1943, I got a telegram from Harvard, saying if I would get my credentials in for the class starting in March, they would consider me along with the other 1,200 applicants, because there had been one vacancy that appeared at the last minute. And about the first of March, I got a telegram from Harvard saying I'd been admitted. We didn't have any money, really. We sold everything we had to get train fare to Boston. Then Dottie got a job as a secretary with the Navy while I was getting into medical school, becoming a private first class, which is what we were in medical school. Then Dottie and I talked it over, and we decided that if we were going to spend time together, which it turned out we liked to do, that she probably ought to change her profession. She'd taken a lot of science in her time in school, much more than most journalists. She liked science. She left her job in the Navy and went to the medical technology training program at the New England Deaconess Hospital under the direction of Dr. Shields Warren. Then she worked as a medical technician for some doctors in Boston, until eventually, I had my own laboratory, and then she began to work with me. She worked half-time when our children were small, but otherwise full time.

- How do you make that work?

It's because I'm so easy to get along with. That's what she says, too. She says SHE'S easy to get along with. For many years, she was doing the laboratory work with me. And then, after the Hutchinson Center came into being, she had evolved into being more in administration. For the last 20 years, before I stepped down as chief of the clinical division, she served as the chief administrator for the clinical division. In the laboratory days, my sometime friends pointed out that Dottie, who had the library experience, would go to the library and look up all the background information for a study that we were going to do, and then she would go into the laboratory and do the work and get the data, and then with her writing skills, she'd write the paper and complete the bibliography. And all I would do is sign the letter to the editor.

- Obviously, I'm interviewing the wrong person! My apologies to you both. But since we're here, tell me about how you became interested in bone marrow. Was it something about bone marrow in particular, leukemia, or the challenge?

It was all of those. As a medical student, I had some very stimulating teachers, and a couple of them were hematologists. Because Dottie was a hematology technician, we used to look at smears and bone marrow together when we were students. I found the bone marrow to be a fascinating organ. I can't think of any particular time when I decided to make that my specialty, but by the time I was a senior in medical school, I knew that's what I would do.
- Were there a lot of unknowns about bone marrow then?

There had been a lot of studies, but in retrospect, it seems we didn't know much at that time. There were people who had been studying bone marrow for 50 years, but a lot of its functions were still a mystery, and its diseases were poorly characterized. It used to be thought that pernicious anemia was a form of leukemia. Going back to my father, I can remember as a kid, his being so excited when (George) Minot and (William) Murphy got the Nobel Prize in 1934 for their earlier work on pernicious anemia. His enthusiasm was catching. Little did either one of us know at that time that I would later be personally acquainted with both Minot and Murphy.

- You were inspired by some studies involving mice and radiation. Would you explain why these studies were so important to you?

By the time I had graduated medical school and was a fellow, I spent my first year in hematology with Dr. Clement Finch. He was then in Boston, but he moved to Seattle in 1949 to establish a division of hematology at the then-newborn School of Medicine at the University of Washington. His interest was in iron metabolism. And of course, red cells are made in the bone marrow. Also about that time, it was realized that radiation kills animal and people primarily by damage to the bone marrow. It's the most sensitive organ in the body as far as radiation damage is concerned. And of course, in the late '40s, after the atomic bomb explosions, everybody was interested in this. And I became very interested in what governed the bone marrow's production of white cells and red cells and its other functions. At that time, there were some early experiments that suggested there were some growth hormones for bone marrow. Specifically, a little was beginning to be known about erythropoietin, which stimulates bone marrow production of red cells. I took a year off from my clinical work and went to the Massachusetts Institute of Technology, and worked in the Biology Department there, with a man named (Dr. John) Loofbourow whose interest was in wound healing substances that stimulate cells to proliferate. I worked on substances that are released from irradiated yeast that stimulate yeast cell growth. And my real interest was in transferring this to bone marrow. That's what I did for a year at MIT.

- But that didn't prove to be something you'd stick with.

No, but I worked on that topic from 1950 to 1955. And it proved to be a very difficult area of endeavor. I set up cultures of bone marrow, and tried to study factors that would stimulate in vitro growth. The followup on that story is that other people tried to do this, and no real progress was made for 20 years, until recombinant technology came along, and then it became possible to manufacture erythryopoietin, to have it in sufficient quantities. And now, of course, thrombopoietin, and interleukin-2, and all these cytokines are hot topics in current research. So if I had continued in that field, I would have continued to have some frustration for 15 years. So I switched my frustrations to a different area. In 1955, I was moving from Boston to Cooperstown, N.Y. -- the Mary Imogene Bassett Hospital there is a branch of Columbia University's teaching system. Let me go back: In 1949, Leon Jacobson of the University of Chicago showed that if you put a lead foil around a mouse's spleen, so it's not exposed to radiation, he could give the mouse lethal radiation, but the mouse would recover. He thought this was a hormone released from the spleen. So of course, this is what I was working on. I met Dr. Jacobson in 1950, to talk about these
experiments. He also had great trouble trying to isolate any "hormone." In 1955, as I was moving to Cooperstown, a paper appeared in the Journal of the National Cancer Institute. What the authors had done was to give the mouse lethal irradiation, give it an infusion of bone marrow or of spleen cells, since in the mouse, the spleen is a bone marrow organ. They gave lethal irradiation, they gave an infusion of marrow cells, and the mouse recovered. The marrow cells came from a different strain of mouse. They followed this up by doing a skin graft from the donor mouse to the recipient mouse. Now ordinarily, this skin graft would be rejected. What they showed was that in fact, the skin graft was accepted, as though it was the mouse's own skin. These are different strains of inbred mouse. By that time, it was well known that if you gave bone marrow cells from the same inbred mouse, the mouse would recover from irradiation. Here, they took marrow from a white mouse after this gray mouse had been irradiated lethally, but given marrow from the white mouse. When the (gray) mouse had recovered, they put on the skin graft, and it was accepted. Later on, another investigator showed that a skin graft from a third strain would be rejected. Only the marrow donor's skin would be kept.

- And you said . . . .

Bingo! And so did Dr. Joseph Ferrebee, who was also in Cooperstown. I was going there; we were going to work together. He'd seen the same paper.

- What did this paper say to you?

You couldn't explain what happened on the basis of a hormone. A graft rejection is a cellular phenomenon. So this had to be on the basis of induction of tolerance by cells. We looked at this, and we said: If we can do this in a mouse, we ought to be able to do it in human beings. That was 1955, I was 35 years old. I went to Cooperstown as physician-in-chief of the hospital there.

- So you thought you could do it in humans. And you did. How did the first ones go?

Terribly. By then, of course, it was well known that leukemic cells were very sensitive to irradiation, just like normal bone marrow. And we had patients dying of leukemia or lymphoma. It was logical to say: We could give lethal irradiation to all the leukemic cells, also killing the normal bone marrow cells, but prevent the death of the patient by an infusion of bone marrow. By then, through the work of others, it was known that you could give bone marrow intravenously in mice, and it would grow in the bone marrow. So we actually started to do this, to give irradiation to these patients and to give bone marrow. At the same time, we started studies in dogs. Other people were working with inbred mice, as were we. But we felt we needed an outbred species where clinical procedures could be done, so we could transfer information from inbred mice to outbred species to human beings. Like humans, dogs come in families. We started the dog as a counterpart of our clinical studies. Now, the clinical studies at that time, I guess you could say, were disasters. We didn't get any grafts. We did find that some patients actually had appreciable remissions after 300 or 400 rad of radiation, getting close to the lethal dose. But we didn't have any success with grafts. The marrow didn't engraft. But at that time, the lethal dose for human beings was then and now thought to be about 400 rad, which is now called centiGray -- they changed the terminology. We started with about 200. We worked our way up to 400, and didn't get grafts. In the dog model, we also didn't get grafts. And then we decided that since we weren't getting grafts, maybe the grafts
were getting rejected by the recipient. So we doubled the irradiation. We went up to 800 rad in the
dog, which is twice the lethal dose. Lo and behold, we began to get grafts. We went up to 1,000
rad, and we got pretty consistent engraftment, especially with littermate donors. At that point, an
investigator in Paris named Mathe, ((accent on e)) who had come to work with us for brief period
of time, was doing similar studies in patients, and he didn't get grafts, either. We decided that well,
we must not be giving enough irradiation, and that really what we ought do is give 1,000 rad to
human patients. Yeah, scary. We didn't even know that intravenous bone marrow in human beings
would ever work. We knew it would work in mice, and in dogs. One of the first problems was that
we couldn't give that much irradiation to human patients with the then-existing equipment. The
most high-energy x-ray machines then were about 300 kilovolts. The thickness of the human body
prevents getting homogenous irradiation. We set up a special radiation unit involving opposing
cobalt-60 sources. This followed consultation with radiation oncologists, radiation physicists at
MIT and at Columbia. And we got their advice. Cobalt-60 has two gamma rays, on the order of 1.2,
1.3 million volts. It's a much higher energy, so we could get enough penetration to do this. We
continued these studies in dogs while we were setting up.

We published those first papers (on the irradiation of human patients) in the New England Journal
of Medicine in 1957. They were basically all failures. We had one transient graft. But after about
six weeks, the graft ceased to function. This is what we now call graft rejection. But by late 1957,
we had set up our cobalt-60 sources. And also, through various professional colleagues, we knew of
some sets of twins, one of whom had leukemia. I think it was in late 1957, we treated the first of
these sets of twins, who had all the then-available treatment for acute lymphoblastic leukemia. At
that time, there were only steroids, methotrexate and 6MP. We didn't have any of the other anti-
leukemic agents that we have now. This girl was in the final stages of advanced leukemia. We
decided to give her 800 rad, and an intravenous infusion of marrow from her twin sister. In those
days, we didn't have these long, complicated informed consents. All we did was sit down with the
patient and family, and explain everything, and explain what we didn't know. Of course, the
alternative was that she was going to die within a few days or weeks. She was in the final days or
weeks of her leukemia. By the way, in the introduction to the book, we acknowledge the courage of
our patients and their families.

- How did you talk to the families about what you wanted to do? You knew the outcome was
very likely to be grim.

Yes, we did. We'd have to sit down, put all the cards on the table. Say what we know, point out that
one option was dying quietly in bed. It's tough, but that's the way it is. With one twin, the parents
hesitated. We hesitated. But the alternative was to simply watch her die. We went ahead, and gave
her 800 rad. The night before we were going to do this, one of the pediatricians called Dottie, and
said, "Are you really going to put that child in there and cook her?" Dottie cried all night. The girl
was 7. To make a long story short, she tolerated what was then horrendous irradiation with almost
no ill effects. And after the intravenous infusion from her sister, she recovered her blood counts
very quickly, within a couple of weeks. She was discharged from the hospital. She was an
outpatient 30 days later, with no sign of leukemia. Unfortunately, six months later, her leukemia
came back, and she died of leukemia. We owe her for being able to show that an intravenous
infusion of bone marrow would protect against twice the lethal dose of irradiation.
After those first twin experiments, then you had some dismal failures.

We were all trying to do transplants in human patients. I think basically we stopped in 1959. By that time, a number of other places had tried to do this, and all without success. We concentrated on the dog model, and worked out a lot of the problems: how to get grafts, how to handle the bone marrow, how to freeze bone marrow. We can freeze bone marrow for years if we want to now. And we worked out the radiation requirements. All told, it was 15 years of work. Let me go back a little way again. When I started as an attending physician at the Brigham Hospital in Boston, when I finished my chief residency, that first year, which was 1953, we had a patient with renal failure who had an identical twin. After a lot of soul searching, it was decided to carry out a kidney transplant from the normal twin to the one with kidney failure. I was the medical attending; I helped take care of this patient on the medical ward before the transplant. The transplant team was headed by Dr. Joseph Murray (the co-winner of the 1990 Nobel Prize with Dr. Thomas). It was decided to do this transplant, and that transplant was successful. That was the first one.

What was the message of that transplant?

That told me, and everybody, that the tissues of identical twins were entirely compatible. We didn't know how to do tissue typing then. And then, actually, at that time, it was thought that if one could do a marrow transplant, one could follow it with a kidney transplant, like the skin graft. Which was one of the reasons I was very interested in this, even before this paper appeared. We did that in our dog model. And Dr. John Mannick took a year off from his surgical training and worked with us in Cooperstown, and we did marrow transplants and kidney transplants in dogs that were successful. But about that time, some immunosuppressive drugs had been developed. And again, Dr. Murray and the Boston team were able to show that they could get kidney grafts to survive even from individuals who were not identical twins if they gave enough immuno-suppression. So this irradiation approach was abandoned for kidney transplants. By the way, during my medical residency, Dr. Murray was a surgical resident. We had worked together as doctors together on the ward. What a thrill to get together in Stockholm (for the Nobel Prize).

Despite some successes, though, you stopped working on human patients during the '60s.

Except for identical twins, we did all the laboratory work with dogs. We were working on dog tissue typing. Now, at that time, a lot of people were working on human tissue typing. The human tissue-typing people were way ahead of us. We were simply trying to transfer what they had learned to the dog model, because in the dog model, we could test it. In the human model it was difficult.

In the 1970s, when we started in again with people, we were very heavily criticized. There were very many responsible people who said this shouldn't be allowed to go on, because our success rates, in the past, had been so poor. In the dog, we were finally able to develop an antibody that recognized dog leukocyte antigens, what we call the DLA system. The human leukocyte antigen system had been developed to a greater degree than we were able to do in the dog. In fact, Jean Dausset got the Nobel Prize, in 1980 for developing the HLA system, the human leukocyte antigen system. For marrow, that turned out to be crucial. In the dog, we studied brothers and sisters, so we didn't accidentally have identical twins. What we found, once we'd developed these typing sera, was that if we irradiated one littermate and gave marrow from a mismatched donor, either the grafts
were rejected, or the dog died of graft-versus-host disease. But if the donor were matched, about half of those dogs became long-term survivors. And if we gave a few weeks of immuno-suppression, to sort of stop the graft-versus-host reaction, more than 90 percent of those dogs became long-term survivors. Now at that point, we were ready to go back to doing human transplants between brothers and sisters.

- In the '70s, one of your early papers showed something like 12 out of 100 patients surviving. Some people thought you should stop. You kept going. Why?

This is what we call "the 100-patient paper." This is when things really got hot. We had 100 patients; 46 with AML (acute myeloid leukemia) and the others with ALL (acute lymphoblastic leukemia). But they were all in the end stages of leukemia. To have 12 of them become long-term survivors was, to me, very impressive. But other people were saying, "Well, you know, only 12 out of 100 isn't worth all this effort and expense." To me, it meant if we can do this with patients with far-advanced disease, even if there's no other progress, we should be able to do much better if we do it much earlier, before they get to the end stage of the disease. Of those 12, 8 of them are living now. And they are all beyond 22 years. That was published in 1977. Unfortunately, a marrow graft does not confer immortality. One of those patients was killed in an automobile accident. At first, we were not doing transplants over age 40. It's known that the older you are, the less well you tolerate cytotoxic therapy, chemotherapy or irradiation. Then we increased the age limit to age 50, after we'd had some success. We had this lady come to us when she was 51, with the blastic crisis of chronic myeloid leukemia that is basically untreatable. When chronic myeloid leukemia becomes an acute leukemia, it's called the blastic phase. It's essentially untreatable. I called her doctor and said our protocol cuts off at age 50. And he said "!#%#!, I don't care where it cuts off, this lady doesn't have any other chance!" We did her transplant, and it was remarkably successful. But she died just a year or so ago -- 17 years later -- of a dissecting aortic aneurysm. She'd been a heavy smoker. As I say, it doesn't confer immortality. Another humorous footnote: There were many young people who came to work with me in the '60s. When we cut off at age 40, they were all in their late 30s. Then we cut off at age 50, and they were in their late 40s. Now, we cut off at age 60, and they're all in their late 50s. So we decided that old age is just a little older than you are.

- Many other scientists in this field abandoned the idea of human transplants during the '60s and early '70s. Why did you persist?

People ask me how we succeeded in this. I say well, one, I'm stubborn, and two, I picked some very good young people to work with. Like the development of the DLA typing system: I had four young fellows who came to work with me in the 1960s: Bob Epstein, Rainer Storb, Alex Fefer, Paul Neiman. All of them are full university professors now and have been for some time. Three of them are still here. I tell them I picked them because they came as fellows, so their salaries were very low, and I picked them because I could afford them. Actually, they were young physicians, but they had proved their brilliance in their training period. And even then, we were having a lot of young people who wanted to come work with us. We could pick the cream of the crop, because we were doing something new and exciting.

- How did you manage a bunch of hotshot young scientists all eager to make a name for themselves?
One of the wonderful things about our team has been our stability. In American medicine, especially academic medicine, it's generally said in order to get a promotion, you have to move somewhere. So people are moving around all the time. That hasn't been true of our team. In fact, we've pretty well stayed together for 30 years. After those first four, many others came along. Many of them are still here. We had fun working together. One of the interesting things about this is it led into so many areas: radiation biology, immunology, transplantation biology, infectious diseases, liver diseases, adult medicine, pediatric medicine. As a doctor, I always found all these things very interesting. We had immunologists come to work with us, pediatricians, hepatologists. All of these people working together is what made it so much fun, and so interesting. We've had large numbers of people come to work with us for months or two or three years, and then go back to their institution. The last time, Dottie counted, she had a list of close to 400 people who had been here for a period of training.

- **Are there particular qualities a person must have to become a good scientist?**

Scientists are accused of being obsessive-compulsive. But it works like this: You get interested in something, and one problem crops up. If you're lucky, you can solve this, but it discloses three more problems. So you're led forward by curiosity.

- **Do you play games or puzzles?**

No, not so much. I don't find them relaxing. Maybe because I've spent so much time taking care of terribly sick patients, that's one reason, outside of my boyhood, I've decided I like the out of doors. I go fishing or hunting to get out and appreciate nature. I don't shoot anything unless I'm going to eat it, and most of the fish I catch I release. If I'm not out hunting or fishing, maybe I'm just out hiking. I've hunted all kinds of things in the past -- I've shot one bear. I ate him. But I didn't like him, particularly, which is why I haven't shot any more. I haven't done much big game hunting in recent times. Now, mostly, Dottie and I hunt ducks and pheasants.

- **In your work, your curiosity led you in a number of directions. Did you realize early on that solving the mysteries of the marrow transplant was going to involve tissue typing, immune-suppression and a whole host of different areas?**

We were learning things as we went along. Again, the dog system was very informative. For example, we were learning about the fact that in the first two or three months after a marrow transplant, dogs and humans are very immuno-deficient. They're susceptible to all sorts of opportunistic infections. Some of those things we learned that the hard way. Some of our early human patients were dying of Pneumocystis carinii infections. It was a surprise at autopsy to find that. Cytomegalovirus. We learned about all the infections that AIDS patients get long before AIDS patients came along.

- **In the early ’70s, a lot of physicians had very negative attitudes about bone marrow transplant, and they wouldn't refer patients until they were very, very sick.**
In the first part of the 1970s, we only took patients who had failed everything else, for ethical reasons. When we began to get some of those patients to be long-term survivors, without their disease, it then became possible to do the transplants earlier, while the patients were in good clinical condition. Back in the mid-'60s, we could get 90 percent of the dogs to be good long-term survivors. We could get 5 percent of the humans to be long-term survivors, in part because the human patients were so sick, and came in with advanced infections and everything else. About 1977, we published a paper about the first patients with leukemia who were considered to have bad disease, but doing the transplants in first remission, while they were considered to be in good clinical condition. Then the survival rate got to be much, much better, very quickly.

- Did you have trouble funding your efforts?

We were lucky that in the '60s and '70s, funding was fairly easy to get -- if you had a good project, you could get it funded. As you know, in recent times, you can have a good project, and not get it funded. In about 1967, we were convinced we could do tissue matching, leukocyte matching, in dogs. And it would work. By that time, we also knew that our human patients, even twins, had to have excellent clinical care, and that probably this needed to be by a devoted team. In 1967, we wrote a grant application that included nursing support. In 1968, that was funded. We were then at the old Public Health Hospital here in Seattle. We were able to hire a team of nurses who really wanted to do this sort of thing, and some support personnel at various levels, and even some money for patient care. That grant was funded in July of 1968, and we had our team set up and ready to work in early 1969; we did our first patient in March of 1969. It was the first in what I call the modern era of transplantation, based on knowledge of tissue typing.

- Who was that?

A man with blast crisis of chronic myeloid leukemia, notoriously untreatable. We gave irradiation only, 1,000 rad. And marrow from his sister. And we got a graft. Which was important to us. And after about three months, he began to get progressively sick, and died. But didn't have leukemia. He was the first of our patients to die of cytomegalovirus pneumonia, this opportunistic infection. We did 10 patients with irradiation only. Only one became a long-term survivor. A boy named David, who died about 10 or 11 years later. He'd had several episodes of pneumonia, and he had impaired pulmonary function. But he was able to go on to finish college. When Mt. St. Helens erupted, he was over in Eastern Washington, and got exposed to dust, and with his impaired pulmonary function, he died very shortly thereafter. Several of these patients had had recurrences of leukemia, as our first twins had had. So we decided to give some chemotherapy before the irradiation. We decided to give what was considered a terribly high dose of cyclophosphamide. We gave 60 mg. per kilo on each of two days, which is about 10 times as much as was routinely used in those days. And then we gave the irradiation. Part of the reason for doing this in these patients with advanced leukemia was to prevent the sudden destruction of a huge number of leukemic cells, because a couple of our patients died of plugged up kidneys from uric acid. We hadn't seen that in our dogs, because the dogs didn't have leukemia. We wanted to destroy the leukemic cells more slowly, and then give irradiation.

- So this was all a series of small steps?
Yes, exactly. My good friend and colleague at Johns Hopkins, George Santos, had been working with cyclophosphamide in the rat population, which is why we knew about cyclophosphamide. All these little pieces fall together; we learn from other people, they learn from us. People keep asking me what was the breakthrough for this or that. I always say there aren't any breakthroughs. It's always a step-by-step process. A couple of the reporters at Channel 5 have a "breakthrough" every day. I tease them about it -- the "daily breakthrough."

- I'll ask it this way, then: What were the areas in which those small advances turned out to be crucial to success?

Later on, additional chemotherapeutic agents became available. Control of infections was one of the major problems. We began to have better antibiotics for bacteria. In those early days, the majority of our patients died of bacterial infections, gram-negative organisms that over the course of a decade, we were able to control. Through the work of others, agents became available for controlling pneumocystis infection -- preventing it. One of the big advances in the early '80s was the development of acyclovir for the control of herpes infections. And in the late '80s, the development of ganciclovir for the control of CMV, cytomegalovirus infections. Better immunosuppressive agents for control of graft-versus-host disease. Increasing knowledge of the nature of the gastrointestinal problems, and how to manage them. George McDonald, one of our colleagues on the book we're working on, wrote a beautiful chapter on the gastrointestinal system. It's the definitive work in the field. Esophageal ulcers, veno-occlusive disease of the liver, graft-versus-host disease of the gut are all major problems in marrow transplant patients. First you have to recognize the problems, then you have to figure out what you're going to do about them. It's just a series of steps. It's interesting looking back that some of the problems we spent several years on could now probably be solved in a month or two -- the technology is amazing. I used to go in about 5:30 in the morning to set up these tissue typing trays, because the anti-sera we used were so imprecise, I was afraid that the technician might make a mistake, so I'd do it myself. But now, with the advent of the actual molecular nature of these antigens, and doing the tissue typing by molecular techniques, it's rapidly replacing all these imprecise serological things. It's an entirely different ballgame. By the way, some of those failures, when we thought we were transplanting matched brother or sister, it turns out they weren't matched. Now, we can go back retrospectively and repeat the typing. So some of our inexplicable failures are now explicable.

- You've also used the transplant for other diseases.

The original emphasis was on leukemia. But we also did transplants early on for aplastic anemia. It's simply a failure of the bone marrow -- one doesn't have to destroy leukemic cells. So even early on, the success was much better with aplastic anemia. All we had to do was give sufficient immunosuppression with cyclophosphamide -- now, with other things. We had always thought that we would like to do marrow transplants for genetic diseases. But because of the high risk involved, we didn't do that until the spring of 1981. I gave a lecture at the thalassemia meeting in Italy. Thalassemia is also called Cooley's Anemia, where the children are born without the ability to make hemoglobin. At that point, I said that I thought marrow grafting was getting safe enough so that we should again consider it if we had the ideal patient; that is, a patient who had the minimum number of transfusions, so they're not sensitized, and a patient who had a sibling who is HLA matched, and who also has normal hemoglobin production. I gave that lecture, I think it was in
June. In October, one of our colleagues in Italy called up and said, "I think I have an ideal patient." We brought that patient here to Seattle, and the little boy was 16 months old. He had what we call beta-zero thalassemia; he couldn't make any beta chains for hemoglobin. His older sister was HLA matched. We did the transplant. Thank goodness, he sailed through. He's well now. His development has been normal.

- And the alternative for him would have been what?

It would have been to have blood transfusions every three weeks, and get chelation, an infusion of chelating agents to promote the excretion of iron. These children typically died in the first few years of life. Because their bones expanded as the bones tried to make hemoglobin, which it couldn't do, they were grotesque. Back about the end of World War II, it became known that one could keep them alive by transfusing them, and prevent the grotesque distortion of bone. But they were dying of iron overload, and so it was then discovered that a chelating agent had to be given intravenously or subcutaneously to help prevent the buildup of iron. And now these children, most of them, live two decades, even three decades. Many of them as teenagers rebel, and don't get their transfusions or their chelating agents. There were very few of them in their 30s. The argument now is whether to transplant these children or not. In the United States, the majority of them are not transplanted. Right now, with a matched sibling, the risk of death during the transplant is about 5 percent. And the risk of having the thalassemia come back, that is, of having the graft rejected, is about 5 percent. The survival is 90 percent if they're transplanted before they have problems of iron overload or hepatitis from the transfusion. This is because there are very good doctors, very good friends of mine, who are reluctant to subject their patients to that risk. It's a real risk. In Italy, where this is a much greater problem, many transplants are now done for thalassemia.

- Is expense also an issue?

This is one of the situations where a bone marrow transplant is cost effective. Because the chelation, the transfusions, the clinic visits, even conservatively, are $20,000 a year, if they don't have any complications whatsoever. This goes on for 20 or 30 years. For a marrow graft, because we do a lot more of this on an outpatient basis, the cost has been coming down progressively. Let's say this was in the 1980s, when the cost was about $180,000, approximately. It's still a lot cheaper than transfusions and chelation. I don't want to name names, but some of the leaders, the experts on thalassemia, they have large clinics where they're doing transfusions and chelation. And because this is what they do -- and it's better than it was 20 years ago. It's a legitimate argument. This way, survival in the first 10 years should be 100 percent. Now, there's talk that maybe gene transfer will make it possible to cure these patients. I have to tell you, in 1982, when I presented this first patient -- there's an annual thalassemia meeting; this one was in Bangkok -- two very responsible investigators got up and really jumped on me, saying it was really not ethical to do this, because in a year or two, we would have gene transfer, which could cure these patients. That was 16 years ago. We aren't any closer to having it now. I keep pointing out that you still have to destroy this rapidly proliferating marrow. It grows very well, it just doesn't make hemoglobin. So some of so-called leaders in the field are coming around. David Nathan in Boston is now doing some transplants; he was opposed to it originally.

- What are some of the big problems left to solve with bone marrow transplants?
Control of graft-versus-host disease is still not perfect. We still have patients dying of graft-versus-host disease. We are doing more and more transplants using unrelated donors. And with the modern molecular typing, this is getting to be much more feasible, but there are still many problems. The problem of recurrence of leukemia, which still happens despite our best efforts. There is a long list of problems, which is why the survival rate is not 100 percent.

- Is there a magic bullet?

I don't think so. For example, one of the annoying problems -- that's putting it mildly -- is this: We've controlled bacterial infections; we're now pretty much controlled viral infections and parasitic infections. We still have fungal infections. The candidal-type infections we can control pretty well. But there is still a class of fungal infections which -- the class of molds, like Aspergillus, which we don't have a good way of controlling. Somewhere between 5-10 percent of our patients die of Aspergillus infections. We thought back in the '80s that this could be solved if we set up laminar air-flow rooms. We did that. Half of our rooms -- 30 rooms -- were laminar air-flow rooms. We spent 10 years studying it. The bottom line was we decided we didn't need them. We don't need them for bacterial infections -- we can control those. They don't prevent fungal infections, because the patients come in with fungal infections. And particularly the patients with leukemia -- this is not so much true with inherited diseases -- but patients with leukemia have all had chemotherapy for their initial treatment, and many of them get fungal infections. The reason the laminar air flow rooms didn't control the aspergillus infections was that the patients already had them when they came in; they were already on board, so to speak. Another problem is the fact that some patients, even with molecular matches, still get graft-versus-host disease. This is due to antigen systems that are outside the HLA system. We call them minor transplantation systems, to distinguish them from the major. We've known for a long time from inbred mice that they exist, but it's been very difficult to study them, to define their nature, in human beings. One of the major laboratories here is directed at that problem -- looking at ways to type for these other systems, if you will. When Dausset won the Nobel Prize for the HLA system, one of the co-winners was George Snell of Bar Harbor, who had worked out these systems in mice. He had shown very clearly that there is a major system in the mouse, as there is in man, but also because he could do inbreeding and back-crossing, he defined many of these other systems in the mouse. Well, we can't do controlled mating and back-crossing in human beings, so we have to have another approach.

- Which brings up a question: Why did you pick dogs in the beginning?

There's a history there. Surgeons have used dogs for a long time for experimental procedures. Alexis Carrel, who got the Nobel Prize about 1910, had shown that he could transplant kidneys in dogs. The kidney would function, but after about 10 days, it would stop functioning, because it was being rejected. When I was a medical student, everybody knew that you could never transplant tissues from one individual to another because they would be rejected. You can see why I got excited about that picture (of a mouse with a skin graft). Dogs had been studied, and they're relatively inexpensive. Some people -- Dr. van Bekkum back in the '50s -- had been trying to do these studies on non-human primates, but they were all infected, they didn't come in families, so he had big problems. Dogs were much less expensive than primates, pleasant to work with, and they come in families. And one can get a daily blood count, do blood transfusions.
- Some people have ethical problems with research on animals. What's your view on that?

Every time I talk to a reporter, I worry about this. We've had remarkably little difficulty with the animal-rights people. I like to think that one of the reasons was that early on, and even now, we do some of these things to ((italics)) treat ((end italics)) dogs. About 15 years ago, one of the Seattle papers had a major article with pictures of dogs with leukemia or sarcoma that we were returning to their owners. What we've been learning is just as applicable to dogs as it is to human beings. Maybe that influences them. There are rational people in the animals rights movement and there are irrational people. The rational ones, we've always been willing to have them come and see what we're doing, and see how we're taking care of the dogs, and they see how human beings are benefitting. It would have been impossible to do this without mice or dogs. You can do a lot of things in test tubes and tissue, but ultimately, let's face it, the living patient or living animal is so much more complex than we can comprehend, that we have to try these things, as we say, in vivo. When we were first doing these studies in dogs, in Cooperstown, Dottie's good friend, the librarian -- she was always getting books out of the library -- was saying she hoped we stopped using these dogs, it was terrible what we were doing. Dottie said, "Don't you understand? This is going to save the lives of people!" And she said, "People aren't worth it."

- Of course, there were some very worthy people in your life. Would you point to particular mentors?

Obviously, my father. I take that for granted. I had professors along the way -- my professor of chemistry at the University of Texas, Professor (Harry) Lochte -- that I admire. His son later became a doctor, and later came to work with me, and is a co-author of our first paper on human marrow transplants. And then, as I've told you, I did my first hematology work under Dr. Clement Finch, who lives here in Seattle, retired. He's a brilliant man. He and Dr. Robert Williams, the first chairman of the department of medicine here at the University of Washington -- I knew both of them when I was a medical student in Boston; I knew Dr. Williams when I was a medical student, and he stimulated everybody he came into contact with. They were very important people. They were both workaholics -- much more than me. Dr. Finch and Dr. Williams were notorious for that.

- What would you tell young people who might be interested in medical research?

I've derived tremendous satisfaction from this life. I can't visualize any other, really. Where you can have important problems to work on, that involved lots of scientific disciplines. Where you can have bright, stimulating colleagues to work with. Where it's not only challenging and interesting, but fun. It's satisfying. Here I am, about to be 79, and I'm still coming to work every day, because I can't think of anything I'd rather do.

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