milestone

THE HISTORY OF BONE MARROW TRANSPLANTATION

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In a journey fraught with heartache and persistence, medical research giants paved the way for successful bone marrow transplantation.

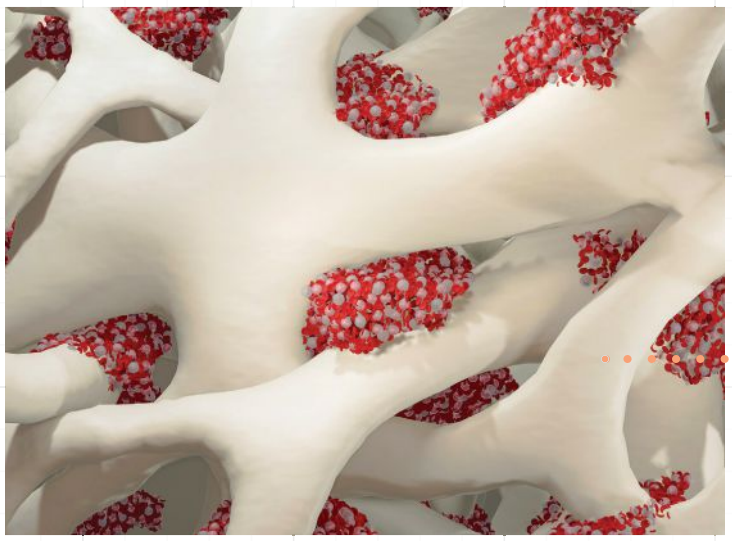
The idea of replacing damaged tissues or cells with healthy versions from a donor has existed since ancient times (1). In 1891, Charles-Édouard Brown-Séquard and Jacques-Arsène d'Arsonval from the Collège de France proposed the idea that bone marrow extracts may be used to treat leukemia and other diseases (2). Yet, it wasn't until the ravages of World War II that tissue transplantation rose to the foreground of medical research.

MID 1950s The first bone marrow transplants

During World War II, doctors applied skin grafts to burn victims and used blood typing for blood transfusions. The war also revealed that high doses of radiation led to bone marrow failure and death (1). A young doctor named E. Donnall Thomas had a revolutionary idea for treating patients with damaged bone marrow. He knew from animal studies in cattle that if a fetus was exposed to genetically different cells in utero, it would develop neonatal tolerance to those cells. He reasoned that if he could use radiation to wipe out the entire damaged bone marrow, it would return the marrow to a fetus-like state receptive to new healthy cells from a donor.

In 1955, Thomas set up his laboratory at the Mary Imogene Bassett Hospital and acquired funding from the Atomic Energy Commission to investigate the possibility of transplanting donor bone marrow (3). In 1956, he put his idea to the test. He treated six patients with leukemia with high doses of radiation and donor bone marrow, but all the patients died within one hundred days post-transplant (4). Thomas tried again in 1957, this time with a bone marrow transplant between twins. While the transplant was initially successful, the leukemia recurred, and the patient later died (5).

One year later, across the Atlantic, an accident at the Vinca Nuclear Reactor near Belgrade, Yugoslavia, exposed six workers to high doses of radiation. Georges Mathé, an oncologist and immunologist from the University of Paris attempted to reconstitute the patients' bone marrow with bone marrow collected from volunteers. Although the patients initially survived, they eventually died due to immune complications, which Mathé later defined as graft versus host disease (6)



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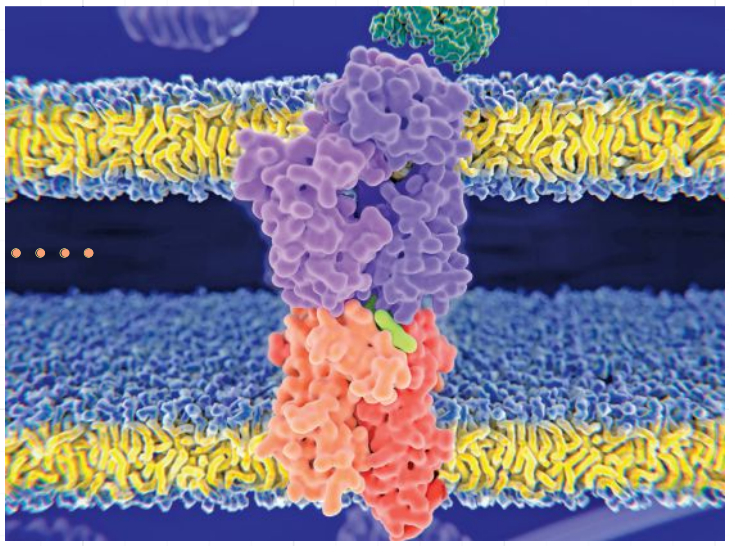
Bone marrow contains a wealth of immune and hematopoietic stem cells.



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Understanding the rules of histocompatibility opened the possibility of performing bone marrow transplants between patients with genetically matched HLAs.

1960s The first bone marrow transplants between non-twin siblings

In 1958, Jean Dausset, an immunologist at the University of Paris discovered human leukocyte antigens (HLAs), cell surface proteins that help the immune system distinguish between self and non-self by presenting antigens to T cells. This gave researchers hope for understanding the complexities of the immune system and overcoming host versus graft disease (7).

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Jean Dausset won the Nobel Prize in Physiology or Medicine in 1980 for his discovery of the human major histocompatibility complex, also known as HLA.

In 1968, Fritz Bach, an immunologist at the University of Wisconsin–Madison, developed the mixed leukocyte culture test to determine the compatibility of HLA genes between a patient and a donor (8). The test worked by combining a patient and a donor's white blood cells. If the patient's cells proliferated in the presence of the donor's cells, this indicated an immune reaction, and the two individuals were not HLA compatible. "Histocompatibility was a critical changer," said Richard O'Reilly, a pediatric oncologist and immunologist at Memorial Sloan Kettering Cancer Center.

Relying on the histocompatibility principles established by Dausset, and the test developed by Bach, Robert Good, a physician at Memorial Sloan Kettering Cancer Center performed the first bone marrow transplant between non-identical siblings (9). As a medical school intern at the time, O'Reilly was invited by his attending physician, Richard Hong, to observe the procedure. As they watched, Hong discussed Good's thoughts on how histocompatibility would allow for the procedure's success. "I trained in immunology in medical school, and I remember listening to this wild idea Robert Good had about the T cell and B cell system, which is now fundamental to immunology," reflected O'Reilly.

The procedure was indeed a success. The pediatric patient was a young boy with a rare immune deficiency that had claimed the lives of 11 other male children in his family. After two rounds of transplants, his sister's bone marrow engrafted, transforming all the blood cells in his body to hers, and he went on to live a normal life. "It just completely changed the whole history of transplants because after that everybody obeyed the rules of finding someone appropriately matched, and there was a concentration on histocompatibility," said O'Reilly.

1973–1977 The first transplants from unrelated donors

Following the histocompatibility principles allowed researchers to identify HLA matches between unrelated individuals. In 1973, a two-year-old boy in England became the first person to receive a bone marrow transplant from an unrelated individual. He was diagnosed with chronic granulomatous disorder, which causes immune system malfunction. His older brother had previously died of the same disease. Upon learning about HLA matches, his mother asked her friends to be tested. Her efforts caught the attention of the local press, prompting others to get tested, and an unrelated HLA match was identified (3). On April 13, 1973, a team led by physician John Hobbs at London's Westminster Children's Hospital successfully performed the transplantation for the boy using this unrelated donor's marrow.

Meanwhile, researchers continued to make strides in characterizing histocompatibility requirements. Bo Dupont, an immuno-geneticist at Memorial Sloan Kettering Cancer Center, discovered that if an individual inherited two loci of the same HLA gene, someone who had inherited just one of those loci would not react to cells from that donor. This allowed Dupont to perform transplants in animals with HLA incompatibilities. It also laid the framework that certain ethnogeographic groups of people tend to inherit certain HLA haplotypes, which made searching for matches more targeted (9).

Dupont, O'Reilly, and Good joined forces in 1977 to perform the first successful HLA-compatible bone marrow transplant between unrelated individuals in North America (10). "I did the transplant, but Bo did literally thousands of mixed leukocyte cultures to identify a donor in Copenhagen for a young child with severe combined immune deficiency who was from Ohio," said O'Reilly.

1979

Matching unrelated donors to treat cancer

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A team led by Donnall Thomas (center back row, wearing a tie and suit) at the Fred Hutchinson Cancer Center performed the first bone marrow transplant between unrelated individuals to treat leukemia.

While bone marrow transplantation saw success in treating patients with immune deficiencies and disorders, researchers still struggled to use the method to treat patients with blood cancers. After his initial attempts at bone marrow transplant treatments for leukemia in humans in the 1950s, Thomas spent a decade investigating bone marrow transplants in dogs before trying the procedure again in humans. However, researchers in the field were still skeptical that bone marrow transplants could treat leukemia. "Others had tried it, and it didn't work. And so they abandoned the field, but Donnall Thomas kept at it," said Frederick Appelbaum, Executive Director of the Fred Hutchinson Cancer Center, where Thomas joined as the first Director of Medical Oncology in 1974.

In 1979, Bob Graves, a veterinarian from Colorado, walked into the Fred Hutchinson Cancer Center and asked to speak with John Hansen, who oversaw HLA typing for bone marrow transplants. He explained that his daughter, Laura, had leukemia and had already undergone multiple chemotherapy treatments, but the disease had returned.

"He took it upon himself to read about HLA, and he understood that while Laura did not match her sisters, he knew that there were different frequencies of different HLA types," said Appelbaum. Graves bet the team that they could find an unrelated HLA match for his daughter. Hansen spoke with Thomas, and they decided they would try.

"A lot of us knew our own HLA types because we served as platelet donors for our patients. I'd given platelet lots of times," said Appelbaum. The team had files of their platelet donors stored in little card boxes, and serendipitously, a laboratory technician at the center who had given platelets previously turned out to be an HLA match for Laura. Thomas' team then performed the first bone marrow transplant between unrelated individuals to treat leukemia (11).

1980–1984

Expanding possibilities and improving transplant outcomes

Initially, the transplant was a success. However, about two years later, Laura's leukemia returned and ultimately caused her death. The Graves family's story inspired other families to reach out to them, seeking help to find HLA matches for their children. That sparked an idea in Graves to develop a national registry of potential bone marrow donors, but it seemed unreasonable to raise enough money to HLA type hundreds of thousands of donors.

During this time, researchers were improving bone marrow transplant outcomes by developing more effective drugs for bacterial, viral, and fungal complications that often killed patients in the first few months post-transplant. In 1980, O'Reilly extended the possibilities of bone marrow transplants to half-matched donors by depleting T cells from donor transplants (9). "It worked in two kids and then a whole flock of kids with severe combined immune deficiency, who are out there doing all sorts of interesting stuff to this present day," said O'Reilly. The therapy also worked for patients with leukemia, and demonstrated by removing T cells, researchers could prevent graft versus host disease.

In 1984, George Santos, an oncologist at Johns Hopkins University pioneered the use of the chemotherapy drug cyclophosphamide as a less damaging alternative to total body irradiation by mitigating host versus graft disease. Santos' work quickly became the new standard in bone marrow transplantation (12).

CREDIT: RICHARD O'REILLY

Richard O'Reilly extended the possibilities of bone marrow transplants to half-matched donors by removing T cells from donor transplants.

1986–PRESENT

Finding a match and propelling discovery

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The National Marrow Donor Program, which later became known as the Be the Match Registry, now lists millions of potential bone marrow donors.

Several years after Laura's death, Appelbaum got a call from one of his colleagues about a patient named Elmo Zumwalt Jr., who had lymphoma and needed a transplant. Zumwalt Jr. was the son of Admiral Elmo Zumwalt, who led the entire naval operation in the Pacific during the Vietnam War. He ordered the release of the herbicide Agent Orange, which was later revealed as a carcinogen, to defoliate riverbanks and prevent hidden attacks.

"His son, who was coming to see me, had been a boat captain in Vietnam and had been heavily exposed to the Agent Orange that his father had ordered. They both knew that is probably why he got his lymphoma," said Appelbaum. While Zumwalt Jr. did not recover, Admiral Zumwalt asked how he could help with the bone marrow transplantation efforts. Appelbaum introduced him to Thomas, who then introduced him to Graves. Together, Zumwalt and Graves convinced the United States Department of Defense to put forward millions of dollars to start the National Marrow Donor Program in 1986, which now lists millions of potential donors.

"Mr. Graves was just extraordinary in terms of getting funds and interest in the development of banks of volunteers who would potentially give a marrow transplant," said O'Reilly. "Now you have literally millions of volunteers around the world who are HLA typed, who said if needed, they would give their marrow. And we're now doing thousands of those transplants a year."

Appelbaum further expanded the field in 1986 with the first documented autologous bone marrow transplantation, in which he replaced localized lymphoma cells with the patient's own healthy cryopreserved cells (13). "We did that in a small group of patients, and of the first eight, three of them turned out to be cured of their lymphoma. Today, there are 15,000 transplants for lymphoma done, and probably 40,000 autologous transplants done worldwide," said Appelbaum.

In 1988, Joanne Kurtzberg, a physician at Duke University Medical Center, transplanted a young patient with Fanconi anemia using umbilical cord blood from his soon-to-be-born younger sister (3). As of 2019, more than 35,000 umbilical cord blood transplants have been performed worldwide (14).

Today, researchers continue to advance the field, but in the early years, the collaborative competition among researchers across the globe made huge leaps and pushed the field forward. While they argued ideas, they propelled each other and recognized good science. "It was something where everybody sort of knew the common goal," said O'Reilly. "Now, we're looking at long term survivals with healthy kids 95 percent of the time."

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