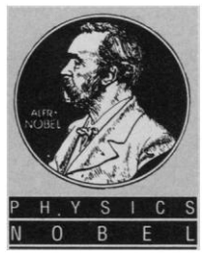
Overcoming Rejection to Win a Nobel Prize

Work begun over 30 years ago has ushered in a new age of medical therapy using transplanted organs and tissue



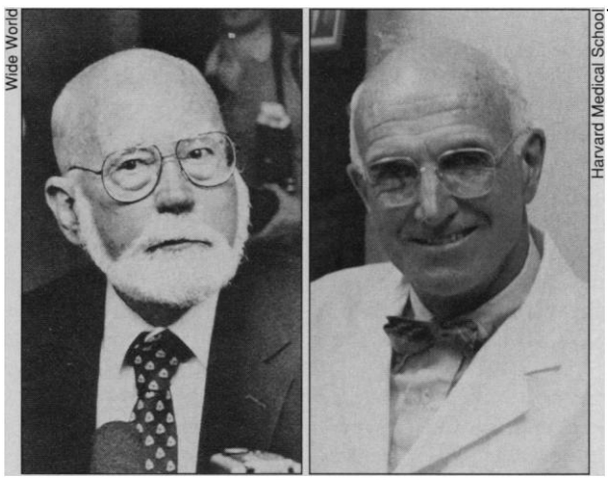
TO THE DELIGHT OF CLINICAL researchers, this year's Nobel Prize in Physiology or Medicine goes to two medical doctors who led the way in using transplanted organs and tissue to treat human patients. Joseph E. Murray, 71, emeritus professor of surgery at Harvard Medical School, performed the first successful kidney transplant in a pair of identical twins. E. Donnall Thomas, 70, of the Fred Hutchinson Cancer Research Center in Seattle, first deomonstrated that bone marrow cells could be safely transplanted from one individual to another. "They were really pioneers," says Emil Frei, III, director of the Dana-Farber Cancer Institute. "They opened the field that everybody plays in today."

What makes Frei and others particularly pleased is that Thomas and Murray are representatives of what some fear is a diminishing breed: physicians who have spent their careers in clinical research. In recent years, most medicine Nobels have been awarded for more basic research. "I was totally surprised by this," says Thomas. "I really felt the prize would never go to patient-oriented research."

Thomas and Murray helped turn what had been a medical pipe dream into a reality. From the beginning of this century researchers had known that there was some "biological force" preventing the transplantation of organs between individuals. But chance threw Murray an opportunity to overcome that force. While a resident at the Peter Bent Brigham Hospital (now Brigham and Women's Hospital) in the late 1940s, Murray joined a team of clinicians who were studying end-stage renal disease. The Harvard researchers, led by David Hume and John Merrill, had been experimenting with transplanting a third kidney taken from a cadaver into the thigh of patients with renal failure. Although the organ wasn't instantly rejected by the recipients' immune system, it was obviously an awkward approach. Murray began developing surgical techniques in dogs that would make a true replacement possible.

Then, in late 1954, Richard Herrick turned up at Peter Bent Brigham Hospital with end-stage renal failure. His identical twin brother Ronald Herrick was prepared to donate a kidney and Murray reasoned that, since Ronald's healthy kidney would be genetically identical to Richard's diseased kidney, there should be no problem with rejection. The operation, performed on 23 December 1954, was a "spectacular success," says Murray.

Murray spent the next decade looking for ways to overcome the rejection problem. The key insight, says Murray, came from work by two Boston hematologists, William Dameshek and Robert Schwartz, who demonstrated that the compound 6-mercaptopurine would prevent a host animal from rejecting a foreign protein. Working with George Hitchings and Gertrude Elion of Burroughs Wellcome (themselves winners of the Nobel Prize in 1988), Murray developed a drug regimen based on 6-mercaptopurine that suppressed the immune system and allowed the transplanted kidney to establish itself in its new host. Murray performed the first successful transplant from an unrelated donor in 1962.



Transplant pioneers. *E. Donnall Thomas (left) and Joseph Murray win one for clinical research.*

The excitement generated by the successful organ transplants "led to the enormous increase in research" in the rejection phenomenon, says immunologist David H. Sachs of the National Cancer Institute. Specifically, immunologists began to unravel the nature of the major histocompatibility complex (MHC) that is not only important in rejecting foreign tissue but, as later research has shown, plays a central role in other immune reactions.

Understanding the MHC turned out to be crucial for the success of the bone marrow transplants pioneered by Thomas. Bone marrow cells are the precursors of all cellular components of blood, including cells responsible for cellular immunity. When these marrow cells stop functioning, as in aplastic anemia, or become cancerous, as in certain forms of leukemia, the body's immune defenses are decimated and severe illness and death usually follow.

Thomas, who began his medical career with Murray at Harvard, reckoned that if he could first eradicate the diseased marrow and then replace it with healthy marrow cells, he could restore patients with these diseases to health. But he faced two major hurdles. First, he had to overcome the host's own immune defenses against the foreign tissue. Then, if the new bone marrow started producing immune cells, these new cells might attack their new host, causing a kind of autoimmune reaction called graft-versus-host disease, a potentially fatal complication.

In 1963, Thomas moved to the University of Washington and began assembling a team of researchers, including Rainer Storb and Dean Buckner, to work on overcoming these problems. Their technique involved a combination of whole-body irradiation to wipe out a patient's own marrow cells and a drug called methotrexate to suppress an immune response. They also began typing tissues based on MHC, vastly improving the odds of finding suitable donors. Since those early experiments, the Seattle team has made steady improvements in their techniques. The results have been remarkable: "What was once a high risk, last ditch operation with a 12 or 13% survival is now a curative approach which works in 40 to 50% of patients with leukemia," says Richard J. O'Reilly, chief of marrow transplantation at Memorial Sloan Kettering Cancer Center.

This year's prize sends a useful message, says Emil J. Freireich, director of adult leukemia research at M. D. Anderson Hospital in Dallas: "It acknowledges that physicians can do the same kind of high-quality science Ph.D.'s can do." And that should give a boost to policy-makers who are worrying about attracting enough physicians into careers in science. ■ JOSEPH PALCA