

## The Early Days of Transplantation

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Although the fantasy of performing tissue and limb transplantation can be traced to antiquity, not until this century was the possibility of engrafting vital organs broached. The attempt began with failed kidney xenograft trials in Europe,<sup>1</sup> followed by the first recorded attempt at a renal allograft in 1936 by the Russian physician Y. Y. Voronoy. The modern era of transplantation truly began in 1944, when Peter Medawar demonstrated that allograft rejection is an immunologic process.

In a burst of clinical interest between 1950-1952, French surgeons René Kuss, Charles Dubost, and Marceau Servelle independently described essentially the same pelvic renal transplantation operation that is standard today; in 1952 Louis Michon and Jean Hamburger reported the first live kidney donation (mother to son).<sup>2</sup>

Immunosuppression was not used for these recipients, nor for those of David Hume at the Peter Bent Brigham Hospital, Boston, Mass, who transplanted allografts subcutaneously in the thigh.<sup>3</sup> Consequently, the few kidneys that had functioned up to the end of 1954 were doomed to be rejected. In the 1930s E. C. Padgett and J. B. Brown had shown that genetic identity was essential to permit the permanent exchange of skin in monozygotic twins. In a bold application of this knowledge, a team led by Joseph Murray and John Merrill successfully transplanted an identical twin kidney on December 23, 1954.

On January 24, 1959, the same Boston team successfully transplanted a kidney between dizygotic twins.<sup>4</sup> The successful breaching of such a genetic barrier makes this the single most important case in the history of transplantation. The claim was enhanced a few months later when a similar case was reported by Jean Hamburger's team in Paris. The recipients, who received total-body irradiation for immunosuppression, survived 20 and 26 years, respectively, before dying of cancer. Using irradiation, Hamburger's group<sup>5</sup> and a second Paris team headed by Kuss<sup>6</sup> produced four additional long-surviving recipients between 1959 and 1962, this time with more distant donors—a non-twin sibling, a cousin, and in the two Kuss cases, nonrelatives.

While encouraging, these six cases were exceptions. Unable after 11 more attempts to duplicate his 1959 achievement, Murray took an alternative historical step. On April 5, 1962, he transplanted an unrelated renal allograft that functioned for 17 months.<sup>7</sup> This was the first human example of successful chemical immunosuppression using azathioprine.<sup>8</sup>

Expectations from Boston and Paris generated a world-wide ripple that did not spare me in Chicago, where I had been experimenting with canine liver transplantation. By the end of 1960, I concluded that liver transplantation could never be tried until consistent success in renal grafts was achieved. In 1961 I joined William Waddell, at the University of Colorado School of Medicine, to begin a kidney transplant program that would be a forerunner for our liver program.

Which method of immunosuppression to use for our

first kidney recipients remained undecided. Although total-body irradiation was considered dangerous and relatively ineffective, the best results were being obtained by Hamburger and Kuss in France,<sup>5,9</sup> who sporadically gave adrenal corticosteroids to their irradiated patients or even—in one of Kuss' 1960 patients—6-mercaptopurine, the drug from which azathioprine is derived.

Our contribution was to combine azathioprine with prednisone.<sup>9</sup> Rejection could be reversed with prednisone in most azathioprine-treated recipients and, in many, the immune barrier could be reduced without general immune deficiency. During the year after the repeatedly successful use of this drug combination became known, nearly 50 US kidney transplant programs were formed. These "double-drug cocktails" also justified the first liver transplant trials in Colorado, beginning on March 1, 1963. When these failed, liver replacement suffered its own protracted birth pangs. The "baby" was finally delivered in 1967, with several recipients surviving more than 1 year. This success was quickly followed by attempts at other organ transplants.

Although transplantation of the liver and heart was sporadically successful during the next dozen years, the results of these procedures were unpredictable. The introduction of cyclosporine in 1978<sup>10</sup> and its systematic combination with prednisone<sup>11</sup> was followed by a proliferation of liver, cardiac, pancreas, lung, and intestinal transplant programs—as well as increased use of cadaveric kidneys. The consequence, by the late 1980s, was a shortage of all cadaveric organs and a drift back to live donors.

When transplantation procedures finally became routine, the social ramifications thrust a range of unfamiliar problems on health care providers. Ironically, the scientific and medical problems of transplantation have resolved more ingeniously and definitively than derivative ones associated with the dissemination of the fruits of scientists' labor of love.

### References

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