



Review

A brief history of clinical xenotransplantation

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HIGHLIGHTS

- Clinical xenotransplantation has involved skin, corneas, and blood.
- Nonhuman primate kidney and heart grafts were transplanted into patients.
- The first clinical attempt at pig islet transplantation was in 1993.
- There are advantages in the use of the pig as the source of organs and cells.

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ABSTRACT

Between the 17th and 20th centuries, blood was transfused from various animal species into patients with a variety of pathological conditions. Skin grafts were carried out in the 19th century, with grafts from a variety of animals, with frogs being the most popular. In the 1920s, Voronoff advocated the transplantation of slices of chimpanzee testis into elderly men, believing that the hormones produced by the testis would rejuvenate his patients. In 1963–4, when human organs were not available and dialysis was not yet in use, Reemtsma transplanted chimpanzee kidneys into 13 patients, one of whom returned to work for almost 9 months before suddenly dying from what was believed to be an electrolyte disturbance. The first heart transplant in a human ever performed was by Hardy in 1964, using a chimpanzee heart, but the patient died within 2 h. Starzl carried out the first chimpanzee-to-human liver transplantation in 1966; in 1992 he obtained patient survival for 70 days following a baboon liver transplant. The first clinical pig islet transplant was carried out by Groth in 1993. Today, genetically-modified pigs offer hope of a limitless supply of organs and cells for those in need of a transplant.

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The concept of xenotransplantation (cross-species transplantation) is not new, and there have been numerous clinical attempts during the past 300 years or more [1–3].

1. Mythology

A review of Greek mythology and of religious tracts—particularly, for example, from the Hindu religion—draws attention to the fact that humans have been interested in the possibility of merging physical features from various animal species for hundreds of years. For example, the lamassu has been selected as the mythological figure to represent the International Xenotransplantation Association and its official scientific journal, *Xenotransplantation*.

The late Keith Reemtsma pointed out that possibly one of the earliest examples of xenotransplantation was the attempt by Daedalus and his son, Icarus, to fly across the sea from Crete to mainland Greece with the help of bird wings attached to their arms [4]. Icarus failed in the attempt, but Daedalus made the journey successfully.

2. Blood xenotransfusion

If we look beyond the realm of mythology and legend, we come to the 17th century, when Jean Baptiste Denis began the clinical practice of blood transfusion from animals to humans [5]. Perhaps not surprisingly, the results were mixed. As a result, xenotransfusion was banned in France for a number of years.

3. Skin xenotransplantation

In the 19th century, skin grafts became relatively popular between various animal species and humans [6,7]. The grafts were either free or pedicle grafts. Pedicle grafts were complicated because they required the donor, e.g., a sheep, to be strapped immobile to the patient for several days, during which time the graft would reputedly be vascularized by the recipient. If this occurred, the graft could be disconnected from the donor. It is almost certain that none of these grafts was in any way successful, although some “successes” were reported.

The fact that many of the species used as donors—sheep, rabbits, dogs, cats, rats, chickens, and pigeons—had hair, feathers, or fur growing from the skin did not appear to disconcert the surgeons involved, but the trend was to use animal species in which these accoutrements were not present. The ideal graft would appear to have been from frogs, which were sometimes “skinned alive.” It is possible that some of these grafts were “successful” in that, when used to cover a skin ulcer, they provided protection, at least for a number of days, while the ulcer healed beneath the graft. However, probably none of the grafts actually became permanent.

4. Corneal xenotransplantation

Remarkably, in 1838 the first corneal xenotransplantation (from a pig) was performed in a patient, whereas the first corneal

allograft (human-to-human) was not carried out until more than 65 years later, in 1905. The field of corneal xenotransplantation has been reviewed by Hara and Cooper [8,9].

5. The surgery of blood vessel anastomosis

More scientific efforts had to wait until the 20th century, when the French experimental surgeon, Alexis Carrel, working first in France and subsequently in North America, developed surgical techniques for anastomosing blood vessels, which enabled organ transplantation to be carried out successfully for the first time. For this work he was awarded the Nobel Prize in 1912. He developed an interest in cross-species transplantation from an experimental perspective.

6. “Rejuvenation” by cell xenotransplantation

A few years later, Serge Voronoff, a Russian émigré working in Paris, developed the concept of transplanting cells that produced a hormone in which the recipient was deficient. This is another example of a visionary scientist who was ahead of his time. Today we are doing exactly what he envisaged, namely transplanting human pancreatic islets that produce insulin in patients with severe type 1 diabetes. In view of the limited number of human pancreases that become available each year, there is a growing interest in using pig islets for this purpose.

Voronoff’s main interest, however, was in reversing the effects of aging in elderly men who had lost their “zest for life.” He carried out a significant number of chimpanzee or baboon testicular transplants in male human recipients [10]. His technique was to slice up the animal testicle and insert the slices into the recipient’s testicle. The procedure became popular on both sides of the Atlantic, and several hundred of these operations were performed. It is inconceivable that any of them had any beneficial effect whatsoever, except psychological, but there were reports of remarkable “rejuvenation” of men who reported much increased energy after the operation. Surprisingly, reports of complications appear to have been uncommon.

The concept of transplanting glandular tissue to produce hormones that would benefit the recipient was continued in the United States by a much less scientific doctor, John Brinkley, whose work was carried out largely in Kansas and Texas [11]. His chosen donor was the goat, as he had been convinced by a local farmer of its sexual potency.

7. Kidney xenotransplantation

By the 1960s, Keith Reemtsma (Fig. 1)—at that time at Tulane University in Louisiana—hypothesized that nonhuman primate kidneys might function in human recipients and thus be a successful treatment for renal failure. At that time, the concept of kidney transplantation had been established largely by French and American surgeons, but the availability of kidneys from deceased humans was extremely limited and chronic dialysis was not yet being

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