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Review Article

History of xenotransplantation

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Abstract: The present historical review reports the clinical experiences of transplantations from animal to human. The first transplantation attempts were made without any knowledge of the species barrier. The pioneers of xenotransplantation realized xenotransfusions as early as the 16th century, then cell and tissue xenotransplantations in the 19th century. At the beginning of the 20th century, xenotransplantation of testicles became the latest craze. At the same time, and later in the 1960s, organ xenotransplantations were attempted, with disappointing results. Mathieu Jaboulay, Serge Voronoff, Keith Reemtsma, James Hardy, Denton Cooley, Thomas Starzl, Christiaan Barnard and Leonard Bailey were among the pionneers of xenotransplantation. Recent trials concerned above all tissue and cell xenotransplantations. Nowadays, with encapsulation, transgenesis, and cloning, great advances have been made for controling xenograft rejection, but ethical questions linked to the risk of infections have become a major pre-occupation within the scientific community and the general population.

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Introduction

The history of xenotransplantation shows that crossing the species barrier has not always been a concern; in fact, the first transplantation experiments in humans used animal organs more often than human organs. The present review reports the clinical experiences of transplantations from animal to human.

Chimeras in folklore

Before xenotransplantations were envisaged, the folklore already included stories of half man–half beast chimeras. Pre-historic cave paintings rarely represent people but, in the Lascaux cave in France (ca 15 000 BC), the only representation of a human being shows a man with a head of a bird (Fig. 1). The gods of Ancient Egypt are often represented with the body of a man and the head of an animal: Anubis has the head of a jackal; the Great Sphinx of Giza (ca 2500 BC) is a lion with the head of a woman. The first description of a xenotransplantation is reported in Indian mythology, in a text in Sanskrit from the 12th century BC [1–3]. Shiva and Parvati were Indian gods. According to the legend, their child Ganesha was born while Shiva had gone hunting. As in many myths, Ganesha was born a giant. When Shiva returned and saw this stranger with his wife, he beheaded him. Parvati told him that he had just killed his own son and she threatened to destroy the universe if Ganesha was not resuscitated. Shiva, unable to replace Ganesha's head, ordered his servants to bring him the head of the first living being they meet. And so Ganesha was returned to life with a head of an elephant. In Ancient Greece, Minotaur was a man with the head of a bull, Esfinge was a winged lion with the head of a woman, Centaurs were horses with the trunk and head of a man. In Homer's Odyssey (ca 750 BC), the companions of Ulysses were transformed into half man-half swine chimeras by Circe the sorceress. Closer to us, the legends of werewolves and vampires (man to bat) evoke hybrid beings, half man–half beast.

First reports on transplantation: allotransplantations

The earliest reports on transplantations concern allotransplantation experiments. Ca 600 BC, an Indian surgeon, Susrata, supposedly used skin flaps to replace cut-off noses (the nose was often cut-off as a punishment) [4]. Ca 255 BC, a famous Chinese surgeon, Pien Ch'iao, tried to restore the Ying and

Fig. 1. Man with a head of a bird in the Lascaux Cave in France, ca 15 000 BC. By courtesy of Norbert Aujoulat, © National Centre of Pre-history, France.

the Yang between two soldiers by exchanging their hearts while they were anaesthetized with "magnificent and powerful drugs" [5]. Both patients were said to have completely recovered. In the second century, the concept of transplantation was first evoked by a Chinese surgeon, Hua-To, who replaced sick organs by healthy organs while making it clear that his purpose was to cure patients [6]. The most famous legend concerning early transplants probably is the "miracle of the black leg". In the 3rd century AD, in Rome, Italy, two Syrian doctors, Cosmas and Damian (died in 287) amputated the cancerous leg of a sacristan suffering from gas gangrene and replaced it with the leg of a dead black man [7,8]. In the 16th century, an Italian surgeon, Gaspare Tagliacozzi, took up and improved the nose graft techniques of Susrata [9]. He noted the difficulties associated with transplantation.

Although these attempts did not cross the species barrier, it is likely that they were unsuccessful. However, from ancient times, the idea was born to prolong or to improve life by replacing a failing organ by an organ taken from a healthy donor and immediately transplanted [3].

The pioneers of xenotransplantation

The first xenotransplantations were made with cells and tissues (blood, bone, skin, testicle, etc.) (Tables 1 and 2); xenotransplantations of organs (Tables 3, 4 and 5) came later because no technique was available to control bleeding after resection of the sick organ and to restore circulation after transplantation [10].

Xenotransfusions

The first documented description of a transfusion to man is a xenotransfusion realized on June 15, 1667, in Paris. Jean-Baptiste Denis, a French

Table 1. Xenotransfusions

Year (of the report)	Author	Place	Animal source	Number of cases	References
1667	Denis	Paris, France	Lamb	A 15-yr-old man	[11–14]
			Lamb	A 45-yr-old man	
			Calf	A 34-yr-old man	
1668			Lamb	A paralyzed woman	
1667	Lower	London, UK	Lamb	A 22-yr-old man	[15–17]
1872	Albini	Italy	Sheep	A woman (twice)	[25]
1874	Hasse	Nordhausen, Germany	Lamb	31 cases	[26]
1874	Gradle	Chicago, IL, USA	Lamb	2 men	[27]
2000	Baruah	Sonapur, India	Pig	A 22-yr-old man	[103,104]

Table 2. Tissue and cell xenotransplantation – the pioneer's era

Year (of the report)	Author	Place	Tissues or cells	Animal source	Number of cases	References
1501	Baha' al-Dawla	Iran	Bone	Dog	One case	[34]
ca 1501	Ala-ul-Din	Herat, Afghanistan	Bone	Dog	One case	[34]
1668	Job van Meeneren	The Netherlands ?	Bone	Dog	A Russian	[31,32]
1875	Houzé de l'Aulnoit	France	Cheeks	Rabbit	45 cases	quoted by [6]
1893	Williams	Bristol, UK	Three fragments of pancreas	Sheep	A 15-yr-old diabetic child	[37]
1889	Brown-Séquard	Paris, France	Extract of crushed testicles	Dog and Guinea pig	?	[38,39]
1920 to 1951	Voronoff	Paris, France	Testicles, ovaries	Ape	More than 2,000	[40,41]

Table 3. Kidney xenotransplantation modified from Taniguchi and Cooper [59]

Year	Author	Place	Animal source	Number of cases	Survival	References
1905	Princeteau	Bordeaux, France	Rabbit (slices)	1 child	16 days	[45]
1906	Jaboulay	Lyon, France	Pig	48-yr-old woman	3 days	[46]
			Goat	50-yr-old woman	3 days	[46]
1910	Unger	Berlin, Germany	Macaque	21-yr-old woman	32 h	[47]
1913	Schonstadt	?	Monkey	Young girl	60 h	Quoted by [48]
1923	Neuhof	New York, USA	Lamb	1 patient	9 days	[49]
1963	Hitchcock	Minneapolis, MN, USA	Baboon	65-yr-old woman	4 days	[66]
1963	Reemtsma	New Orleans, LA, USA	Rhesus monkey	43-yr-old man	63 days	[67–69]
1964	Reemtsma	New Orleans, LA, USA	Chimpanzee	23-yr-old woman	9 months	[67]
1964	Reemtsma	New Orleans, LA, USA	Chimpanzees	12 patients	63 to 270 days	[70]
1964	Starzl	Denver, CO, USA	Baboons	6 patients	19 to 98 days	[73]
1964	Hume	Richmond, VA, USA	Chimpanzee	1 man	1 day	[74]
1964	Traeger	Lyon, France	Chimpanzees	3 patients	<49 days	[75]
1966	Cortesini	Rome, Italy	Chimpanzee	19-yr-old man	31 days	[76]

Twelve publications reported one or more kidney xenotransplantations.

Table 4. Heart xenotransplantation modified from Adams [64], Taniguchi and Cooper [59]

Year	Author	Place	Animal source	Number of cases	Survival	References
1964	Hardy	Jackson, MS, USA	Chimpanzee	68-yr-old man	90 min	[72]
1968	Ross	London, UK	Pig	48-yr-old man	4 min	[141]
				?	Immediately	
1968	Cooley	Austin, TX, USA	Sheep	48-yr-old man	10 min	[78]
1969	Marion	Lyon, France	Chimpanzee	Young woman	``Quickly''	[80]
1977	Barnard	Cape Town, South Africa	Baboon	25-yr-old woman	5 h 30	[87]
			Chimpanzee	60-yr-old man	4 days	
1984	Bailey	Loma Linda, CA, USA	Baboon	14-day-old baby	20 days	[89]
1992	Religa & Czaplicki	Sosnowiec, Poland	Pig	31-yr-old man	23 h	[96]
1996	Baruah	Sonapur, India	Pig	32-yr-old man	7 days	Unpublished [100]

There have been eight heart xenograft experiments. Donors were chimpanzees in three cases, baboons in two cases, pigs in two cases, and sheep in one case. The longest survival was 20 days (baby Fae). To this attempts, it is necessary to add the two experiments by Donald Ross who inserted a pig heart into an extracorporeal circulation and perfused a pig heart with human blood.
There has never been any lung xenotransplantation experiment [65].

Table 5. Liver xenotransplantation modified from Taniguchi and Cooper [59]

Year	Author	Place	Animal source	Number of cases	Survival	References
1969	Starzl	Denver, CO, USA	Chimpanzee	28-month-old child	9 days	[81]
1969	Bertoye & Marion	Lyon, France	Baboon	22-yr-old woman	>4 months	[79]
				7-month-old boy	39 h	
1970	Leger	Paris, France	Baboon	23-yr-old woman	72 h	[84,85]
1970	Giles & Starzl	Denver, CO, USA	Chimpanzee	7-month-old child	26 h	[82]
1971	Pouyet & Bérard	Lyon, France	Baboon	28-yr-old woman	<2 days	[86]
				34-yr-old woman	<2 days	
1974	Starzl	Denver, CO, USA	Chimpanzee	A child	14 days	[83]
1992	Makowka	Los Angeles, CA, USA	Pig	26-yr-old woman	34 h	[97]
1992	Starzl	Pittsburgh, PA, USA	Baboon	35-yr-old man	70 days	[93]
1993	Starzl	Pittsburgh, PA, USA	Baboon	62-yr-old man	In a coma for 26 days	[95]

There have been 11 liver xenograft attempts. The longest survival was 70 days.

physician, doctor of King Louis XIV, and Paul Emmerez, surgeon, transfused the blood of a lamb to a 15-yr-old young man [11,12]. The man, with severe fever, was cured. Denis and Emmerez thus proved ''the effects that the mixture of different bloods could produce''. Supported by this ''success'', Denis realized other xenotransfusions. One was a xenotransfusion of calf blood to a 34-yr-old mentally ill man named Antoine Mauroy, in the hope that this would cure his madness. In December 1667, after a first success, the signs of madness reappeared and two other transfusions were made. After the last one, on Monday December 19, 1667, the patient died the following night [13,14]. Prompted by the detractors of Denis, the wife of the deceased patient pressed charges. On April 17,

1668, the Court concluded that the patient had been poisoned with arsenic by his wife and it exonerated Denis from any responsibility. However, the Court decided that "in the future no transfusion could be made to man without prior authorization from a doctor from the Paris Faculty of Medicine". On January 10, 1670, the French Parliament prohibited transfusions, soon imitated by the English Parliament, then by the Pope.

Having realized the first transfusion between two dogs on February 1665 in Oxford, Richard Lower transfused the blood of a lamb to a 22-yr-old patient named Arthur Coga on November 23, 1667, in London [15–17]. The experience was a success. One of the objectives was to estimate which qualities could be passed on by the instilled blood. Coga sent a humorous letter to the Royal Society [18]: "Sheep's blood possess a symbolic relationship with the blood of Christ, since Christ is the lamb of God". In spite of the prohibitions from the Courts, some documents describe xenotransfusions that were made after 1670. In 1679, the frontispiece of *De ortu et occasu transfusionis sanguinis* of Georges Abraham Merklin includes a copperplate engraving showing a transfusion between an animal (a calf or a goat) and a man [19].

In 1816, a Scottish physician in Edinburgh, John Henry Leacock, showed, based on eight trials between animals, that donor and recipient must be of the same species and recommended interhuman transfusion [20–22]. In 1818, aware of Leacock's works, a British obstetrician, James Blundell, in London, discovered the incompatibility of heterologous blood after repeated transfusions of dogs with sheep blood. Later that year, he realized the first documented human blood transfusion to a woman with post-partum hemorrhage. The patient died [23,24].

In 1872, an Italian, Giuseppe Albini, described how he transfused sheep blood twice to a woman [25]. In 1874, in Nordhausen, Germany, Oscar Hasse reported 31 cases of transfusion from lamb to human [26]. The same year, Henry Gradle (Chicago, IL, USA) reported two cases of transfusion of lamb blood to two men [27].

For the last few years, research has been focused more towards oxygen carriers [28]. Recently, because of the shortage of fresh blood, xenotransfusions were again evoked by Alex Zhu (New York, NY, USA) [29] and encouraged by David Cooper (Pittsburgh, PA, USA) [30].

Tissue xenografts

In 1668 (posthumous publication), a Dutchman, Job van Meekeren, reported a successful bone xenotransplantation made by a Russian; a bone from the skull of a dog was used to repair a human skull [31,32]. The claim that this was the first bone xenotransplantation ever made was rejected by Rodriguez Umana who reported a precedent [33]. In 1501, an Iranian surgeon, Muhammad Baha' al-Dawla, published *The Quintessence of Experience*, in which he described his medical experience. He reported the surgical treatment of osteomyelitis of the skull: during surgery, the surgeon excised a portion of the sick bone and replaced it by a piece of bone from a dog. A slice of cucumber was used to protect the brain. The same author reported the use in Herat, Afghanistan, by an Indian surgeon, Ala-ul-Din, of a fresh dog skin for a patient with eczema over the whole head [34].

In 1771, a Scottish surgeon and anatomist, John Hunter, in his first treatise *Natural History of Human Teeth*, described the transplantation of a human tooth to the crest of a cock. In 1778, he used the term "transplant" for the first time [35]. In 1804, an Italian, Giuseppe Boronio, cut some skin fragments from a sheep and, several hours later, successfully transplanted them onto the back of the same sheep, in another place; quoted by Kuss [6]. Then, he discovered the limitations of xenotransplantation when he found that cow-to-mare transplantations failed. In 1863, Paul Bert (Fig. 2), a French jurist who became a doctor and worked with Claude Bernard, published a doctoral thesis entitled *On Animal Transplantation*. He demonstrated the feasibility of autotransplantation (tails of rats placed under the skin of the same animal

Fig. 2. Paul Bert (1833 to 1886). By courtesy of © Bibliothèque Interuniversitaire de Médecine, Paris.

survive). About xenotransplantation, he showed that blood cross-circulation is possible between two rats but not between a rat and a pig. He concluded by recommending avoiding transplantations between subjects of different species, notably between an animal and a man [36]. In 1875, Houzé de l'Aulnoit made cutaneous transplantations using rabbit cheeks and reported five successes in 45 experiences; quoted by Kuss [6]. In 1893, 28 yr before the discovery of insulin, Watson Williams (Bristol, UK) realized the first transplantation of three fragments of sheep pancreas to a 15-yr-old diabetic child [37]. At first a decrease in glycosuria was observed, but the child died 3 days later.

Testicle xenografts

Testicle grafts have a special place in the interest for xenotransplantations, because of their use for "human revitalization transplantation", a harbinger of endocrinology [38]. Their relative success can be explained by the fact that these glands are immunologically protected.

In 1889, a French-American physician and physiologist, Charles-Edouard Brown-Séquard (Fig. 3) (Paris, France), at the age of 72 yr, injected himself subcutaneously with an aqueous extract of crushed testicles from dog and guinea pig [38,39]. These injections were said to have restored his physical strength and capacities that age had decreased. So doing, Brown-Séquard created opotherapy, a medicine based on juices (from the Greek *opos*, juice), the ancestor of endocrinology. Since that time, numerous drugs made from crushed animal organs have been marketed. Nowadays, extracts of thyroid and pancreas are still used in the palliative treatment of hypothyroidism and exocrine pancreatic insufficiency.

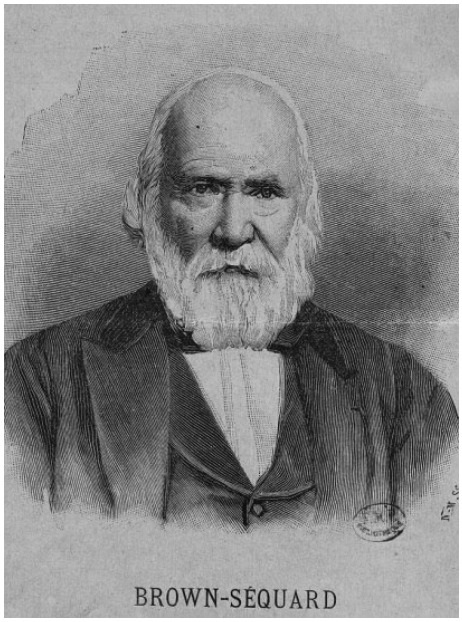

Fig. 3. Charles Edouard Brown-Séquard (1817 to 1894). By courtesy of © Bibliothèque Interuniversitaire de Médecine, Paris.

Fig. 4. Serge Voronoff (1866 to 1951). Photo extracted from the book "Greffe de revitalization humaine" written by Dartigues, Paris, 1925.

With Serge Voronoff (Fig. 4) (Paris, France), endocrinotherapy became a surgical procedure. Born in Russia in 1866 and granted French citizenship in 1895, Voronoff wanted to rejuvenate man by transplanting testicles of apes: chimpanzees and baboons [40,41]. He learned the surgical procedures of transplantation with Alexis Carrel and invented a new type of graft (which he called homografts, although today the term homograft refers to an allograft), i.e. grafts in which the donor belongs to a sister species. On June 12, 1920, he realized the first transplantation of chimpanzee testicles to a man: slices of testicles were placed in the scrotum. Three years later, 43 men had received a testicle homograft [42]; there were 500 in 1930. Women received ovaries of female apes for the treatment of menopause. More surprising still, Voronoff transplanted a woman's ovary into a female chimpanzee named Nora, whom he then inseminated with human sperm, unsuccessfully; Nora was to become the subject of a novel [43]. At his death in 1951, Voronoff had transplanted ape tissues to 2000 human patients.

Already in his time, Voronoff worried about the supply of apes. He envisaged the creation of ape houses in French Guinea to rear apes for expor-

tation. Denigrated by the scientific community and the public, Voronoff gave up transplantation. However, he must be recognized as the first person to describe the difficulties linked to an adequate supply of apes.

Organ xenografts

The main requirement for the success of organ transplantation was to restore the vascularization of this organ by a technique called anastomosis (from Greek *ana*, to join, and *stoma*, mouth: to join mouth-to-mouth). In 1532, in *Pantagruel*, François Rabelais described the reimplantation of Epistemon's head by Panurge and he underlined the necessity of an anastomosis [44]. Two Frenchmen, Mathieu Jaboulay and his pupil Alexis Carrel, pioneered this technique. Logically, the kidney was the organ most transplanted by the pioneers of transplantation: it is a paired organ, vascularized by a single artery, and its proof of function is readily given by urine production [3].

In 1905, a child presenting signs of acute renal failure was treated by Princeteau (Bordeaux, France) who carried out a nephrotomy and included in the kidney two slices of a rabbit kidney. The production of urine increased but, after 16 days, the child succumbed from lung congestion. [45].

Mathieu Jaboulay (Fig. 5) (Lyon, France) perfected the technique of vascular anastomosis and he used it to make, on January 24, 1906, a heterotopic transplantation of the kidney of a pig killed 3 h earlier to the bend of the elbow of a 48-yr-old woman [46]. The same day and the next, he collected 1.5 l of urine but, on the third day, he was forced to remove the kidney because of thrombosis. On April 9, 1906, he transplanted a goat kidney to the bend of the elbow of a 50-yr-old nephrectomized woman [46]. The result was the same: the kidney had to be removed after 3 days. This transplantation is often reported as being the first true xenotransplantation experiment and even the first organ transplantation experiment. At that time, it was called heterotransplantation. At the end of his article, Jaboulay concluded, ''heterografts probably create conditions that promote blood coagulation, which is avoided by autografts''.

In 1909 (published in 1910), Ernst Unger (Berlin, Germany) attempted to transplant the kidneys of a macaque onto the thigh of a 21-yr-old woman who survived for 32 h [47]; an autopsy showed venous thrombosis. In 1913, Schonstadt transplanted the kidney of a Japonese monkey to the arm of a young girl suffering from renal failure caused by poisoning; quoted by Kuss [6] and Morel [48]. After producing a few drops of urine, the patient died 60 h after surgery. In 1923, Harold Neuhof (NY, USA) transplanted a lamb kidney to a man with mercury poisoning; the patient survived for 9 days [49]. No other experiment was to be attempted for the next 40 yr.

Fig. 5. Mathieu Jaboulay (1860 to 1913).

The contemporary period

The failures of early transplantation experiments were directly caused by the absence of immunosuppression; the arrival of immunosuppressive drugs rekindled interest in transplantation.

Notion of species barrier

After an interruption of 40 yr, xenotransplantation experiments resumed in 1964 and sporadically in the 1970s, but constant failures lead to a new interruption that lasted for almost 20 yr, leaving the stage to the search for a better approach to immunosuppression. Real progress came only with the discovery of cyclosporine.

In 1961, Peter Gorer (London, UK) proposed to replace the term ''heterotransplantation'' with ''xenotransplantation'' when referring to transplantations realized between a donor and a recipient belonging to two different species [50]. In 1965, Ben Eiseman (Denver, CO, USA) showed that a heterologuous liver survived better ex vivo with perfusion than in vivo and he concluded that better

Fig. 6. Sir Roy Calne (born 1930). Photo kindly provided by Sir Roy Calne.

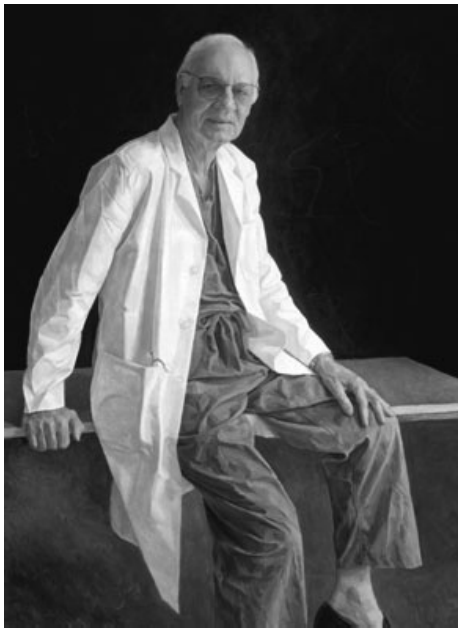

Fig. 7. Keith Reemtsma (1925 to 2000). By courtesy of Judy Reemtsma, Dr Reemtsma's widow and Sarah Belchetz-Swenson. Oil 97 × 71-cm © 1996 Sarah Belchetz-Swenson Collection, College of Physicians and Surgeons of Columbia University, with permission.

immunosuppression was needed [51]. In 1965, Keith Reemtsma distinguished the terms heterograft and xenograft: heterograft must be used to "designate grafts along the lines of species, genus and family" and xenograft to designate "transplants between individuals of greater genetic disparity" [52]. In 1966, Robert Perper and John Najarian showed that hyperacute rejection is faster when the donor and the recipient belong to species farther away in the zoological classification [53, 54]. In 1968, the British surgeon, Sir Roy Calne (Fig. 6) (Cambridge, UK) realized pig-to-baboon liver xenotransplantations [55]. This was a logical approach before attempting clinical trials on man, which had been the approach preferred so far. In 1970, Calne suggested replacing the terms intraordinal and interordinal xenografts by the terms concordant and discordant xenografts, respectively [56]. In 1976, Jean-François Borel (Basel, Switzerland) discovered cyclosporine A [57], which introduced true immunosuppressive therapy.

Resumption of experiments in 1963

In the 1960s, there was a resumption of clinical attempts at xenotransplantation [6,58–65]. On February 16, 1963 (published in 1964), Claude Hitchcock (Minneapolis, MN, USA) transplanted the kidney of a baboon to a 65-yr-old woman [66]. She survived for 4 days but the artery clotted.

On November 5, 1963 (published in 1964), Keith Reemtsma (Fig. 7) (New Orleans, LA, USA) attempted a kidney xenotransplantation from a rhesus monkey to a 43-yr-old docker named Jefferson Davis [67–69]. For the first time, the procedure included immunosuppression treatment with azathioprine, actinomycin C, prednisone, and total body irradiation. The patient died of shock following a pneumonia 63 days after transplantation. On January 13, 1964, a 23-yr-old schoolteacher received a chimpanzee kidney [67]. When she died 9 months later, an autopsy showed that acute electrolyte imbalance was the only cause of death. The 9-month survival without rejection of the chimpanzee kidney gave evidence of the feasibility of xenotransplantation. This is the longest survival ever recorded for the xenotransplantation of an organ. In 1964, Keith Reemtsma reported on a series of 12 heterotransplantations of ape kidneys in which he did not obtain better results than previously [70,71].

On January 23, 1964, James Hardy (Fig. 8) (Jackson, MS, USA) attempted the first heart transplantation: he gave the heart of a chimpanzee named Bino to a 68-yr-old man, Boyd Rush, in a state of cardiogenic shock secondary to ischemic cardiomyopathy [72]. The patient died after 90 min. The authors blamed the small size of the heart of the donor and the bad condition of the patient for the failure. However, data from the post-mortem exam suggest a vascular hyperacute rejection.

In December 1963 and January 1964, Thomas Starzl (Denver, CO, USA) and Claude Hitchcock

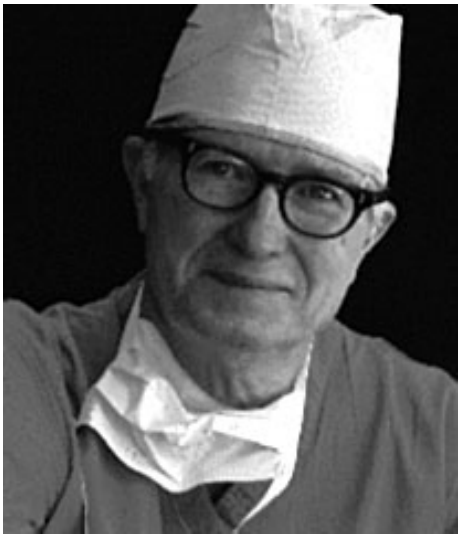

Fig. 8. James Hardy (1918 to 2003). Courtesy of The University of Mississippi Medical Center, Office of Public Affairs, USA.

transplanted the kidneys of baboons to six human patients who survived for 19 to 98 days but died eventually, four of them from sepsis and the other two from rejection [73]. In 1964, David Hume (Richmond, VA, USA) reported xenotransplantation of the kidney of a chimpanzee to a man [74]; the patient lived only 1 day. In 1965, Jules Traeger (Lyon, France) transplanted chimpanzee kidneys to three patients [75]; the longest survival period was 49 days. In 1966 (published in 1969), Raffaello Cortesini (Rome, Italy) transplanted the kidney of a chimpanzee to a 19-yr-old man who survived for 31 days [76].

At the same time, on December 3, 1967, at the Groote Schuur Hospital in Cape Town, the South African surgeon Christiaan Barnard realized the first human-to-human heart transplantation to a man named Louis Washkansky [77]. The patient died from a lung infection 18 days later. After this success, surgeons concentrated their efforts essentially on allografts.

In 1968, Denton Cooley (Fig. 9) (Houston, TX, USA) described the transplantation of the heart of a sheep to a 48-yr-old man with terminal ischemic cardiomyopathy [78]; the transplant failed 10 min after restoration of the circulation.

In 1969, A. Bertoye and Pierre Marion (Lyon, France) attempted two xenotransplantations with the livers of baboons to a 22-yr-old woman who survived for more than 4 months (she was still alive at the time of publication) and to a 7-month-old boy who died 39 h after the beginning of surgery [79]. Later, the same team transplanted the heart of a chimpanzee to a young woman after the failure of

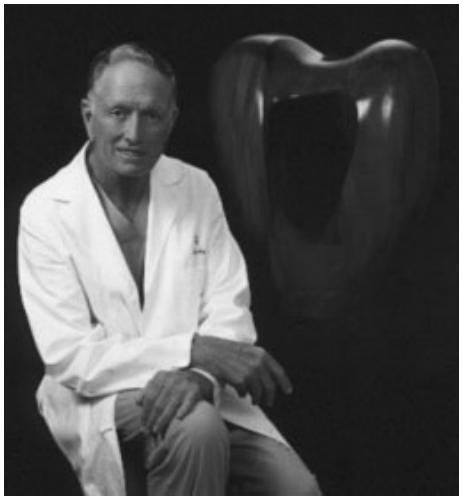

Fig. 9. Denton Cooley (born 1920). By courtesy of Denton Cooley.

the replacement of a mitral valve. This attempt is little documented: the authors only indicated that the heart failed "quickly" [80].

After realizing the first hepatic allotransplantation in 1963, Thomas Starzl (Denver, CO, USA) transplanted chimpanzee livers to three children between 1969 and on 1974. A 28-month-old child survived for 9 days [81], a 7-month-old boy survived for 26 h [82], and the third child lived for 14 days [83].

In 1969 (published in 1970), Lucien Léger (Paris, France) achieved a heterotopic xenotransplantation of the liver of a baboon to a 23-yr-old woman in a coma with fulminant hepatitis [84,85]; the liver functioned for 55 h but had to be removed after 72 h. The patient died 12 h after ablation of the transplant. In 1971, M. Pouyet and P. Bérard (Lyon, France) transplanted the livers of baboons to a 28-yr-old woman and a 34-yr-old woman; both patients died after 2 days [86].

In 1977, Christiaan Barnard (Fig. 10) (Cape Town, South Africa) attempted heterotopic heart transplantations on two patients supported by extracorporeal (pump) circulation following failed routine cardiac surgery [87]. In the first case, the heart of a 30-kg baboon was transplanted to a 25-yr-old woman. The heart stopped beating after 5½ h. Although the cause of death is attributed to the difference in size between the heart of the donor and that of the recipient, signs of hyperacute rejection were already present [88]; immunosuppression was not reported for this case. The second case involved the transplant of the heart of a chimpanzee to a 60-yr-old man. In spite of strong immunosuppression, rejection caused death in 4 days.

Fig. 10. Christiaan Barnard (1922 to 2001). By courtesy of the Groote Schuur Hospital Transplant Museum, Cape Town, South Africa.

Era of immunosuppression

On October 26, 1984, Leonard Bailey (Fig. 11) (Loma Linda, CA, USA) realized the most famous xenotransplantation to a 12-day-old female baby named "Baby Fae". Fae was born prematurely on October 14, 1984, with hypoplastic left-heart syndrome. Fae received an ABO-mismatched baboon heart [89,90]. In a preliminary study with newborn lamb-to-goat xenotransplantations, Bailey had obtained a mean survival time of 72 days, with one subject surviving for 165 days [91]. With Fae, except for the ABO incompatibility, the conditions for success were present: the heart of the donor and

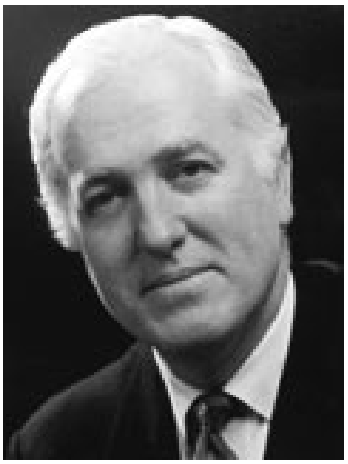

Fig. 11. Leonard Bailey (born 1942). By courtesy of Loma Linda University, CA, USA.

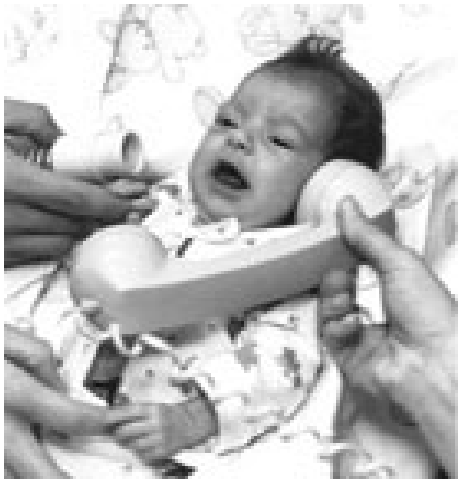

Fig. 12. Baby Fae (October 14, 1984 to November 15, 1984). By courtesy of Loma Linda University, CA, USA.

that of the recipient were of comparable sizes, the recipient was immunologically immature, and cyclosporine was now available. Among six available baboons, the one triggering the weakest reaction on lymphocyte cultures was selected. After surgery, heart function remained stable until the 11th day (Fig. 12). At that time, the first signs of rejection appeared, and then Baby Fae died on November 15, 20 days after surgery. Most of the hopes put on xenotransplantation died with Baby Fae. The accumulation of failures during this and previous experiments led to a de facto moratorium. It was only in 1992, at the instigation of Starzl, that attempts resumed.

In 1992, a new immunosuppressive agent, FK506 (tacrolimus), was marketed [92]. It was immediately used by Thomas Starzl (Fig. 13) (Pittsburgh, PA, USA): on June 28, 1992 (published in 1993) Starzl transplanted the liver of a

Fig. 13. Thomas Starzl (born 1926). By courtesy of Thomas Starzl and the University of Pittsburgh Medical Center, PA, USA.

baboon to a 35-yr-old man with active chronic hepatitis, who was also infected by hepatitis C virus and HIV [93]. The baboon liver has this advantage over the human liver that it is resistant to infection by the virus of hepatitis B [94]. The patient survived for 70 days. The cause of death was cerebral aspergillosis associated with other infections. Starzl tried again on January 10, 1993, when he transplanted a baboon liver to a 62-yr-old man dying from chronic active hepatitis B. The patient never regained consciousness and died 26 days later [95].

In 1992, Zbigniew Religa (Sosnowiec, Poland) transplanted a pig heart to a man with Marfan's syndrome (published by Czaplicki) [96]. The natural xenoantibodies had been previously adsorbed, using the heart of a control pig. The death of the patient 23 h later was attributed to the small size of the heart. Rejection is more likely, although this possible cause was dismissed by the author.

In June 1992 (published in 1995), Leonard Makowka (Los Angeles, CA, USA) transplanted the liver of a pig to a 26-yr-old woman with fulminant hepatic failure, history of autoimmune hepatitis, and hepatitis C infection [97]. This xenotransplantation was intended to be temporary until a human liver could be found. Natural xenoantibodies had been previously removed by plasmapheresis. The liver showed signs of function but the neurological status of the patient did not improve and she died 34 h after transplantation due to diffuse cerebral edema.

On the night of December 31, 1996, Dhani Ram Baruah (Sonapur near Guwahati, India) transplanted the heart of a pig to Purno Saikia, a 32-yr-old man with ventricular septal defect (unpublished) [98,99]. The patient died the seventh day from septic shock. Baruah was arrested on the night of January 9, 1997, for violating the Human Organ Transplantation Act of 1994 [100–102]; he was detained for 40 days but he said that he will continue xentransplatation attempts. Indeed, in 2000, Baruah gave more than half a pint of pig blood to a 22-yr-old laborer named Hussan Ali suffering from severe anemia [103,104]. Four weeks later, the patient was still alive and was discharged from the hospital. Test results confirmed Ali had "non-human" circulating blood cells.

Xenoperfusions

Liver

Xenoperfusion via the liver of a pig was first proposed in 1965 by Ben Eiseman (Denver, CO, USA) [51], 1 month after Profulla Kumar Sen (Bombay, India) reported in 1964 (published in 1966) the use of extracorporeal liver perfusion using human livers to treat five patients [105,106]. In December of 1967 (published in 1969), David Hume (Richmond, VA, USA) first tested cross-circulation between the arm of a woman in deep hepatic coma and the leg of a 35-pound baboon, for clearing the human blood [107]. After 12 h, the patient had excreted about 5 l of fluid through the baboon's kidney and regained consciousness. Twenty-two days later the patient went home, and the baboon was alive and healthy. A similar procedure was successfully used later by SC Bosman, John Saunders, John Terblanche, and Christiaan Barnard [108–110] and George Abouna (Philadelphia, PA, USA) [111–113].

Extracorporeal xenogeneic liver perfusion has been regularly used in the treatment of hepatic encephalopathy [114–116] but, because of the success of liver transplantation, this procedure was abandoned in the 1980s. More recently, it was again used to support patients with fulminant hepatic failure and patients awaiting liver transplantation [117,118]. In spite of the interest elicited by this technique, which has been considered to be successful [119], a recent and exhaustive retrospective study showed that long-term survival does not exceed that observed with conventional intensive care [106].

In 2000, Marlon Levy (Dallas, TX, USA) reported the first two successful extracoporeal hepatic supports with transgenic (hDAF/hCD59) porcine livers used as a bridge to human liver transplantation [120]. The first patient was a 17-yr-old man with idiopathic fulminant hepatic failure; he was perfused for 6.5 h, until the arrival of a human liver. During the perfusion, the porcine liver produced 115 ml of bile. The second patient was a 18-yr-old woman with Wilson's disease who was perfused for 10 h; the porcine liver produced 270 ml of bile. In both cases, successful allotransplantation ensued, with excellent graft function and patients in good health.

Bioartificial liver devices

Xenoperfusion with bioartificial liver devices has also been used as a bridge to liver transplantation [121–124]. After developing, in 1957, the first model of a biological artificial liver (BAL), Motokazu Hori (Tokyo, Japan) treated, in October 1958, for the first time, a human patient in hepatic coma due to liver cirrhosis with a BAL using four live dog's livers [125]. In 1963, Yukihiko Nose (Sapporo, Hokkaido, Japan) treated four patients

with a BAL using fresh liver slices and freeze-dried canine liver granules; all patients improved but two of them died shortly after treatment [126,127].

In 1987, Kenneth Matsumura (Berkeley, CA, USA) used a filtration system based on rabbit hepatocytes to treat a single patient with hepatic failure caused by an inoperable cholangiocarcinoma [128]. All other clinical experiences with xenogeneic sources had used porcine hepatocytes. In 1989, MS Margulis (Latvia, USSR) compared the mortality in 59 patients who had received treatment using bioartificial liver devices with pig hepatocytes (37% mortality) to that observed in 67 patients who had received classic extensive therapy (59% mortality) [129].

In 1994, the American company, Circe Biomedical (Lexington, MA, USA), developed the HepatAssist 2000 System®, a BAL device using primary porcine hepatocytes. The first clinical trials were realized shortly after [122,130–133]. In 2004, in the first prospective randomized multicenter controlled trial of an extracorporeal liver support system, including 171 patients with fulminant/subfulminant hepatic failure, Achilles Demetriou et al. [134] showed that HepatAssist® was safe and improved survival.

Since 1999, two other extracorporeal hemofiltration devices using primary porcine hepatocytes have been developed by American companies: LIVERx2000 System® developed by Algenix (Shoreview, MN, USA) and BLSS® developed by Excorp Medical (Oakdale near Minneapolis, MN, USA). Excorp Medical and John Patzer from the Thomas Starzl Transplantation Institute (Pittsburgh, PA, USA) collaborated to develop the Bioartificial Liver Support System (BLSS®) [135, 136]. In 2001 (published in 2002), George Mazariegos and John Patzer described the first clinical use of BLSS for the support of a 41-yr-old woman with fulminant hepatic failure [137]. Another publication reported on the safety aspect of the treatment of the first four patients [138]; three of them died several days after treatment but one patient was successfully transplanted 16 days after a single perfusion.

In Europe, the Academic Medical Center of Amsterdam developed the AMC-BAL system® using primary porcine hepatocytes. A phase I clinical trial was carried out in Italy. In 2002, Maarten-Paul van de Kerkhove and Robert Chamuleau (Amsterdam, the Netherlands) reported the first clinical cases. The first patient was a 35-yr-old woman with acute liver failure due to hepatitis B infection who received a liver transplantation after two AMC-BAL treatments of 21 and 14 h [139]. Among the first seven patients treated, six received a successful orthotopic liver transplantation and one patient improved after two treatments and did not need transplantation [140]. Because it is not allowed by law to use animal tissues or cells to treat patients in the Netherlands or in Western Europe, the research group at the Academic Medical Center is developing a human-derived hepatocyte cell line BAL.

Heart

In 1968, Donald Ross (London, UK) performed a heterotopic heart transplantation in a patient with cardiopulmonary bypass; the heart stopped beating after 4 min. The same day, he perfused a pig heart with human blood without transplantation; there again, the heart immediately stopped beating [141].

Lung

After Waldhausen in 1957 [142], Lester Bryant used in 1968 pig lung xenotransplantation for oxygenation of human blood during cardiac surgical procedures. A rapid failure of the lungs occurred [143,144].

Kidney

In 1996, Michael Breimer (Göteborg, Sweden) realized an extracorporeal connection of pig kidneys to two patients under dialysis [145–147]. In spite of preliminary plasmapheresis to reduce anti-pig xenoantibodies, the experience failed: the kidney was rejected by the first patient after 65 min, the second patient developed an anaphylactic reaction in 15 min, but recovered.

Spleen

Extracoporeal splenic perfusion through spleens from pigs was used in Russia for treatment of pneumonia [148], septic complications after surgery [149,150], sepsis [151–153], shock [154,155], and lupus erythematosus [156].

Tissue and cell xenografts

Recent trials at xenotransplantation concerned above all tissues and cells (Table 6).

Burns

In 1983, Robert Ersek (Austin, TX, USA) experimented the transplantation of pig skin for the

Table 6. Tissue and cell xenotransplantation – the modern era

Year	Author	Place	Tissues or cells	Animal source	Number of cases	References
1983	Ersek	Austin, TX, USA	Skin	Pig	3 burned patients	[157,158]
1994	Groth	Stockholm, Sweden	Pancreatic islets	Pig	10 diabetic patients	[160]
1994	Aebischer	Lausanne, Switzerland	Chromaffin cells	Calve	85 patients with severe pain	[166,167]
1995	Ildstad	Pittsburgh, PA, USA	Bone marrow	Baboon	A 38-yr-old man	[163,164]
1996	Aebischer	Lausanne, Switzerland	Fetal kidney cells	Hamster	6 patients with amyotrophic lateral sclerosis	[168]
1997	Deacon	Belmont, MA, USA	Dopaminergic neural cells	Pig	12 patients with Parkinson's disease	[169]
1999	Vogt	Bochum, Germany	Skin	Pig	15 burned patients	Quoted by [159]
2002	Valdes	Mexico city, Mexico	Pancreatic islets	Pig	12 diabetic children	[161]

Recent trials at xenotransplantation concerned above all tissues and cells.

treatment of burns [157,158]. More recently, Peter Vogt (Bochum, Germany) used pig skin grafts to treat 15 patients for burns (unpublished data, quoted by Paradis et al. [159]).

Diabetes

Between 1990 and 1993, (published in 1994), Carl Gustav Groth (Stockholm, Sweden) treated 10 insulin-dependent diabetic kidney-transplant patients with fetal porcine islet-like cell clusters injected intraportally or placed under the kidney capsule of the renal graft [160]. Four patients excreted small amounts of porcine insulin during 200 to 400 days, but insulin injections had to be continued for all patients.

After the New Zealand government refused to authorize a trial for transplantation of pig pancreatic islet cells into humans, the New Zealand company, Diatranz, arranged to conduct trials in Mexico and in the Cook Islands. In August 2002, at the XIXth International Congress of the Transplantation Society (Miami, FL, USA) Rafael Valdes (Mexico City, Mexico), David White (Ontario, Canada) and Diatranz Ltd. (Auckland, New Zealand) reported the transplantation in May 2001 of islets from 1-week-old piglets mixed with testicular Sertoli cells to 12 children aged 10 to 17 yr with type 1 diabetes [161]. Five of the patients required less insulin, and all of them received additional islets at 20 weeks. During a follow up extending for more than 1 yr, a 17-yr-old girl did not require insulin or any other drug. The last six patients did not benefit at all. Because of a simultaneous transplantation of pig Sertoli cells, no anti-rejection drug was necessary.

AIDS

In 1994, Camillo Ricordi (Pittsburgh, PA, USA) suggested xenotransplantation of hematopoietic cells resistant to HIV as a potential treatment for patients with AIDS [162]. In 1995, on December 14, Susanne Ildstad (Pittsburgh, PA, USA) realized the first baboon bone-marrow transplant to a 38-yr-old man with AIDS named Jeff Getty [163]; 1 month later, there was no evidence to prove that baboon cells were present in Getty's bone marrow [164], but the clinical state of the patient improved [165], perhaps because of the radiation therapy he received before the procedure.

Pain and neurological disorders

In 1994, Patrick Aebischer (Lausanne, Switzerland) transplanted encapsulated bovine chromaffin cells from newborn calves to the spinal canals of patients with severe pain [166,167]. In 1998 and 1999, a placebo-controlled blind study sponsored by the American company CytoTherapeutics (Sunnyvale, CA, USA) was performed in Poland, the Czech Republic and Switzerland on 85 patients. This clinical trial showed insufficient efficacy of the treatment.

In 1996, Patrick Aebischer (Lausanne, Switzerland) transplanted genetically engineered baby hamster kidney cells to the spinal canals of six patients suffering from amyotrophic lateral sclerosis [168]. In spite of the presence of neurotrophic factor in the spinal fluid, there was no clinical amelioration.

Between 1995 and 1997, in a phase I trial sponsored by the American company Diacrin (Charlestown, MA, USA), Terrence Deacon (Belmont, MA, USA) transplanted fetal porcine dopaminergic neural cells into the brains of 12 patients with Parkinson's disease; in one patient who died 7.5 months post-transplant, a small number of surviving neurons were identified [169]. Other clinical trials were performed by Diacrin for treatment of Parkinson's disease, Huntington's disease [170], epilepsy [171] or paralyzed patients but results were disappointing.

The modern era

A renewed interest

From 1967 on, date of the first successful heart allotransplantation, human donors were preferred as being more compatible. However, because of the successes of allotransplantation, the availability of human organs or tissues is insufficient. In view of the shortage of organs, the use of animal sources was recently again considered.

Recent progress in control of rejection

Although primates are immunologically very similar to humans, they are no longer considered as potential donors for clinical xenotransplantation because of shortage and risks of infectious disease transmission. Pigs are preferred today. In size, anatomy, and physiology, they are similar to man; they are prolific and it is possible to produce specific pathogen-free pigs. However, pigs are genetically more distant to man than primates. Hyperacute rejection may occur when organs from a pig (or other animals) are transplanted into human patients.

Many strategies for preventing xenograft rejection have been studied: immunosuppression, preformed natural antibody depletion, immunomodulation, immunological tolerance, encapsulation and genetic manipulation [63]. A research program was initiated by the Company Imutran (Cambridge, UK) to produce pigs transgenic for human decay-accelerating factor (hDAF), a protein that inhibits complement activation in man [172]. After David White, director of research at Imutran, injected a small amount of human DNA into fertilized sow eggs, the first hDAF transgenic pig, named Astrid, was born on December 23, 1992.

In 1995, the company Nextran (Princeton, NJ, USA) developed transgenic pigs expressing both human complement regulatory proteins, DAF and CD59 [173].

The PPL Therapeutics (Blacksburg, VA, USA), the company that produced Dolly, the first cloned mammal, announced the birth on March 5, 2000, of the first cloned pigs, five piglets named Millie, Christa, Alexis, Carrel, and Dotcom [174]. Pig cloning is a useful technology for developing transgenic pigs. The same year, Akiri Onishi (Tsukuba, Japan) reported the birth on July 2, 2000, in Japan, of a cloned female black piglet named Xena using a different method [175].

The galactose alpha-1,3-galactose epitope on the vascular endothelium surface of pigs is a major obstacle to successful xenotransplantation. Two separate groups announced the production of knockout pigs for this gene and then cloned the pigs. Liangxue Lai from the team led by Randall Prather (Columbia, MO, USA) and the company Immerge BioTherapeutics (Charlestown, MA, USA) reported that four cloned miniature piglets that were missing the gene were born in September and October 2001 [176]. On December 25, 2001, Yifan Dai and the US-Scotland-based firm PPL Therapeutics (Blacksburg, Virginia, USA) reported the birth of five similar knock-out cloned piglets [177,178]; because they were born on Christmas Day, they were named Noel, Angel, Star, Joy and Mary. On July 25, 2002, the first four cloned double knock-out piglets lacking both copies of the gene were born at PPL Therapeutics (Blacksburg, VA, USA). Shortly after, Immerge BioTherapeutics announced the birth on November 18, 2002, of a double knock-out miniature piglet.

With transgenesis and cloning, a great step was made in control of hyperacute rejection, the most important immunologic hurdle in xenotransplantation. The immune barrier has now been breached.

Assessment of infectious risk

During the last decades, new infectious diseases resulting from adaptation to humans of animal diseases have spread in the world (Ebola hemorrhagic fever, AIDS, Creutzfeld-Jacob disease, SARS, etc.). The potential infectious risks associated with xenotransplantation became a major preoccupation within the scientific community. The risk of pig endogenous retrovirus (PERV) sequence expression was taken seriously [179]. This risk of xenozoonosis concerns not only the recipient but also the general population [180].

In 1997, in a co-culture of porcine and human cell lines, Clive Patience (Immerge BioTherapeutics, Charlestown, MA, USA) and Robin Weiss (London, UK) showed that porcine endogenous retroviruses could infect human cells in vitro [181]. In 1998, a vast campaign calling for a moratorium was launched in *Nature* with the support of Fritz Bach (Boston, MA, USA) [182]. In 1999, Khazal Paradis, director of clinical research at Imutran (Cambridge, UK), in a large international study including 160 patients who had been treated with living pig tissues, reported that no PERV infection was detected [159]. Other clinical studies did not reveal any retroviral cross-infection [183–185], but in vivo experiments in severely immunodeficient mice gave grounds for caution: in 2000, Maarten-Paul van de Kerkhove (Amsterdam, the Netherlands) and Daniel

Salomon (Los Angeles, CA, USA) [186] showed that pig pancreatic islets produce PERV and can infect human cells in culture and that PERV is transcriptionally active and infectious cross-species in vivo after transplantation of pig tissues. The same year, a similar observation was reported by Yi-Mo Deng (Sydney, Australia) [187].

Supervised practices

France was the first nation to adopt a law on the therapeutic use of organs, tissues, or cells of animal origin (law number 98 to 535 of July 1st, 1998). This law does not explicitly authorize xenotransplantation; it only defines preliminary obligations, which is an implicit acceptance of the practice (or a de facto moratorium if the necessary authorizations are refused). Since then, many countries have adopted the French position. Many regulatory authorities and companies have become involved in xenotransplantation surveillance [188–190]. After Patience's publication [181], in October 1997, the FDA halted all clinical trials until researchers could prove they can detect low levels of PERV infection. The moratorium was lifted in January 1998, but the FDA requires monitoring of recipients of living pig tissues for evidence of PERV infection. In 1999, the FDA banned the use of primates as donors in xenotransplantation, citing the risk of cross-species infection.

Diatranz's clinical trial of islet xenotransplantation in Mexico has sometimes been condemned because it was performed in a country that has no appropriate regulatory conditions in place to safeguard public health or monitor patients and their contacts for viruses on a long-term basis [191, 192].

Ethical aspects and social acceptability

At the beginning of the 20th century, Voronoff was slandered by public opinion to the extent that he had to abandon his practices. The medical feat constituted by the transplantation of the heart of a baboon to Baby Fae rekindled the ethical debate on xenotransplantation [193,194]. The Baby Fae case was heavily covered by the media. *Time* first wrote, ''Baby Fae stuns the world'' [195] but later concluded ''Baby Fae loses the battle'' [196]. The public is not currently well-informed about xenotransplantation. Some surveys showed that xenotransplantation, particularly of pig tissue, is rather well accepted by patients and by the general population, although most subjects would prefer a human or even a simian donor [197–199], but the population is not as aware as the scientific community of the specific health risks.

Conclusion

To this day, there has been no long-term survival of any xenogeneic graft, but the proof has been made that an animal organ can survive and function within a human being. The best demonstration was made by Reemtsma who succeeded in keeping alive for 9 months a patient transplanted with the kidneys of a chimpanzee. In an experiment with better media coverage, Bailey managed to keep alive a baby for 20 days after xenotransplantation of a baboon heart, showing to the world the perspectives offered by xenotransplantation.

Because of easier control of rejection, modern clinical xenotransplantation trials are conducted, not on organs, but on tissues or cells. At present, xenotransplantation is finally taking off in an unexpected field, that of the treatment of diseases of the nervous system.

With microencapsulation of cells or small tissues, production of transgenic pigs, and pig cloning, great advances have been made for controlling xenograft rejection. Today, the most important problem is the risk of viral transmission to recipients and to the general population. Then, it will be necessary to overcome ethical and social hurdles before a wider clinical application of xenotransplantation can be considered.

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