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HISTORY OF TRANSPLANTATION MEDICINE

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Трансплантация органов является одним из наиболее эффективных методов лечения в случае органной недостаточности. Историю трансплантации можно проследить в прошлом в таких сферах, как мифы, легенды и сказания. Хорошо известными примерами служат древнеегипетская и древнегреческая мифологии: древнеегипетский бог Гор, которого символизирует человек с головой сокола, Сфинкс с человеческим лицом, но телом кошки или греческий Минотавр с верхней частью тела, как у человека, и головой быка. Даже у первых христиан были «сообщения о трансплантации»: Косма и Дамиан, святые покровители врачей и парикмахеров, заменили у верующего ногу с раковой опухолью на ногу темнокожего эфиопа, который умер накануне.

Достижения в асептической, сосудистой хирургии, анестезиологии, а также первой успешной пересадки кожи проложили путь к трансплантации органов целиком. Алексис Каррель описал новый успешный способ сшивания сосудов в 1901 году. Между тем, новая научная область трансплантационной иммунологии открыла важные аспекты в понимании трансплантации органов. Это привело к переходу от экспериментального и теоретического этапов к реальным клиническим испытаниям в первых центрах трансплантации.

Значение трансплантации в современной медицине не может быть недооценено. В этой статье освещаются основные вехи в трансплантационной медицине, помещая их в более широкий контекст творческого процесса.

Ключевые слова: история медицины, трансплантационная медицина, подавление иммунитета

Transplantation of organs is one of the most effective therapies for organ failure. The history of transplantation can be traced way back into the spheres of myths, legends and sagas. Well-known examples are the ancient Egyptian and Greek mythology: The old Egyptian god Horus, symbolized by a falcon-headed man, the sphinx with her human face but a cat-like body or the Greek Minotaurus with the human upper body and head of a bull. Even the early Christians had «reports of transplantation»: Cosmas and Damian, patron saints of the doctors and barbers, replaced the cancerous leg of a believer with the leg of a dark colored Ethiopian who died the day before.

Advantages in aseptic, vascular surgery, ether anesthesiology as well as the first successful skin transplants paved the way for full organ transplants. Alexis Carrel described a new successful way of connecting vessel end-to-end in 1901. Meanwhile the new scientific field of transplantation immunology contributed important aspects to the understanding of organ transplantation. This lead to the transformation from an experimental and theoretical stage to real therapeutically trails in the first transplant centers.

The value of transplantations in modern medicine cannot be underestimated. This article highlights the milestones of transplantation medicine and puts them in the greater context of a creative process.

Keywords: history of medicine, transplantation medicine, immunosuppression

Introduction

Transplantation of organs has fascinated mankind since many hundreds of year, making it subject of myths, sagas and legends. Milestones arose from its legendary history.

The history of transplantation as well as its establishment cannot be understood without the curative and creative aspect of this relatively young sector of medicine. Without doubt this creative process rose from certain milestones. This article highlights the most relevant breakthroughs in the history of transplantation and puts them in the greater context of a creative process.

Material and methods

Review article based upon research in the databases medline, pubmed and the Cochrane Library as well as analysis of so far unpublished

Fig. 1. Ganesha, 12th century B.C.

valuable foreign language literature.

1. History of transplantation

1.1 Origins

Transplantation of organs and tissue has fascinated mankind ever since. The oldest report are found in Hindu mythology (12. B.C.): Ganesha was beheaded and given the new head of an elephant (fig. 1) [1]. Even the early history of Christianity contains reports of transplantation: St. Cosmas and St. Damian, Syrian healer and patrons of the doctors and barbers (martyrs after their execution on September 27th in 287), replaced the leg of a Christian during his sleep using the leg of a dark skinned Ethiopian who died the day before (fig. 2), [2].

Fig. 2. St. Cosmas und Damian

First transplantations were conducted in the 16th century: nowadays known as the refining of plants. The first documented transplants of skin are found in the literature of the 19th century. 60 years after big steps in vascular surgery, antisepsis and anesthesiology paved the way for transplantation of organs.

1.2 First organ transplantation (1901-1912)

The Frenchmen Alexis Carrel published in 1901 in Lyon his experiences with a new method to connect blood vessels end-by-end (fig. 3) [3, 4]. At this early stage he seemed to oversee the impact of his invention and noticed: «Nowadays a surgical-technical curiosity, could transplants…one day be of clinical interest».

Europe as well had its share in the development of transplantation medicine. Over 70 en-bloc kidney transplantations were done by Unger in Berlin, Stich and Makas were the first to implant a kidney in the Fossa iliaca. First initially successful trails of xenogeny kidney transplants from animal to human in 1906 by Mathieu Jaboulay in the hospital Hotel-Dieau in Lyon led the way for the advances in Berlin.

These developments of technics, new operative methods as well as insights into the genetic and immunological requirements represent the early milestones of transplantation medicine. The final explanation of the immunological nature of the rejection of organs and the subsequent development of effective immunosuppressives in the middle of the 20th century represent the beginning of the revolutionary era of clinical transplantations [5, 6, 7].

1.3 Development of immunosuppressives

«The dream of medicine to initiate immunotolerance in the receiver just for the transplanted organ, not being in need for further medication, seems far away», stated Joseph Murray at the anniversary of his first kidney transplant in 1955.

Full-body radiation in addition to radiation of the spleen led to first successes even in not related donors in the beginning of the sixties. The side effects especially the routinely found aplasia, prevented successful long-term results. *Roy Calne* was the first to conduct trails using azathioprine instead of

6-mercaptopurine. Azathioprine replaced 6-mercaptopurine shortly afterwards because of its better usability.

The department of microbiology of Sandoz in Basel, Switzerland did research on spores from HardangerVidda, Norway in 1970 with the goal to develop new antibiotics. One of the strains Tolypocladiuminflatum produces cyclic polypetides, later known as cyclosporine (fig. 4) [8].

Nowadays we can use broad range of immunosuppressives with different targets in the complex process of organ rejection. They are used as induction as well as basic therapy to make use of synergetic effects and lower dosages minimizing side effects.

2. History of kidney transplantation

The kidney was predestined as a pilot organ for transplantation, because animals could survive with the remaining kidney, relatively large vessels and the ureter which can be used as a real-time measurement for the successful transplantation during the operation itself.

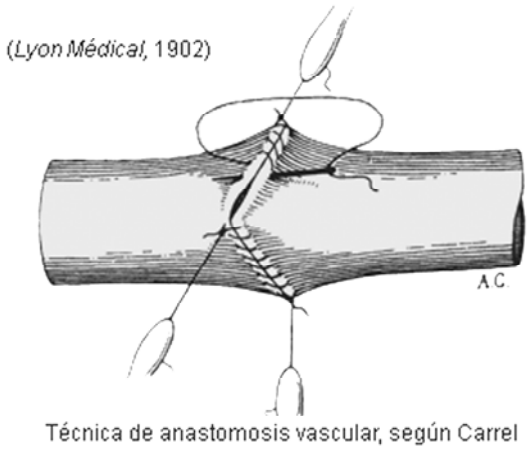
Emmerich (Imre) Ulmann born in Pecs, Hungary, reported on the the «Medical Society Meeting» in Vienna in 1902 of his first case of kidney (auto)transplantation in a dog, placing the autotransplant in the neck [9]. A so far unresolved problem was the anastomosis of the vessels. He explaning of having used «small pipes of magnesium, which I had ordered custom-made with one half of the pipe smooth, the other half with two notches».

Ernst Unger conducted his first experiment of kidney transplantation in animals (laboratory dog) in Berlin in 1909: he transplanted the kidney of a fox terrier to a boxer [10].

The Russian Yuri Voronoy was the first to conduct a homologous human kidney transplant in 1933 (Kherson, Ukraine). The cadaver kidney of a donor with blood type B was transplanted after six hours of anoxia into the upper thigh of a receiver with blood type 0 [11]. However, the kidney was just for a couple of days in function be of a major-mismatch-reaction. Without doubt, the pioneer Voronoy from the former USSR, remained due to the political situation unrecognized in the western world [12].

The first true success in humans was achieved shortly before Christmas in 1954 by the team of Moore, Murray, Merril and Harrison in the Peter Bent Brigham Hospital in Boston (fig. 5) [13, 14]. The Boston group made used of an operative technique developed in Paris, in which the donor kidney (twin brother of the patient) was placed in the fossa iliaca and the ureter in the bladder of a

Fig. 3 a. Alexis Carrel



Técnica de anastomosis vascular, según Carrel

Fig. 3 b. End-to-side-anastomosis from Alexis Carrel

Fig. 4. Fungi imperfecti (Cyclosporin)

Fig. 5. Operation team (Moore, Murray, Merril und twins)

23-year old patient with chronic progressive nephritis. The transplant started to work after 90 minutes of anoxia and the remaining functionless kidney was explanted because of a persisting hypertonia after six months. The patient later married a nurse from the hospital in Boston and had two children with her before dying eight years later during an acute cardiac failure.

The first kidney transplantation of relatives was conducted by the urologists Brosig and Nagel in 1963 in Berlin. On June 3rd in 1970 after the foundation of Eurotransplant it had come to the point where a kidney explanted in Brussel fitted extremely well to a patient in Berlin. The US air force helped by flying the organ into the isolated (West-) Berlin. The transplantation was done at the university hospital Benjamin Franklin (formerly know as KlinikumSteglitz) and made the foundation for the «transplantation program of Steglitz» [15].

Nowadays, the kidney transplantation is gold standard for chronic terminal irreversible renal failure [16]. Not only the quality of life, but also the survival are improved compared to the long-term dialysis.

3. History of heart transplantation

The history of cardiac surgery began on September 9th in 1896 by the first suture of the heart by Ludwig Rehn in Frankfurt. An important step was taken with the discovery to use hypothermia in open-heart surgery, which was firstly very limited in effect, using hypothermia of the body surface. Systemic hypothermia was developed later.

During the 19th century Charles Edouard Brown-Sequard was able to show that muscles in the status rigor mortis (examination of the muscles of beheaded murderers) were by infusion of fresh blood regaining the ability for electric stimulus-response [17]. Frey and Gruber invented the first ex vivo organ perfusion apparatus in 1885.

The aviation pioneer Charles A. Lindbergh did also participate in the development of extracorporeal circulation in order to operate on the heart. Due to a mitral valve defect of his sister-in-law Elisabeth Morrow he searched for the possibility of correcting the defect operatively. He was told, that the heart could not be put in a state of rest along enough to repair the defect. Lindbergh and Carrel presented in 1935 the results of their research: The world's first extracorporeal pump for isolated organs – and a lifelong friendship of Lindbergh and Carrel.

However, many people call John H. Gibbon and his wife Mary Gibbon from Jefferson Medical College as father and mother of the "artificial heart" [18]. During the congress of the American Association of Thoracic Surgeons in 1939, the former president Leo Eloesser recalled having thought of the initially unbelievable, fantastic and still visionary stories of Jules Vernes during the presentation of Gibbons.

In 1960 Norman Shumway and Richard Lower started a long-term and very detailed experiment with animals in Stanford [19]. They aimed at developing a method for human heart transplantation. They were able to reduce the operation time significantly. Therefore Norman Shumway and Richard Lower are as well pioneers of the heart transplantation. After a long period of preparation Shumway was able for his first heart transplantation. The honor of the first heart transplantation went to Barnard, what was percieved negatively by many people, because they expected Norman Shumway at the Stanford University in Paolo Alto to be honored. The reason was that Barnard visited during four months Richmond, Denver and Stanford in order to gain the necessary knowledge for his own heart transplantation – without letting anyone know about it.

The fate of heart transplantation decided in favor for Captown: On Saturday, December 2nd of 1967

Barnard and his team were the first to transplant the heart in a 54-year old patient. The female donor, a 25-year old student died shortly before the transplantation due to fatal injuries caused by a traffic accident.

«Jesus! Ditgantwerk!» – Jesus, it works! – this sentence was said by Christian Barnard. The transplanted heart started to beat in this very moment. On December 17th the receiver developed a therapyresisting pneumonia and died on December 21st due to terminal cardiac output failure (fig. 6) [20]. The operation was of great public interest and initiated a still ongoing debate about juristically and ethical framework of transplantation medicine.

On January 6th in 1968 Shumway at Stanford University did his own first heart transplantation: The receiver died 2 weeks afterwards. On April 27thChristian Cabrol who had worked together with Barnard and Shumway at Lillehei in Minneapolis did the first heart transplantation in Europe (Paris). He was honored for his service with the highest medal of France: Commandeur de la Lйgiond'Honneur, Officier de l'Ordre Na Mйrite.

Following the first heart transplantation in 1967, it soon became an established method to cure irreversible myocardial diseases. Current reports in Germany for the year 2004 list 398 heart transplantation with 761 patients listed at Eurotransplant [21]. One year after surgery 75% of all transplants were in function, five years after surgery – 67%.

Fig. 6. Christian Barnard during his first heart transplantation

4. History of liver transplantation

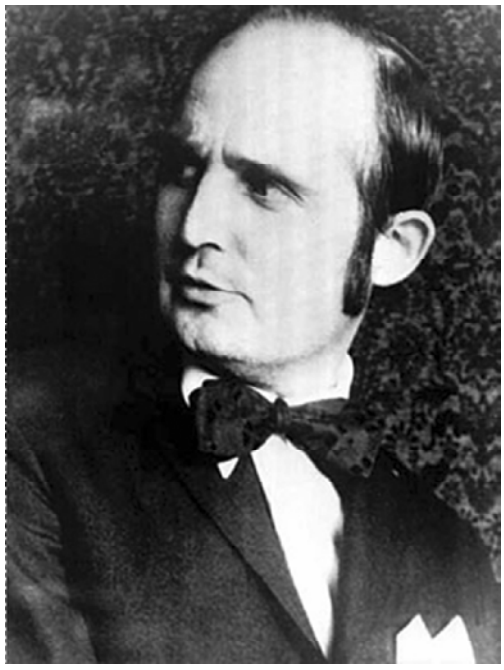
Two names are closely associated with liver transplantation: Thomas Starzl from Denver and Roy Calne from Cambridge [22]. On March 1st in 1963 Starzl was the first to transplant a liver in humans: A three-year-old child with biliary atresia received the liver of another child suffering from brain tumor [23]. The receiving child survived just five hours postoperatively. The second liver transplantation was done by Starzl in May 1963. The patient died after 22 days due to a foudroyant pulmonary embolism. The third liver transplantation in August 1963 Starzl used a pure abdominal instead of a combined thoraco-abdominal approach. However, the patient died on the 8th day postoperatively due to primary transplant failure.

On June 19th of 1968 Alfred Gutgemann did his first liver transplantation in Bonn, Germany. The patient a 30-year-old student with advanced liver malignoma survived seven months – much longer than most of the so far almost 50 transplanted patients in foreign countries (fig. 7). The operation team of the first liver transplantation in Germany consisted of 40 doctors and nurses. The operation took 5,5 hours. Rudolf Pichlmayr started in Hannover in 1972 the for a long period of time largest liver transplantation program in Germany.

Liver transplantation soon became in a short period of time an established curative method. Although liver transplantations did not receive as much attention by the media as the first heart transplantation the medical and scientific importance remains undisputed.

The recommendation of the Consensus Conference to offer a liver transplantation as a therapeutical approach to more patients in end-stage

Fig. 7. The first patient in Germany recieving a liver transplantation



liver disease led to an enormous development in Europe and the USA. Just in 2003 5330 livers were transplanted in Europe and 5214 in the USA. The one-year-survival rate of liver transplants in benign liver disease exceeds 80%. The survival rate in acute liver failure currently exceeds 60%.

Discussion

Transplantation of organs has been ever since a dream of medicine. The vision of successful transplantation of organs fascinates humans since many hundreds of years. This article summarized some of the most important milestones in the history of transplantation.

Scientific approaches of transplantation reach back to the 18th century. In the 19th and early 20th century the experimentation of transplantation had a wide distribution. The early years of this relatively new era of organ transplantation of the 20th century were characterized by a high rate of mortality, a high incidence of acute rejections and severe side effects of the immunosuppressives. The development of Cyclosporine in 1978 led to revolution in transplantation medicine starting with its application in kidney transplantation.

The development of transplantation medicine as well as the establishment of this new sector of medicine cannot be understood with the creative and curative approach of this relatively young sectors of medicine. Without doubt some of the milestones led to a creative process. The creation of knowledge cannot come out of nowhere – a deep foundation had to be present in order to allow new insights.

This review article draws outlines the most relevant milestones of transplantation medicine and its legendary but oftentimes unsuccessful history. We appreciate the necessary creative process that led to the development of Transplantation medicine.

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