

Transplantation at 100 Years: Alexis Carrel, Pioneer Surgeon

Robert M. Sade, MD

Institute of Human Values in Health Care, Medical University of South Carolina, Charleston, South Carolina

The Beginning of Transplantation

On December 23, 1954, Ronald Herrick became the first healthy human being to subject himself to a major surgical procedure for the benefit of someone other than himself. He was the donor of a kidney to his identical twin brother, Richard, who was dying of end-stage renal disease. His brother's donated kidney allowed Richard to survive for another 8 years [1]. The surgeon, Dr Joseph Murray of the Peter Brigham Hospital in Boston, had done extensive preliminary experimental work and continued to be a leader not only in clinical transplantation, but also in the study of the immune phenomena surrounding transplantation. Dr Murray, along with E. Donnell Thomas, was awarded the Nobel Prize in Physiology or Medicine in 1990, "for their discoveries concerning organ and cell transplantation in the treatment of human disease" [2].

Last year, the semi-centennial anniversary of the procedure was widely celebrated as the beginning of clinical organ transplantation. Although the 1954 procedure launched clinical transplantation, the science of organ transplantation actually began a half-century earlier. The year 2005 marks the centennial anniversary of Alexis Carrel's publication of his first article on successful organ transplantation in October 1905 [3].

The critical technical prerequisite for successful transplantation surgery was the development of techniques for suturing blood vessels. Such methods had not been developed yet in 1894 when the president of France, Sadi Carnot, was assassinated in Lyon. Carnot was stabbed in the abdomen and bled to death from a laceration of the portal vein. Surgical opinion held that the president could not have been saved because of the nature of his injury. A young medical student at the University of Lyon, Alexis Carrel, argued to the contrary that Carnot could have been saved if surgeons could repair blood vessels as they repaired other tissues. In 1896, Carrel was an intern at Lyon's Hôtel Dieu, and he was aware that Matthieu Jaboulay at the University of Lyon had successfully repaired a divided carotid artery experimentally, using everting interrupted mattress sutures. However, his method did not work in the repair of small blood vessels. In that year, Carrel started his own experiments, and before long his work gained local notoriety. He recognized that extremely fine needles and thread were needed, and he found what he needed, but not in surgical

supply houses, but at a wholesale haberdashery not far from his home. He attributed his noteworthy manual dexterity in working with these materials to the lessons he received from a well-known embroideress of Lyon. He carried out his early experiments in his spare time, while working full-time as a house officer. He published his first articles on vascular anastomosis in 1902 [4, 5], and the methods he developed are still in use today.

A critical event in his life occurred in May 1903, when Carrel accepted an invitation to join a pilgrimage to Lourdes, known for the miracle cures of its waters, although he was highly skeptical of miracles. On the train to Lourdes, he examined a 17-year-old girl who was near death with tuberculous peritonitis; she had a fever with rapid respiratory and heart rates, as well as abdominal distention due to solid masses and fluid. That afternoon Carrel saw the tuberculous girl and found her to be unconscious with extreme skin pallor and with a pulse more rapid than it had been before. He announced that she was on the verge of death. Her companions poured healing water on her abdomen, and in a few minutes, her abdomen was flat and she had regained consciousness. Later that evening Carrel found her abdomen to be flat with no distention and no masses. Although flabbergasted by this event, Carrel believed he had witnessed a miracle and considered it his responsibility to report his objective observations, which he did. Subsequently, he was criticized by his colleagues for being incredibly gullible, and at the same time was he was criticized by the church for being too skeptical. A senior colleague told him that his implausible report had hurt his reputation so much as a scientist that there was no possibility he could pass the examinations required for a faculty position. Disillusioned and angry with the academic establishment, Carrel resolved to travel to North America.

In 1904, he left France, sailed to Canada, and stopped in Montreal where he presented an article on vascular anastomosis, which was enthusiastically received and led to an invitation to visit Chicago. At the University of Chicago he worked with Dr Charles Guthrie, and together for the next 22 months they wrote 21 articles. Carrel refined his techniques of vascular anastomosis, using ever-finer needles and sutures made slick with petroleum jelly, developing the triangulation method of small vessel anastomosis, and perfecting the everting anastomosis technique (Fig 1). By replacing segments of carotid artery with jugular vein, and using vein as an arterial patch, Carrel and Guthrie demonstrated for the first time that veins could be used as a substitute for

Address correspondence to Dr Sade, Department of Surgery, 96 Jonathan Lucas St, Suite 409, PO Box 250612, Charleston, SC 29425; e-mail: sader@muscc.edu.

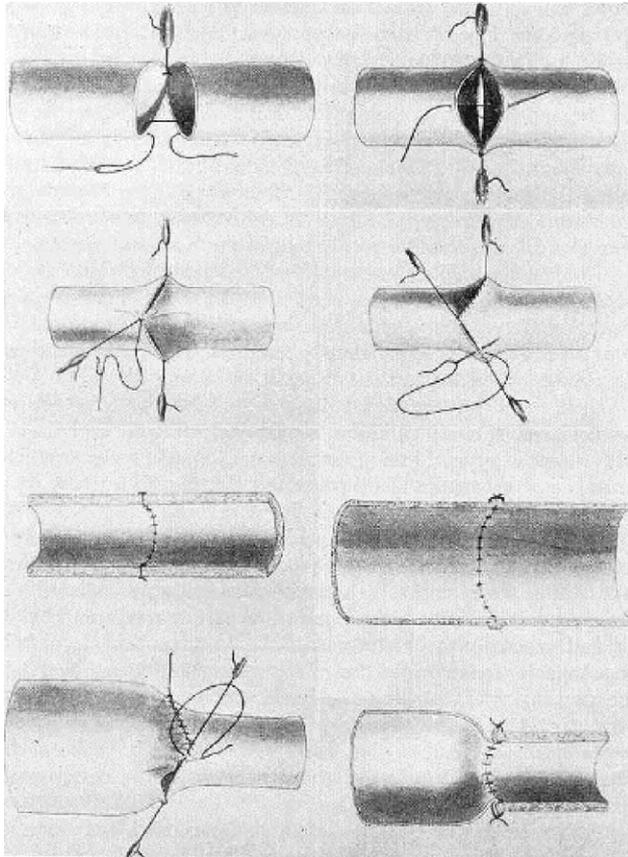


Fig 1. Upper four panels (left to right): The triangulation technique of small vessel anastomosis. Three fine stay sutures are placed at regular intervals around the circumference of a small vessel. Gentle traction on two of the sutures at a time allows the surgeon to achieve a smooth, everting anastomosis without touching the delicate vessel wall with forceps. Lower four panels: These show anastomoses of a small vessel, larger vessel, and small vessel to larger vessel. (Reprinted from Edwards, Edwards. *Alexis Carrel: Visionary surgeon*, 1974, 64-83 [13]. Courtesy of Charles C. Thomas Publisher, Ltd, Springfield, Illinois.)

arteries and could tolerate arterial pressure without aneurysm formation.

Carrel's interest in transplantation was first manifested in 1902 in Lyon, when he transplanted a kidney from a dog's abdomen to its neck. The kidney produced urine immediately, and the animal died after a few days from an infection. Carrel first published his work on organ transplantation in October 1905 (ie, the "Functions of a Transplanted Kidney"), which was co-authored by Charles Guthrie [3]. It was a short article, stating simply that a dog's kidney was transplanted into the neck with vascular anastomoses to the carotid artery and external jugular vein, and the ureter implanted in the esophagus; subsequent renal function was described. This article and two others, including one on thyroid gland transplantation, published in the same year, mark the beginning of the science of organ transplantation [6, 7]. Carrel and Guthrie successfully transplanted kidneys and ovaries from one dog to another, and developed the so-

called Carrel's patch for kidney transplantation. This technique, still used today, removes a patch of aorta with the renal artery attached, in order to avoid the dangers of thrombosis posed by a small blood vessel anastomosis (Fig 2). They transplanted the heart of a small dog into the neck of a larger dog and observed effective contractions of the transplanted ventricles within an hour of the operation [8].

By 1906, Carrel's work in vascular suture and transplantation was well known, yet he was poorly financially supported at the University of Chicago. Consequently he accepted an invitation to continue his work in the laboratories of the Rockefeller Institute in New York. There he preserved arteries and veins from dogs in cold saline solution for several days or weeks, then implanted them in the abdominal aorta of cats, demonstrating for the first time that blood vessels could be preserved with hypothermia. He worked on other methods of preserving vascular grafts, including treating them with heat or dehydration, or storing them in glycerin, formalin, or petroleum jelly, which was the most successful. He discovered that both homograft and heterograft vessels degenerated slowly and were replaced with host scar tissue, resulting in an autogenous collagen tube that could function as an arterial conduit for long periods of time. While working with vascular replacement of the descending thoracic aortic, he also discovered that

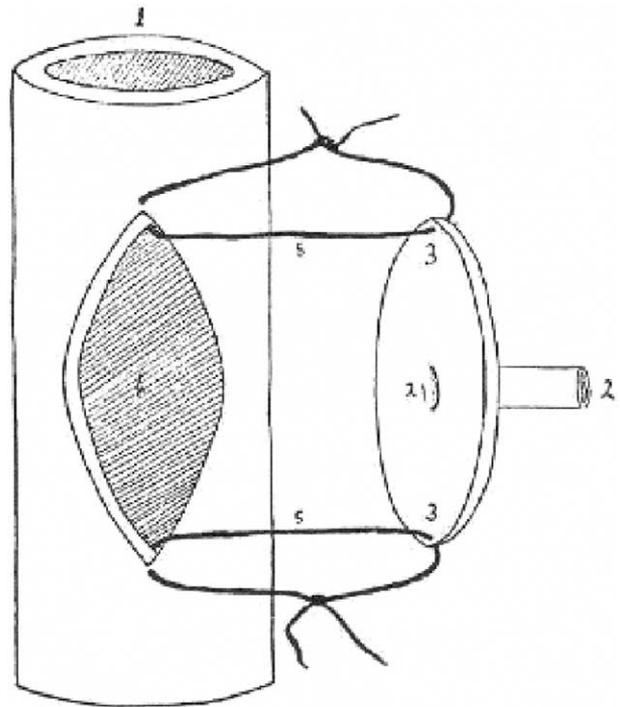


Fig 2. The Carrel patch. By removing a patch of aortic wall (3) containing the orifice of the renal artery (2), the surgeon places the arterial anastomosis (5) distant from the small renal artery, so that anastomotic blood clots cannot obstruct flow to the kidney, but remain in the much larger aorta (1). (Reprinted from Edwards, Edwards. *Alexis Carrel: Visionary surgeon*, 1974, 64-83 [13]. Courtesy of Charles C. Thomas Publisher, Ltd, Springfield, Illinois.)



Fig 3. Alexis Carrel at the time of his Nobel Prize presentation, 1912. (Courtesy of the Nobel Foundation.)

paraplegia resulted from lengthy occlusion of the aorta. Between 1902 and 1909, Carrel successfully transplanted many different organs (ie, the kidney, the thyroid gland, the adrenal gland, the ovary spleen, the intestine, the heart, and a heart-lung block) [9]. He reported successful limb replantation in 1906, transplanting the thigh from one dog to another, thus anticipating by more than 50 years the first successful human limb replantation in 1962 [10].

In 1909 and 1910, Carrel focused his research on surgical procedures on the heart. He was many decades ahead of his time, performing mitral valvulotomy, mitral valvuloplasty, and coronary artery grafting. He did the world's first coronary artery bypass graft, suturing one end of a long segment of canine carotid artery to the aorta and the other to a coronary artery [11].

Carrel was rewarded for his groundbreaking work by receiving the Nobel Prize in Physiology or Medicine in 1912, "in recognition of his work on vascular sutures and the transplantation of blood vessels and organs" [12]. He received the prize 78 years before the same honor was bestowed to Murray for clinical transplantation. The 1912 Nobel Prize was groundbreaking in several ways. Although he had always retained his French citizenship, Carrel became the first scientist working on American

soil as well as the first surgeon to win a Nobel Prize. At the age of 39 years, he was also the youngest Nobel Laureate (Fig 3).

Carrel's Later Years: Science, Politics, and Charles Lindbergh

The purpose of this article is to recognize Alexis Carrel's creation of the field of transplantation 100 years ago. The story of his contribution is told by the events of his life leading up to and including the award of his Nobel Prize. However, the story of his life is too compelling to stop the telling it in 1912. His subsequent scientific contributions included developing techniques of tissue culture (including the culture of embryonic heart cells), corneal grafting, and cancer research. During the World War I, he served in the French army and developed methods of improving wound healing and minimizing infection through the design of devices to deliver Dakin's solution directly into healing wounds [13].

Carrel's interest in the physiology of organ function had been stimulated by his experiments in organ transplantation. In 1929 he attempted to construct a perfusion pump that could support organs under sterile conditions, but his trials consistently failed because of infection of the perfused organs. He was to receive help in this project from an unexpected source.

Charles Lindbergh married Anne Morrow in 1929, 2 years after his internationally celebrated solo flight from New York to Paris. Anne's older sister, Elisabeth, had rheumatic mitral valve disease, and Lindbergh observed the progressive deterioration of her health. Lindbergh's inventive engineering mind became curious about why a heart-lung machine could not keep a patient alive while surgeons operated inside the heart. In 1930, his inquiries led him to the laboratory of Alexis Carrel [14]. During the next 5 years, Lindbergh and Carrel collaborated in constructing a pump that perfused organs with pulsatile flow and oxygenated the perfusion fluid (ie, the world's first functional pump oxygenator) [15].

Lindbergh's work with Carrel was interrupted on March 1, 1932, when his 2-year-old son, Charles, Jr, was kidnapped, and his dead body was found 10 weeks later in a shallow grave. It took 2½ years for a suspect to be apprehended; Bruno Richard Hauptmann was arrested on September 19, 1934, and was later put on trial. Because of Lindbergh's celebrity, the events surrounding the kidnapping, murder, and trial received enormous attention from the press; it was billed as the trial of the century. Hauptmann was convicted and executed. The United States Congress passed a law in response to the kidnapping, which made kidnapping across state lines a federal crime for the first time. Both Charles and Anne Lindbergh were intensely private people; therefore, to escape public attention they boarded a ship for Europe in 1935, and they remained there until 1939 when they were forced home by the start of the war in Europe [16]. Certain events during that time placed Lindbergh on a downward spiral of public condemnation, parallel to a similar fall by his colleague, Alexis Carrel.

Carrel reached the age of 65 in 1939, and under a long-standing rule he was forced to retire from the Rockefeller Institute. Efforts to seek a waiver of this requirement fell on deaf ears, and a bitterly disappointed Carrel returned to France in July 1939. Two months later, in September 1939, World War II began with the invasion of Poland by the armies of the Third Reich. In support of the war effort, Carrel worked on techniques of blood preservation and designed a mobile military hospital, later used effectively by the British in North Africa. In an important humanitarian gesture, he helped obtain large amounts of vitamins through his contacts in the United States, as he intended to help ameliorate severe problems of malnutrition in France. When permission to distribute the vitamins in France was denied, he arranged for their distribution in Spain instead, where they were equally sorely needed.

The French government capitulated to Hitler by a treaty signed in mid-1940, and Germany set up a puppet French government at Vichy. Later that year, the Vichy government offered Carrel the opportunity to continue his investigations at his own institute, to be called the "Institute of Man." Carrel recruited a wide variety of professionals from both the biological and the social sciences under the belief that all the problems of humankind were deeply interrelated and therefore not solvable within a single domain of knowledge. The institute opened in 1941.

Because of his relationship with Nazi-supported Vichy, as well as certain distinctly undemocratic statements he had made during the late 1930s, Carrel was widely regarded by his countrymen as a Nazi collaborator. After the liberation of France in 1944, he was relieved of all duties related to his institute and was placed under surveillance. An investigation began to evaluate the extent of his collaboration with the Nazis and the Vichy government, but no conclusions were reached. Unremitting attacks by the press left Carrel deeply saddened, embittered, and depressed. He was a broken man when he died on November 5, 1944.

Although Lindbergh and Carrel had similar political views that led them both to be widely despised in their own countries, a fate different from Carrel's awaited his friend and colleague. During the late 1930s, Lindbergh toured several countries and visited Germany, where he was still celebrated as an international hero. He openly admired much about the Third Reich, and in 1938, when offered the German Medal of Honor, he accepted. The medal was bestowed by Herman Goering, second to Hitler in the Third Reich. This act produced an outburst of hostility against Lindbergh in the United States. When the war began, the Lindberghs returned to America, and in 1941, Lindbergh became a major spokesman for the "America First Committee," an isolationist organization opposed to the entry of the United States into the war in Europe. The once great man endured widespread condemnation within his own country similar to that of Carrel [17].

Lindbergh's isolationist views changed dramatically after the attack on Pearl Harbor. He wanted to join the war effort, but when he tried to re-enlist and regain his commission, his request was refused due to anger over

his isolationism and suspicions about his foreign sympathies. In a civilian capacity, he became a technical advisor to the United States Army and Navy. Lindbergh worked as an advisor in the South Pacific, and as a civilian during the war years he flew more than 50 combat missions. A decade later, in 1954, President Dwight Eisenhower restored his commission and promoted him to the rank of Brigadier General. He continued working in the aeronautics industry, contributing significantly (eg, to the design of various safety devices and to the design of the Boeing 747 aircraft). Lindbergh's stature as an American icon had been completely rehabilitated by 1974 when he died and was buried near his home on the island of Maui.

Although their stories ended differently, the lives of two of the most illustrious men of the 20th century are forever closely linked (ie, Alexis Carrel [Nobel Laureate scientist] and Charles Lindbergh [pioneering pilot and aeronautical engineer]). Carrel's development of the technical foundations of transplantation and the joint contributions of both men to the development of the pump oxygenator make their lives and surgical contributions of special interest to cardiothoracic surgeons.

References

1. Anonymous. Transplant pioneers recall medical milestone. <http://www.npr.org/templates/story/story.php?storyId=4233669>. Accessed July 30, 2005.
2. Anonymous. The Nobel Prize in Physiology or Medicine, 1990. <http://nobelprize.org/medicine/laureates/1990>. Accessed July 29, 2005.
3. Carrel A, Guthrie CC. Functions of a transplanted kidney. *Science* 1905;22:473.
4. Carrel A. Anastomose bout a bout de la jugulaire et de la carotide primitive. *Lyon Med* 1902;99:114.
5. Carrel A. Presentation d'un chien porteur d'une anastomose arterioveineuse. *Lyon Med* 1902;99:152.
6. Carrel A. The transplantation of organs: a preliminary communication. *JAMA* 1905;45:1645-6.
7. Carrel A, Guthrie CC. Extirpation and replantation of the thyroid gland with reversal of the circulation. *Science* 1905;22:535.
8. Carrel A. Suture of blood-vessels and transplantation of organs. In: *Nobel Lectures, Physiology or Medicine 1901-1921*. Amsterdam: Elsevier Publishing Company, 1967. <http://nobelprize.org/medicine/laureates/1912/carrel-lecture.html>. Accessed July 29, 2005.
9. Carrel A. The surgery of blood vessels. *Johns Hopkins Hosp Bull* 1907;18:18.
10. Malt RA, McKhann CF. Replantation of severed arms. *JAMA* 1964;189:716-22.
11. Carrel A. On the experimental surgery of the thoracic aorta and heart. *Ann Surg* 1910;52:83-95.
12. Anonymous. The Nobel Prize in Physiology or Medicine 1912. <http://nobelprize.org/medicine/laureates/1912>. Accessed July 29, 2005.
13. Edwards WS, Edwards PD. Alexis Carrel: visionary surgeon. Springfield, IL: Charles C Thomas Publisher, Ltd, 1974:64-83.
14. Lindbergh CA. Foreword: Alexis Carrel. In: Edwards WS, Edwards PD. Alexis Carrel: visionary surgeon. Springfield, IL: Charles C Thomas Publisher, Ltd, 1974:v-viii.
15. Carrel A, Lindbergh CA. Culture of whole organs. *Science* 1935;31:621.
16. Berg AS, Lindbergh. New York: G.P. Putnam's Sons, 1998: 236-341.
17. Berg AS. Lindbergh. New York: G.P. Putnam's Sons, 1998: 408-32.