Lindbergh in Carrel's laboratory, circa 1935

The Lindbergh Connection

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While Charles Lindbergh's prowess and accomplishments as an early aviator are general knowledge, few are aware of his contributions to the early research and development of apparatus for extracorporeal perfusion. Lindbergh's childhood upbringing had predisposed him to being an inveterate tinkerer; thus the happenstance of a chronically ill family member and his becoming acquainted with a medical research community found him at work on early attempts at *in vitro* mechanical perfusion. His involvement was to last off and on for a period of over thirty years.

Lindbergh was married in May of 1929 to Anne Morrow, daughter of Dwight Morrow, a U.S. Ambassador to Mexico. Anne's older sister, Elisabeth, suffered from mitral valve disease as a result of having contracted rheumatic fever as a child; consequently she was susceptible to frequent bouts of pneumonia. Her condition was described to the family as hopeless since heart surgery (the only conceivable cure) was impossible—no means were available to provide blood oxygenation and cir-

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culation during the necessary period of cardiotomy.

This explanation for Elisabeth Morrow's inevitable doom was unacceptable to the pensive, nuts-and-bolts Lindbergh: if the heart was essentially a pump, why couldn't an appropriate application of mechanical engineering succeed in temporarily oxygenating and circulating the prospective patient's blood?

The naivete of that question, posed in 1930, would become evident upon Lindbergh's asking it of the right people—physicians. In November of that year, Paluel Flagg, an anesthetist acquainted with the Lindberghs, introduced Charles to Dr. Alexis Carrel. Flagg, also a man of broad interests, was aware that Carrel was engaged in some research involving organs and the pumping of blood. The eagerly awaited meeting was arranged at the Rockefeller Institute in New York City, where Carrel was on staff among a group of many eminent research scientists. Carrel had won a Nobel Prize in 1912 for his work in transplanting organs and in the homograft suturing of blood vessels. In dogs, he had performed heart transplants in 1905, and coronary artery bypass grafts in 1910!

Lindbergh and Carrel became immediate friends and mutual admirers. Carrel explained his interest in the study of *living* organs *in vitro,* the fruits of which might permit diseased organs to be removed from the patient, treated, and subsequently re-implanted. For this approach a mechanical organ preservation unit, or "organ culture" device would be necessary. Carrel's prototypes of such a device were beset by a number of problems, the foremost of which appeared to be sepsis, hemolysis, and unreliable anticoagulation; non-toxic forms of heparin had not yet been elucidated. Of particular interest to Lindbergh was a model designed by Heinz Rosenberger, a German aeronautical engineer and collaborator of Carrel's. This "pump" was constructed of a good bit of glass, but was unsuccessful in preventing eventual sepsis.

Greatly impressed, both by Carrel and by his prototypes, Lindbergh returned home with fresh approaches probably already in mind. Two weeks later, he returned to the Institute with a one-piece glass perfusion device, hand blown for him at Princeton University (Figure 1). The helical pyrex apparatus was described in print in the May 22, 1931 issue of *Science,* with credit anonomously as-

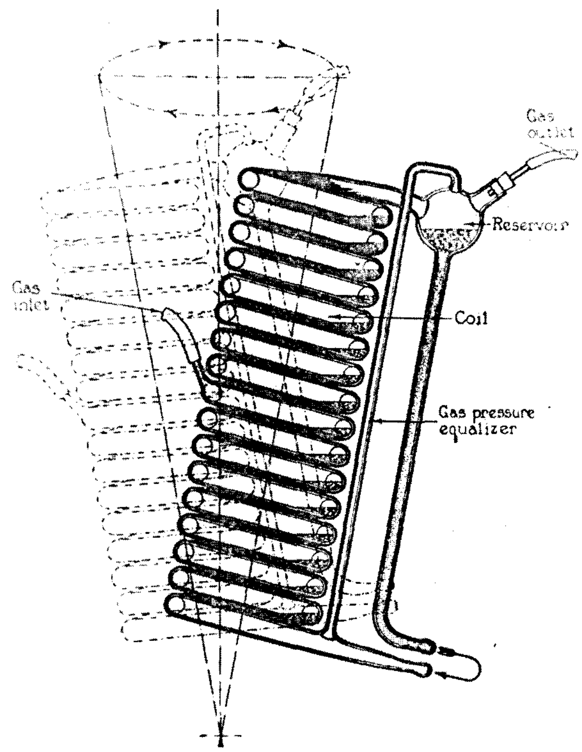

FIGURE 1. Lindbergh's first perfusion apparatus prototype, as published in 1931.

signed to the "Division of Experimental Surgery, Rockefeller Institute for Medical Research". The device was attached to a slanted table base which would then *rotate* eccentrically but not permit *revolving* of the helix. As it rotated, perfusate would be forced upward into a reservoir. Gases could be introduced halfway up the coil, and pressure for delivery of the perfusate was provided by the gravity head which the liquid developed within the reservoir and its downpipe. Problems associated with this earliest model were insufficient perfusion pressures, non-pulsatility, and imperfect asepsis.

Upon further experimentation over the ensuing years, Lindbergh found that he could achieve asepsis by passing the oxygenating gases through a glass bulb packed with sterile, non-absorbent cotton. At about the same time, he seized upon the idea of using these gas pressures to serve an additional use as the driving force behind the perfusate; furthermore, gas pressures could be made to pulsate.

An effective model incorporating these newest improvements was first successfully used in 1935, and published by Lindbergh and Carrel in 1938. A cutaway of the pump is shown in Figure 2. Otto

Hopf of the Rockefeller Institute made the device of blown pyrex glass, again all of one piece except for some floating one-way valves. The "organ chamber" lies at top, the perfusate reservoir at bottom, and a "pressure equalization chamber" runs through the center. The compressed oxygenating/driving gas, an adjustable mixture of oxygen, nitrogen, and carbon dioxide, would be pulsed by external rotating brass valves through the pump via the cotton-filled glass ball filters. The pulse rate of the gas was adjustable, and the pressure the gas maintained in each chamber could be varied. Pressure differences between the three chambers propelled the perfusate along the appropriate path, the valves preventing backflow. Variable "systolic" and "diastolic" pressures could be achieved within the perfusate while the pressure within the organ chamber could be held constant. Since gases are somewhat compressible, the blood and tissue trauma associated with available mechanical pumps was largely avoided.

The *in vitro* organ and its perfusate were visible at all times. Various perfusates (experiments in themselves) consisted of proteins, ions, carbohydrates, homologous serum, hormones, and vitamins. No erythrocytes were used due to agglutination and hemolysis. The fluid was filtered within the device, and could be changed aseptically during long-term use. Variations in perfusion pressure and pulse rate of the fluid were found to have significant effects.

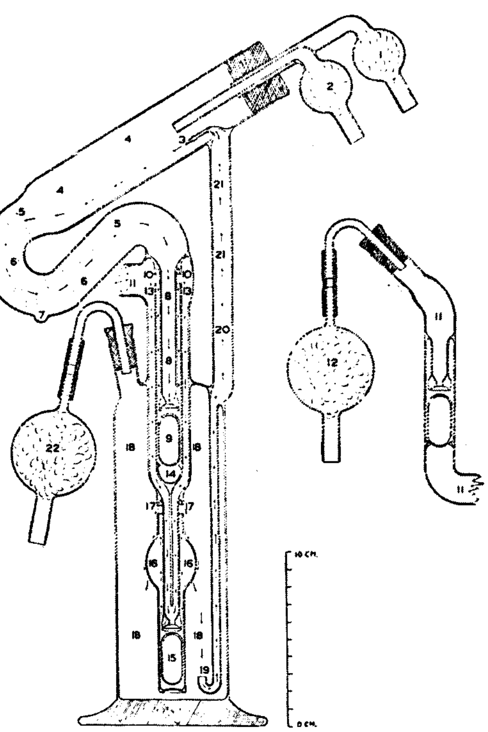

FIGURE 2. The Lindbergh-Carrel collaborative perfusion apparatus, as used successfully in 1935.

Eight hundred ninety-eight experiments in total were carried out using pumps of this design, with perfusion of a wide variety of animal organs. The longest successful trial was the thirty day perfusion of a thyroid gland. However some of the problems posed by the *in vitro* culture of organs eventually proved too difficult for resolution at the time. Specific obstacles included lack of an oxygen-carrying perfusate, degenerative tissue changes, edema, and calcification of arteries. Additionally, by July of 1939 both Carrel and Lindbergh had become involved in the events of World War II, and shortly thereafter separated. The pump, meanwhile, became a popular attraction in the Hall of Medicine at the 1939 World's Fair in New York.

Many years and significant events later, Lindbergh became involved once again in the research use of perfusion apparatuses. In 1964, researchers at the tissue bank of the Naval Medical Research Institute in Bethesda, Maryland wished to follow up on Carrel's work in whole organ perfusion. Their goal was an organ preservation device with which to maintain explanted fresh cadaver organs until their transplantation into the needy patient (as opposed to Carrel's original idea of "treating" the organ *in vitro,* then reimplanting it into the original patient). This experimental design used monkey hearts as the whole organ. However, the 1935 Lindbergh-Carrel pump proved unsuitable to the task for several reasons: 1) it was too small to fit the "large" organ within its chamber, 2) it became too expensive to produce, and 3) since some of the perfusions were to be carried out at temperatures as low as 4 degrees celsius, there was fear of the glass breaking.

Lindbergh's collaboration with Drs. Theodore Malinin, Vernon Perry, and G. H. Mouer resulted in the device published in 1966 and pictured schematically in Figure 3. Two perfusate-containing flexible reservoir bags were immersed in liquid within rigid containers. Pulsatile gas pressure was applied to these containers at adjustable rates (to simulate heart rate) and adjustable pressures (to

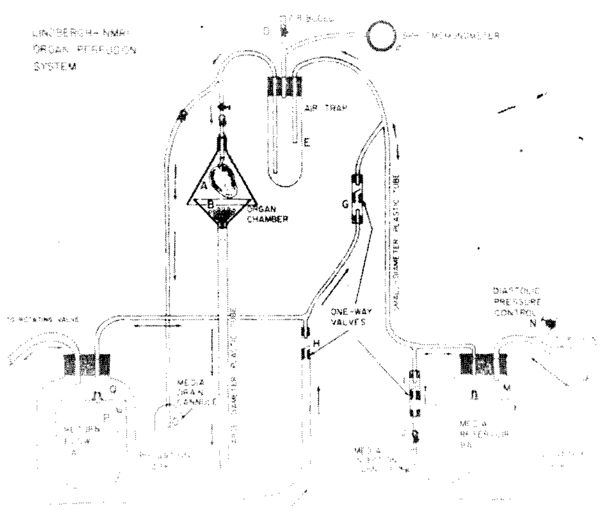

FIGURE 3. Naval Medical Research Institute perfusion apparatus as published in 1966.

create the mimic of systole and diastole). In this fashion, the containers served as pumps. Pulsatile organ perfusion pressures could be monitored on the sphygmomanometer. A variable gas atmosphere ("for pH control") could be maintained in the organ chamber, which remained open to ambient pressure. Both gravity and the second pulsation flask provided for perfusate recirculation; one-way valves prevented backflow. Perfusates were generally mixtures of hypertonic solutions and calf serum.

Over 100 simian hearts were perfused with this apparatus, with "histological survival" from 24 hours to 10 days depending upon the experiment's conducted temperature. The successful performance of the device had as much to do with adherence to Carrel's principles as it did to Lindbergh's expertise as an inventor. Shortly thereafter however, several commercially available self-contained organ preservation devices became generally available, and their integrated compactness as well as the assured asepsis of their disposable organ/perfusate handling sections made them overwhelming favorites for use.

The impact of Lindbergh's pioneering efforts in this field has yet to give way to mere archival status. In 1978, a grant was provided to the University of Miami Surgical Research Laboratories for the purpose of establishing a Lindbergh Organ Preservation Laboratory. Examples of his pump designs are preserved there for student investigation.

Elisabeth Morrow died in December of 1934 following an operation for appendicitis.

Acknowledgements

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