History of Heart Transplant

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Abstract

Cardiac transplantation represents the gold standard therapy for patients with advanced heart failure refractory to medical and device therapy. Decades of clinical and animal-based research laid the foundation for the first heart transplant performed on December 3, 1967, by Christiaan Barnard in Cape Town, South Africa. The initial enthusiasm for transplantation spread quickly and about 100 transplants were performed in the year that followed 1967. Early immunosuppressive regimens consisted of steroids and azathioprine. Early on, due to unthwarted and often undiagnosed rejection, 1-month mortality after cardiac transplant exceeded 50% and most centers abandoned the procedure by 1970. In 1972, Phillips Caves developed the technique for an endomyocardial biopsy and together with Margaret Billingham developed objective criteria for the histopathologic assessment of allograft rejection. Norman Shumway pioneered the use of a calcineurin inhibitor, cyclosporine as a more potent immunosuppressive agent to mitigate rejection after cardiac transplantation. With the successful incorporation of cyclosporine, short and intermediate-term survival improved dramatically and between 1980 and 1990, the

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number of heart transplants performed across the globe grew exponentially from 100 to 4,000 transplants annually.

Keywords

Heart failure · Cardiac transplantation · Cardiopulmonary bypass · Rejection · Immunosuppression

Introduction

The epidemic of heart failure continues to affect millions of patients worldwide. Despite considerable progress in reducing the incidence rates of coronary artery disease and case-fatality through management of blood pressure and dyslipidemia, similar trends have not been observed in heart failure. Further, as the patient population continues to age, the prevalence of heart failure continues to rise. Despite advances in medical and/or device therapy, survival for patients with heart failure still approximates 50% at 5 years (Benjamin et al. 2017). For patients with advanced heart failure, i.e., New York Heart Association Class IV symptomatology that is refractory to medical therapy, cardiac transplantation remains the treatment of choice. Beginning in the 1900s, over half a century of basic science research, surgical technique experimentation and medical forethought carried out by physicians and scientists worldwide culminated in making what was once an experimental surgery into what is now routine clinical practice in major medical centers across the globe. The International Society for Heart and Lung Transplantation (ISHLT) registry has reported 89,000 heart transplants worldwide since 1983 (Lund et al. 2016). It remains the gold standard for heart replacement therapy, albeit available to only 1–2% of patients who benefit from the treatment.

The Pre-clinical Era

Alexis Carrel, a French surgeon, was the first to perfect and describe vascular anastomosis techniques that did not result in thrombosis or failure and essentially establish the basic principles of vascular surgery which made whole organ transplantation possible. Carrel studied at the University of Lyon where he earned his medical degree in 1900. In 1902, Carrel in conjunction with an American physiologist Charles Claude Guthrie published their first landmark articles on vascular anastomosis, and the two are credited with developing the triangulation method of small vessel anastomosis and perfecting the everting anastomosis technique. Their experimental endeavors demonstrated for the first time the utilization of veins as a substitute for arteries. By replacing segments of the carotid artery with the jugular vein and using a vein as an arterial patch, it became evident that these vessels could tolerate arterial pressure without aneurysm formation. Carrel is also credited with the "Carrel patch technique" used in re-implantation of major vascular structures during organ transplantation. Not only a master of vascular surgical techniques his degree of experimental success should also be credited to his emphasis on rigid surgical asepsis (Flexner 1908; Carrel 1910, 2001; Lawrie 1987; Dente and Feliciano 2005; Sade 2005).

In 1905, Carrel and Guthrie published their first work in organ transplantation wherein they described auto-transplantation of a dog's kidney into the neck with vascular anastomoses to the carotid artery and external jugular vein. The ureter was implanted into the esophagus resulting in urine production. During this time, Carrel and Guthrie performed a series of animal experiments, both auto-transplantation and hetero-transplantation. In 1906, Carrel conducted additional work in blood vessel preservation demonstrating for the first time that blood vessels could be preserved with hypothermia (Carrel 1910, 2001).

In several of Carrel's publications, he recognized the difference in survival times between autografts and allografts in experimental animal models but unfortunately did not conceptualize rejection as a distinct entity from other graft-destroying processes. Carrel's groundbreaking research earned him the Nobel Prize in Medicine in 1912 "in recognition of his work on vascular sutures and the transplantation of blood vessels and organs" (Dente and Feliciano 2005).

The work of Carrel inspired research efforts implemented by physiologist Frank C. Mann in

both renal and cardiac transplantation through the 1920s and 1930s. In 1933, Mann and colleagues published an article entitled "Transplantation of the Intact Mammalian Heart" wherein they reported their work on canine heart transplantation. Without the use of hypothermia or cardiac bypass, denervated canine hearts were transplanted into the carotid circulation. In these studies, Mann emphasized the importance of restoring coronary artery circulation as soon as possible to reduce ischemic injury to the allograft, a critical element of heart transplantation today. Canine heart transplant subjects survived for up to 8 days. At autopsy, histological evaluation of the transplanted heart revealed a heart that was "completely infiltrated with lymphocytes, large mononuclear and polymorphonuclear cells" causing Mann and colleagues to postulate that "the failure of the homotransplanted heart to survive is not due to the technique of transplantation but to some biologic factor": essentially allograft rejection (Cooper 1968; Ventura and Muhammed 2001).

In 1937, Vladimir Demikhov, a Russian physiologist, designed a cardiac mechanical assist device which was the first to maintain circulation in animals with the heart excised. While the device was too large to fit inside the chest of his canine hosts, the device maintained cardiac function for approximately 5 h. Between 1946 and 1955, Demikhov conducted a series of experiments in which he attempted to transplant one canine heart into a different canine. His technique involved end to end anastomoses of the donor aorta, pulmonary artery, and vena cava to the corresponding recipient vessels. The donor pulmonary veins were joined together and attached to the left atrial appendage of the recipient thereby avoiding challenging pulmonary vein anastomosis. Survival times for his series of 22 canines in early experiments averaged between 11 and 15 h. This was the first evidence that a cardiac allograft could provide pumping function to a different recipient animal, i.e., orthotopic transplantation (Cooper 1968; Kirklin 2002). Wilford B. Neptune and colleagues pioneered the concept of cold preservation or organ hypothermia in 1953 (Neptune et al. 1953). The group performed successful canine heart and lung transplantation and subsequent return of circulation in the animal to the extent of the return of spontaneous respiration, return of reflexes, normal body temperature, and survival up to 6 h following surgery.

The next pivotal chapter in the history of heart transplantation can be attributed to the work of Dr. Norman Shumway, Dr. Richard Lower, and colleagues at Stanford (Figs. 1 and 2). Shumway and Lower were the first to propose adjuvant local hypothermia with cardiac anoxia revolutionizing cardiac surgery (Shumway et al. 1959). In this method, the body temperature was decreased to approximately 32 °C, and the pericardium was sutured to the surrounding muscular sternal edges creating a cradle or reservoir for continuous cold saline circulation around the heart. The aorta was clamped preventing coronary flow. After a specific period, coronary flow was restored, the heart was defibrillated with an electric shock, and in time the heart could maintain its own circulation independent of the bypass machine. Using this method and a bi-atrial surgical technique, the Stanford team completed their first successful

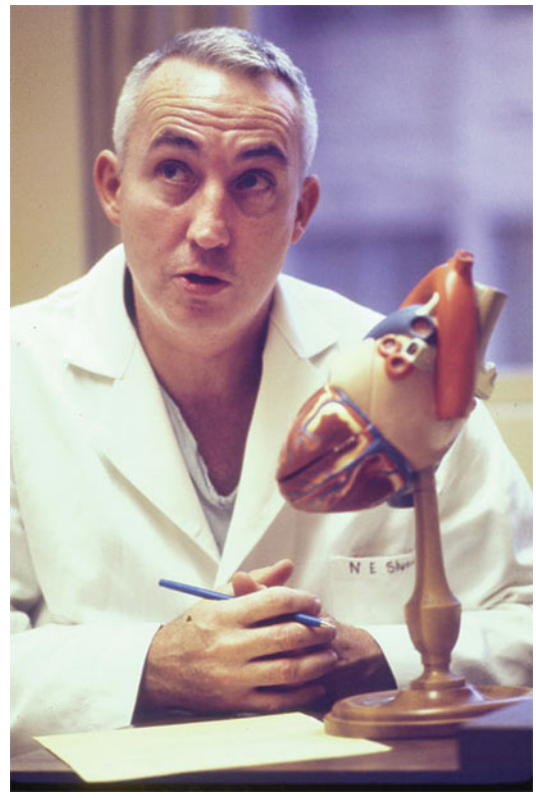

Fig. 1 Norman Shumway

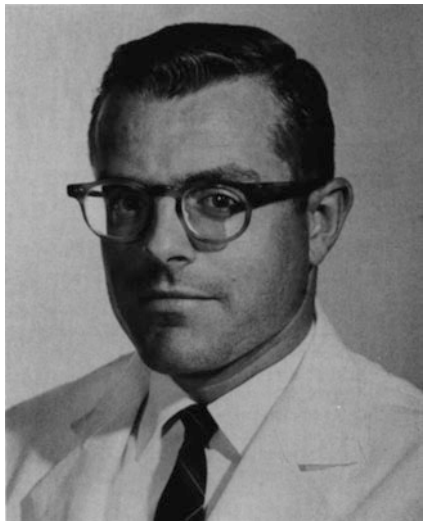

Fig. 2 Richard Lower

heart transplantation in a canine in December 1959 yielding the most impressive survival times to date – 8 days. Afterwards, 8 consecutive transplants were completed and the animals lived between 6 and 21 days. The transplanted dogs reportedly ate and exercised normally (Lower and Shumway 1960).

The theoretical explanation as to the variable lifespan of each animal was thought to be due to individual variation in immunologic response. Description of the postmortem gross examination of each heart revealed areas of myocardial ecchymosis, edema, fibrinous pericarditis, and generalized dilatation. Microscopic examination of sections demonstrated severe myocarditis, with massive round cell infiltration, patchy necrosis, interstitial hemorrhage, and associated regional lymphadenopathy. Shumway and Lower concluded that if the immunologic mechanisms of the host were prevented, destruction of the transplanted allograft would be prevented and it would continue to function adequately for the normal lifespan of the animal. By 1965, Lower and Shumway had extended graft survival to 250 days by using a combination of steroids, azathioprine, and 6-mercaptopurine. Immunosuppression was utilized to promote graft survival and electrocardiography served as a tool to help guide anti-rejection therapy. Ten years of animal experimentation led to the perfection of the pathologic, physiologic, and clinical events associated with orthotopic heart transplantation in animal models (Robbins 2000; Willis Hurst et al. 2000; Kirklin 2002; Pincock 2008).

Clinical Cardiac Transplantation: The Early Days of Heart Transplant in Humans

In 1963, James Hardy, a surgeon at the University of Mississippi, performed the first xenotransplantation into a human (Hardy 1999), Fig. 3. Hardy and colleagues began transplantation research in 1956 using canines, infant calves, and primates. Investigative efforts included trials of several operative techniques, storage, and preservation of harvested organs, evaluation of transplanted heart metabolism, and postoperative management. Hardy cited the operative techniques of Lower and Shumway as the most effective. Organ preservation was trialed with various hypothermic techniques including profound hypothermia via coronary artery perfusion and retrograde coronary sinus perfusion. Postoperative complications seen in canine experiments included bleeding, respiratory failure, arrhythmias, metabolic derangements, infection, and rejection. In 1963 following extensive experimentation and several hundred transplants, the university medical center and researchers decided to investigate orthotopic heart transplantation in a human. The donor heart was from a "young person who had died from brain hemorrhage or trauma" and the designated recipient was a patient near death with terminal myocardial disease.

The patient, a 68-year-old male named Boyd Rush, was found down in his home unresponsive. The patient had a past medical history of hypertensive cardiovascular disease and cardiomegaly. At the time of evaluation, the patient was in atrial fibrillation, cardiogenic shock requiring vasopressors, and acute respiratory failure. Rush's clinical status was described as "unequivocally critical" as a result of heart failure and his life expectancy was deemed to be within a matter of hours. The family

Fig. 3 James Hardy

was consented for cardiac transplantation as a last resort option. Rush's clinical situation deteriorated and the decision was made to proceed with transplantation of a primate heart instead of a human heart. The donor primate heart was preserved using cold oxygenated blood given retrograde through the coronary sinus. Following suturing of the atria, pulmonary artery, and aorta, the donor heart was rewarmed then defibrillated establishing normal sinus rhythm and cardiac output. The first human cardiac transplant had been executed and completed. The transplanted heart was described to have "vigorous contractions" and support a blood pressure ranging 60–90mmhg for approximately 60 min after the removal of bypass cannulas. Unfortunately, soon thereafter, the heart became increasingly unable to handle the venous return without periodic manual massage and the patient expired 90 min after the transplant had been completed. The short-lived success of Hardy and his team proved the technical feasibility of cardiac transplant in man.

Orthotopic Human Heart Transplantation

In his training years, Christiaan Barnard (Fig. 4) worked under the fellowship of Professor Owen Wangensteen and direct mentorship of cardiothoracic surgeons C. Walton Lillehei and Richard L. Varco at the University of Minneapolis in Minnesota. By his mentors, Barnard was described as an "outstanding cardiac surgeon and researcher."

Fig. 4 Christiaan Barnard

Barnard received instruction from these phenomenal surgeons who had successfully completed the first open heart surgery in 1952 and had utilized the newly invented helical reservoir pump oxygenator. Upon completion of his fellowship, Barnard returned to South Africa with a new skill set, a donated blood oxygenator, and a mission to establish a cardiac surgery program at Groote Schuur Hospital in Cape Town. In the years to follow, Barnard developed a high functioning cardiac surgery team with an expertise in valvular surgery and congenital heart defect correction. In 1967, Barnard returned to the United States, and under the mentorship of renal transplant surgeon David Hume at the Medical College of Virginia, learned the fundamentals of transplant immunosuppression. During his 3-month tenure, he also observed the canine orthotopic heart transplant surgical techniques of Richard Lower who had been recruited to the Medical College of Virginia after working with Shumway at Stanford

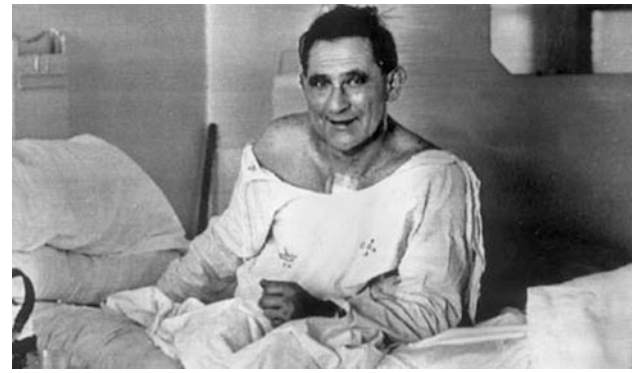

Fig. 5 Louis Washkansky. The first orthotopic human heart transplant recipient

University. Upon returning to South Africa, Barnard successfully completed the first successful single kidney transplant in Cape Town in October of 1967 allowing him to gain personal experience with transplant immunosuppressive therapy. With the culmination of years of experimental research, refining his surgical skill and clinical acumen, and establishing a high functioning surgical team, Christiaan Barnard was now ready to pursue human orthotopic heart transplantation (Cooper 2001; Cooper and Cooley 2001; Brink and Cooper 2005; Toledo-Pereyra 2010).

The first transplant recipient was 54-year-old Louis Washkansky, a diabetic smoker with coronary artery disease and peripheral vascular disease (Fig. 5). On the evening of December 2, 1967, he was taken to the operating room and the operation continued through the night; Washkansky received a heart from a 25-year-old female who was fatally injured in a motor vehicle accident. She was of the same blood type and a similar leukocyte antigen profile. Upon being pronounced dead by the medical examiner, the organ was harvested, and the first human to human cardiac transplantation was successfully completed by Christiaan Barnard and his team in Cape Town South Africa (Barnard 1967). Postoperative care concentrated on maintaining appropriate cardiac output, appropriate immune suppression, and infection prevention. Rejection was thwarted with the use of systemic steroids, local irradiation of the heart, and azathioprine. The patient's early recovery was excellent up until approximately the 12th postoperative day when his condition began to deteriorate. A chest x-ray at that time revealed pulmonary infiltrates. Washkansky was initially treated for acute rejection with augmentation of his immunosuppressive regiment but died on the 18th postoperative day. On autopsy, the heart had no evidence of rejection, but pulmonary evaluation revealed findings consistent with pneumonia.

Three days after Barnard's successful orthotopic heart transplantation, on December 6, 1967, the first heart transplant in the United States was completed by Dr. Adrian Kantrowitz at Maimonides Medical Center in Brooklyn New York (Kantrowitz 1998). The heart from an anencephalic 2-day-old newborn was transplanted into an 18-day-old infant who suffered from Ebstein's Anomaly. Conceptually the newborn infant would have an immature immune system that would adapt to the transplanted allograft without the need for immunosuppression. Postoperatively, the infant was reported to be progressing appropriately and was described to be moving all limbs. Unfortunately, metabolic and respiratory acidosis resulted in cardiac arrest and resuscitation efforts failed. The infant was declared dead a few hours after the operation. Autopsy revealed diffuse lung atelectasis. Gross examination of the heart was normal with no evidence of rejection.

In Barnard's second heart transplant attempt on January 2nd, 1968, he executed a modified surgical technique (Barnard 1969). The incision in the right atrium of the donor heart was extended from the inferior vena cava into the atrial appendage thereby avoiding the area of the sinus node at the

Fig. 6 Philip Blaiberg. Second heart transplant recipient worldwide

roof of the right atrium. The patient, Philip Blaiberg, was the first heart transplant recipient to leave the hospital. The account of his 19-month life after transplant was documented in his novel entitled "*Looking at My Heart"* (Fig. 6). Following his death, an autopsy revealed diffuse coronary artery disease. Between 1967 and 1973, Barnard's team performed 10 orthotopic heart transplants in an era of primitive immunosuppressive therapy and no means to screen or diagnose rejection (Barnard and Cooper 1981).

The fourth heart transplant globally was performed by Norman Shumway at Stanford University on January 6, 1968 (Fann and Baumgartner 2011). The recipient survived 15 days. In the United States, the first overwhelmingly successful heart transplant as measured by patient longevity was completed by Denton Cooley on May 2, 1968 at Baylor College of Medicine in Houston Texas. The patient, a 47-year-old male, received the heart of a 15-year-old girl and survived 205 days. By the end of 1968, 102 transplants were performed at 50 institutions in 17 countries worldwide. Initial enthusiasm for the procedure was blunted by the sobering reality of poor outcomes and limited intermediate-term survival. Of those patients transplanted in that first year, 54 patients (53%) survived to 1 month and 19 patients (19%) survived to 1 year. Given these grim outcomes, by 1970 all but a few centers had abandoned the procedure (Ventura and Muhammed 2001; Fann and Baumgartner 2011).

Understanding the Immune System and Allograft Monitoring

> . . .But it's what happens later with regard to the containment of rejection that makes the real difference. – Norman Shumway

Peter B. Medawar, an English Zoologist, during the early stages of the Second World War was tasked by the Medical Research Council of Britain to investigate why it is that skin taken from one human being would not form a permanent graft on the skin of another person (Billingham et al. 2010). In collaboration with surgeon Thomas Gibson in 1943, the two presented the theory of "active immunization" and immunological memory (Gibson and Medawar 1943). In both human studies and in rabbit models, Medawar's research identified that immune responses characterized by lymphocyte infiltration of the graft; those lymphocytes that were genetically dissimilar were responsible for rejection (Medawar 1944). Subsequent exposure to grafts from the same donor resulted in faster rejection times, demonstrating immunological memory. Additional work with monozygotic and dizygotic cattle demonstrated retention of skin graft with no rejection (Kirklin 2002).

Concurrent research by Sir Frank Mcfarlane Burnet in 1949 argued in favor of the phenomenon of immunological tolerance. Burnet hypothesized that if a foreign substance were introduced

into an embryonic animal before maturation of the immune system, the antigen would "trick" the body into accepting the relevant molecule as "self" rather than "not-self." As a result, no antibody would be formed, even when the antigen was reintroduced later in life. Medawar and Rupert Billingham confirmed this hypothesis by demonstrating that when injecting late-stage mouse embryos of an inbred strain with cell suspensions from another strain, test skin grafts placed on them as young adults were not rejected (Simpson 2015). This was interpreted as the recipient being rendered "fully tolerant" and accepting the foreign grafts as "self." In 1953, Medawar and Billingham published a landmark paper with this initial evidence in mice that demonstrated the concept of actively acquired immune tolerance (Billingham et al. 1953).

A key advance in the understanding of immunology in cardiac transplantation was the introduction of the endomyocardial biopsy technique established by Philip Caves and colleagues in 1972 at Stanford University (Caves et al. 1973). Transvenous biopsy of the endomyocardium allowed for the histological examination of myocardial tissue and the accurate assessment of a recipient's immune response to the donor heart. This paved the way for monitoring patients after transplant for allograft rejection and incorporating immunosuppressant treatment regimens to prevent rejection (Caves et al. 1974a). In a 1974 editorial, Caves et al. described the cardiac biopsy technique and protocol. He described the histological changes seen in the myocardium that typify rejection (Caves et al. 1974b). Stanford colleague Margaret Billingham established a four grade system to classify rejection and provided a basis for treatment (Billingham et al. 1973). Mild acute rejection was characterized by the presence of interstitial fibrinous exudate containing few lymphocytes, myocytes with myofibrillar separation, and myocardial edema. Moderate rejection was characterized by a significant increase in the number of lymphocytes and large mononuclear cells infiltrating the myocardium as well as significant myocardial edema. Severe acute rejection was characterized by profound interstitial cellular infiltrates with polymorphonuclear leukocytes and extravasated red blood cells (i.e., hemorrhage) in addition to the findings of moderate rejection. This allowed for standardization of the pathologic diagnosis of rejection. Endomyocardial biopsy quickly became the gold standard in diagnosing acute rejection episodes as the histopathologic evidence directly correlated with the clinical signs and symptoms of rejection (Singh and Taylor 2015).

Immunosuppression

As the first successful renal transplantation preceded cardiac transplantation by more than 10 years, researchers in that field had already been faced with the issues of allograft rejection. The practical wide-spread application of organ transplantation depended upon the development of pharmacologic immunosuppression. In the late 1950s, the immunosuppressive effects of total body irradiation were explored and used in early human renal transplantation. In 1960, methotrexate and cyclophosphamide were utilized to induce graft acceptance in experiments conducted by William E. Goodman and prednisone was utilized to treat acute rejection. Subsequent work identified the additive and synergistic effects of azathioprine and prednisone making this combination the mainstay of transplant immunosuppression in the early 1960s (Starzl et al. 1983; Müller-Ruchholtz 1999; Rapaport 1999).

The introduction of cyclosporine was a pivotal turning point in solid organ transplantation and patient survival (Colombo and Ammirati 2011). The immunosuppressive effects of cyclosporine A were first reported by J.F. Borel in 1976 (Borel et al. 1976). Cyclosporine, a fungal peptide, inhibits lymphocytes and was the first example of a new generation of immunosuppressive that forms the cornerstone of modern day immunosuppression – calcineurin inhibition (Watson and Dark 2012). In a 1978 publication, cyclosporine A was deemed to be a superior immunosuppressive drug in pigs with orthotopic cardiac allografts, claiming it to be sufficiently tolerated and powerful (Calne et al.

1978). Shumway and his team at Stanford University were the first to implement the use of cyclosporine as maintenance immunosuppressive therapy to prevent cardiac allograft rejection. Analysis of cyclosporine performance at Stanford between 1980 and 1993 showed a significant reduction in the rates of rejection and overall patient survival compared to previous drug regimens (Meine and Russell 2005). The success of cyclosporine and its utilization by Shumway and colleagues revived worldwide enthusiasm for cardiac transplantation. Before 1980, less than 100 heart transplants were being performed annually. However with the approval of cyclosporine, there was an exponential growth in cardiac transplantation growing to just over 4000 cases worldwide per year by 1990; a number that has remained unchanged for the past 25 years (Lund et al. 2016).

Conclusion

Orthotopic heart transplantation represents the scientific dedication of so many investigators and physicians for nearly a century to achieve the unachievable. Perseverance was necessary to develop the best surgical techniques, to identify best practices for organ preservation and cardiopulmonary bypass, and to detect allograft rejection and develop immunosuppression. This perseverance has allowed this therapy to be available to thousands of patients with advanced heart failure each year. Within medicine, the concept of removing a diseased organ and replacing it with a normally functioning organ that can be maintained over time is an outstanding accomplishment and is truly unparalleled.

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